third edition

DEVELOPMENTAL PSYCHOPATHOLOGY

VOLUME 2

DEVELOPMENTAL NEUROSCIENCE

EDITED BY **Dante Cicchetti**

DEVELOPMENTAL PSYCHOPATHOLOGY

DEVELOPMENTAL PSYCHOPATHOLOGY

THIRD EDITION

Volume Two: Developmental Neuroscience

Editor

DANTE CICCHETTI

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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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CHAPTER 1

Evolutionary Foundations of Developmental Psychopathology

MARCO DEL GIUDICE and BRUCE J. ELLIS

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Since its inception in the 1970s and 1980s, the discipline of developmental psychopathology has pursued an ambitious project of theoretical integration. The grand vision of developmental psychopathology is that of a truly multidisciplinary approach to the complex interplay of biological, psychological, and social-contextual aspects of both normal and abnormal development (Cicchetti, 1990, 2006; Hinshaw, 2013). As testified by this volume, the project has been remarkably successful, generating an impressive amount of empirical work while maintaining a shared language and a common theoretical background.

In this chapter we argue that—despite its achievements—developmental psychopathology has yet to realize its full potential, and that its integrative power is limited by the lack of an adequate metatheory. We contend that developmental psychopathology has much to gain by embracing modern evolutionary theory, the unifying metatheory of the life and behavioral sciences. We then review a host of recent theoretical developments in the field of evolutionary-developmental psychology (EDP) that address the organization of individual differences, the nature of environmental risk, the role of early stress, the nature of gene-environment interactions, and many other critical issues. Together, these contributions paint the contours of an integrative theory of human development and provide a sophisticated evolutionary foundation for developmental psychopathology. We aim to show that, far from undermining the tenets of developmental psychopathology, the EDP-based framework we describe supports all its core principles while also extending them,

clarifying their underlying logic, and connecting them at a deeper level than previously possible.

We begin the chapter by considering the role of evolutionary theory in developmental psychopathology. After reviewing the core points of the discipline and the historical reasons for its separation from mainstream evolutionary biology, we present the integrative approach of EDP and discuss its metatheoretical foundations. The basic concepts we introduce here provide a general introduction to evolutionary biology and the overarching background for the rest of the chapter. We also review the main tenets of developmental systems theory (DST; Griffiths & Gray, 2004; Oyama, Griffiths, & Gray, 2001), consider its potential role as an alternative metatheory, and conclude that EDP provides a suitable framework for developmental psychopathology.

The second section explores the interplay between adaptation and maladaptation in the origin of disorders. We build on the distinction between adaptive and desirable traits and discuss how the concept of disorder can be specified in evolutionary terms. We then broaden our view to explore the many ways evolutionary and developmental processes—both adaptive and maladaptive—may result in undesirable outcomes at the individual level.

Next, we introduce the concepts of developmental plasticity and conditional adaptation. We discuss how organisms make use of environmental cues to adaptively match their phenotypes to their developmental context and the ways those processes can fail and result in maladaptive outcomes. We then present a nontechnical overview of life history theory, the dominant biological theory of conditional adaptation and a general framework for understanding the organization of individual differences in physiology, growth, and behavior. Drawing on life history concepts, we take a closer look at the multidimensional nature of environmental risk and examine the logic by which physical and social environmental factors shape and direct individual development.

The chapter then focuses on the central role of stress in the development of individual differences and psychopathology. We argue that the standard framework employed in developmental psychopathology—the allostatic load model (McEwen & Stellar, 1993)—fails to capture the multiple roles of stress in development, and promotes a limited understanding of stress as a risk factor and a source of physiological and behavioral dysregulation. As an alternative, we propose the adaptive calibration model (ACM; Del Giudice, Ellis, & Shirtcliff, 2011), a theory of individual differences in stress responsivity across the life span based on concepts from life history theory and the theory of conditional adaptation. The Adaptive Calibration Model offers a renewed understanding of the role of stress in development and illustrate the heuristic and integrative power of the evolutionary developmental approach.

People vary dramatically in the extent to which they respond to their developmental context. In recent years, it has become apparent that many of the genetic, temperamental, and neurobiological factors that make people more vulnerable to negative, stressful environments also make them more likely to benefit more from positive, supportive environments. Differential susceptibility to the environment is a source of systematic organism × environment interactions, with many implications for both normal and pathological development. We explore the evolutionary logic of differential susceptibility and review the main theoretical models that have been proposed to explain it (Belsky, 1997, 2005; Boyce & Ellis, 2005).

We conclude the chapter by showing how life history concepts provide the foundation for an integrative evolutionary approach to mental disorders (Del Giudice, 2014a, 2014b). The framework we outline is based on the idea that individual differences in life history strategy set the stage for the development of psychopathology. The resulting taxonomy offers a promising alternative to both the atheoretical approach of the Diagnostic and Statistical Manual and empirical classification systems based on the distinction between internalizing and externalizing disorders.

Each section in the chapter shows how an evolutionary developmental approach goes beyond current thinking and contributes to broaden our understanding of psychopathology. At the end of each section, we consider how the concepts and theories we discuss relate to the core points of developmental psychopathology. As our ultimate goal is to catalyze a paradigm shift in developmental psychopathology, we deliberately focus on general principles rather than specific disorders throughout the chapter.

TOWARD AN EVOLUTIONARY-DEVELOPMENTAL FRAMEWORK FOR PSYCHOPATHOLOGY

The Missing Foundation of Developmental Psychopathology

Over the years, a consensus has formed around a set of core points—methodological commitments, goals, and theoretical principles—that define developmental psychopathology as a scientific field. Developmental psychopathology adopts a multidisciplinary perspective; pursues integration across multiple levels of analysis; gives particular consideration to the social and cultural context,

as well as to brain and neurobiological factors; and emphasizes person-centered designs in empirical research. Researchers in the field aim to describe, understand, and synthesize the interplay between normal and pathological development, between developmental continuity and discontinuity, and between risk and protective factors. Finally, developmental psychopathology adopts three key principles from systems theory and developmental biology: the twin principles of equifinality and multifinality, and a view of ontogenetic causality as probabilistic, nonlinear, and involving reciprocal interactions between the developing organism and the environment (see Cicchetti, 1990, 2006; Hinshaw, 2013).

These points are extremely valuable and we subscribe to all of them. At the same time, we recognize that something crucial is missing. Developmental processes are biological processes, and biology is ultimately about function. Yet while developmental psychopathology is highly attuned to the complexities of *how* humans develop, its core points are silent with respect to the *whys* of development. Why do developmental processes unfold in one way rather than another? Why, for example, have they evolved so as to be exquisitely sensitive to contextual factors? And why do different processes show different degrees of context sensitivity? More generally, what is development *for*? Nikolaas Tinbergen (1963) famously summarized the four types of explanation required for a complete understanding of a biological system. With an updated terminology, they can be described as *mechanism* (what is the system like? How does it work?); *development* (how does it come to be over developmental time, and how does it change across the life span?); *phylogeny* (what is the evolutionary history of the system? How did it change across generations and species?); and *adaptation* (why is the system the way it is? What selective advantages does it confer, or used to confer, to the organism?).

Developmental and mechanistic explanations concern the way an organism works in the present, without reference to evolution and adaptation; collectively, they are called *proximate* explanations. In contrast, *ultimate* explanations (phylogenetic and adaptationist) consider the organism in relation to its past and to the evolutionary forces that shaped its body and behavior (Mayr, 1963). The four types of explanation are not mutually exclusive but complementary and synergistic: adaptive function crucially informs the study of mechanism and development, while development and mechanism constrain the range of plausible adaptive explanations (see Scott-Phillips, Dickins, & West, 2011; West-Eberhard, 2003). Restricting one's view to the proximate level of explanation can only result in a partial understanding of the investigated system, in direct contrast with the integrative stance of developmental psychopathology.

In spite of the growing influence of evolutionary theory on the study of human behavior and development (see Buss, 2005; Ellis & Bjorklund, 2005), developmental psychopathology has remained virtually insulated from mainstream evolutionary biology until very recently. Indeed, earlier authoritative introductions to developmental psychopathology (Cicchetti, 2006; Hinshaw, 2013) did not even mention evolutionary biology as one of its contributing disciplines. This state of affairs has historical reasons that should be considered, however briefly. The theoretical foundations of the discipline were largely laid down between the 1970s and the 1980s (Cicchetti, 1990). At the time, the inclusive fitness revolution (discussed in more detail later) was still under way in biology and had had only little impact on the human behavioral sciences. Debates within biology often pitted proximate (developmental) and ultimate (evolutionary) causation against one another rather than acknowledge their complementary nature (West-Eberhard, 2003, ch. 24), and early adaptationist thinking tended to ignore or downplay developmental dynamics. Moreover, initial attempts to apply the logic of adaptation and inclusive fitness to human social behavior were surrounded by heated and often heavily politicized arguments (Segerstrale, 2000).

Coming of age in this intellectual context, developmental psychopathology embraced the holistic, organismic approach prevalent in embryology (Cicchetti, 1990), as did other sectors of developmental psychology and psychobiology. Organismic theories—epitomized by modern DST—stress the hierarchical, self-organizing, active nature of development and the dynamic, reciprocal relationship between the developing individual and its environment (Reese & Overton, 1970). Clearly, this viewpoint has much to offer, and captures some crucial features of developmental processes. However, acceptance of organismic theories has often gone hand in hand with wholesale rejection of the adaptationist approach that informs large part of mainstream evolutionary biology. Psychological theorizing based on adaptationist concepts has been rejected—incorrectly and prematurely, in our view—as implying genetic determinism, a simplistic and unidirectional conception of causality, and an inability to deal with ontogenetic change and transformation. This stance has since become entrenched in developmental psychology (see Lickliter & Honeycutt, 2003; Overton, 2006), and has contributed to insulate the discipline from contemporary evolutionary thinking.

In contrast with this view, and in line with more than two decades of biological and psychological research, we believe that the basic adaptationist approach can be extended and revised to accommodate a sophisticated view of developmental processes. Importantly, this can be done without renouncing its main tenets—such as inclusive fitness theory and the proximate/ultimate distinction (e.g., Bjorklund & Ellis, 2005; Bjorklund, Ellis, & Rosenberg, 2007; Frankenhuis, Panchanathan, & Barrett, 2013; Olson, 2012; Tooby, Cosmides, & Barrett, 2003; West-Eberhard, 2003). Reconciling the logic of natural selection with a truly developmental approach to human behavior is the central goal of EDP, a fast-growing field at the intersection of developmental psychology and evolutionary biology. We now turn to a more detailed analysis of EDP and its theoretical underpinnings.

Evolutionary-Developmental Psychology

Evolutionary-developmental psychology (EDP) is the application of the principles of Darwinian evolution to explain contemporary human development (see Bjorklund & Ellis, 2005; Bjorklund & Pellegrini, 2002). The central assumption of EDP is that cognitive mechanisms, behavior patterns, and the developmental processes that produce them have been shaped by Darwinian selection processes across our phylogenetic history. The primary focus of the field is how evolved psychological mechanisms develop through bidirectional interactions between environmental and genetic factors. The approach of EDP is thus intrinsically interactionist, with a strong emphasis on contextual factors. Consistent with this outlook, EDP views the developing individual as a plastic organism that adapts to the local context while contributing to determine its own environment. Plasticity, however, is not understood as arbitrary malleability; rather, the plastic child responds to the environment following evolved rules that tend to guide development toward adaptive goals. In other words, developmental plasticity is to a large extent *adaptive*—and itself shaped by past selection history.

Universal, species-typical features of human development—such as play, extended immaturity, and language acquisition—are obviously a major research theme of EDP. At the same time, EDP aims to explain individual and gender *differences* in development and behavior—for example in play preferences, pubertal timing, and linguistic abilities. The emphasis of EDP on adaptive variation has been a driving force in the recent surge of interest in the evolution of individual differences in behavior and personality (e.g., Buss & Hawley, 2011; Carere & Maestripieri, 2013). Given the pivotal importance of individual differences in psychopathology, the theories and models we review in this chapter focus on the developmental processes that make individuals different from one another, including more or less at risk for different mental disorders.

Metatheoretical Foundations of EDP

When scientists formulate theories and hypotheses and evaluate them against empirical data, they rely on basic, a priori assumptions that inform theory-building. Once they have been established (empirically or otherwise), these assumptions are usually not directly tested thereafter; instead, they are used as a starting point for further research. Philosopher of science Imre Lakatos (1970) referred to these basic a priori assumptions as the *hard core* of a research program. For example, Newton's laws of motion provide the metatheory for classical mechanics, and the principles of adaptation through natural selection provide a metatheory for evolutionary biology. Metatheories operate like maps of the scientific terrain explored by a discipline: they provide boundaries between plausible and unlikely explanations, guidance in formulating hypothesis and interpreting empirical data, and heuristic rules for discovery. Between metatheories and specific empirical hypotheses are middle-level theories, which have limited scope and are more directly exposed to empirical testing. A metatheory integrates the relevant middle-level theories into an organized, internally consistent whole. Within a given metatheoretical program, scientists build middle-level theories and even narrower conceptual models, which are then used to generate hypotheses and predictions that can be empirically tested (for extended discussion, see Ketelaar & Ellis, 2000).

The metatheoretical foundations of EDP comprise both general and special assumptions (see Bjorklund & Ellis, 2005; Bjorklund et al., 2007; Durrant & Ellis, 2003; Ketelaar & Ellis, 2000). The general assumptions of EDP concern evolution by natural selection and are shared with mainstream evolutionary biology. Special assumptions concern (1) the application of evolutionary principles to the psychological level of analysis, and (2) the conceptualization of developmental processes in terms of probabilistic epigenesis. Assumptions about psychological mechanisms are shared with the sister field of evolutionary psychology, while the assumption of probabilistic epigenesis originates in developmental systems theory (DST). However, it should be stressed that EDP embraces a "soft" version of DST that is compatible with an adaptationist stance, while rejecting the most radical claims of DST proponents

(Bjorklund & Ellis, 2005; Bjorklund et al., 2007). We will examine the distinction between "hard" and "soft" DST in more detail in a later section.

General Metatheoretical Assumptions

Natural Selection. The Darwinian concept of natural selection is the cornerstone of evolutionary biology. For natural selection to occur in a population of organisms, three conditions must apply: (1) individuals differ from one another in their physical or behavioral traits (i.e., their *phenotype*); (2) at least some of these phenotypic traits affect an individual's ability to successfully reproduce in the next generation; and (3) phenotypic traits are heritable—that is, they are transmitted to descendants with some reliability. When these conditions are met, individuals that are better able to reproduce leave more descendants, which in turn carry the physical and behavioral traits that favored reproduction in the previous generations. Over time, successful traits tend to become more common in the population—that is, they are selected for because of their positive effects on reproductive success or *fitness*. Traits that enhance fitness are called *adaptive*, while those that reduce fitness are called *maladaptive*; if a trait does not affect fitness, it is considered *neutral* with respect to natural selection. It is important to note that natural selection is an abstract process, and does not require specific inheritance mechanisms (such as DNA) to work. All is required is the combination of heritable variation and differential reproduction based on that variation.

The most basic measure of Darwinian fitness is an individual's reproductive success, that is, the number of that individual's offspring that survive to maturity. Of course, to reproduce an organism also needs to survive, but—despite popular renditions of natural selection as "survival of the fittest"—survival without reproduction is an evolutionary dead end. It doesn't matter how well an organism is able to survive; if it fails to leave descendants, the traits responsible for its enhanced survival abilities will not be represented in subsequent generations. Organisms thus need to trade off longer survival against increased reproduction, the latter being the ultimate currency of evolution.

In species that reproduce sexually—that is, by mating—physical and behavioral traits can be selected for because they increase the number or quality of an individual's mates. This can happen in two ways: by making individuals compete more effectively with rivals, and by making individuals more attractive to potential mates. When selection arises from competition over mates, it is termed *sexual selection*. While sexual selection is a special case of natural selection, it has its own peculiar dynamics and can have dramatic effects on the evolutionary trajectory of sexual species. As Darwin noted, sexual selection can drive the evolution of extravagant displays designed to attract mates (the peacock's tail is a prototypical example). Even more importantly, sexual selection may lead to remarkable divergence in form (e.g., size, color, natural weapons), behavior (e.g., aggression, sexual behavior, parental behavior), and development (e.g., growth rate, maturation timing, life span) between males and females of the same species.

Adaptation. By constantly weeding out unsuccessful variation, natural selection produces incremental modifications in existing phenotypes, leading to an accumulation of characteristics that are organized to enhance survival and reproductive success. These characteristics are termed *adaptations*. Adaptations are inherited and reliably developing characteristics that have been selected for because of their causal role in enhancing the fitness of individuals that possess them (Williams, 1966). Through this process, adaptations acquire biological functions and the appearance of purposeful design—they are *for* something. The immune system functions to protect organisms from pathogens, the heart functions as a blood pump, and the cryptic coloring of many insects has the function of preventing their detection by predators. The core idea of evolutionary psychology is that many psychological characteristics are adaptations—just as many physical characteristics are—and that the principles of evolutionary biology that are used to explain our bodies are equally applicable to our minds (for extended discussion see Durrant & Ellis, 2003).

While adaptations are the product of evolution, evolution does not always produce adaptations; likewise, not every characteristic of an organism is an adaptation. For example, traits may become fixated in a population by random drift, whereby neutral or even deleterious characteristics become more prevalent due to chance factors. A neutral or weakly maladaptive trait may also spread because it is developmentally or genetically linked to another, positively selected trait (hitchhiking). In addition, many traits are not adaptations in themselves but rather by-products of other adaptations. The sound that hearts make when they beat, the white color of bones, and the human chin are all nonfunctional by-products of natural selection. Finally, random variation in traits can be maintained as residual noise, as long as it is selectively neutral. A variety of approaches can be employed—preferably in combination—to identify adaptations. They include making phylogenetic comparisons, directly measuring the fitness benefits of a trait, and building mathematical models of evolution. An especially useful method is looking for

evidence of *special design*: economy, efficiency, complexity, precision, specialization, and reliability in service of a specific biological function (Williams, 1966).

The logic of adaptation has an important consequence: as evolution proceeds, individual organisms are selected to develop and behave in a way that maximizes their expected fitness. This optimization principle can be aptly described as the *individual-as-maximizing agent* analogy (Grafen, 1999), and is a critical component of the adaptationist approach in biology. Of course, the analogy does not imply that a given individual will always obtain high fitness; of equal importance, optimization does not by any means imply unconstrained perfection—fitness maximization always takes place within the constraints and trade-offs imposed by the physical and social environment, as well as those imposed by previous phenotypic evolution and entrenched developmental biases. Finally, there is no assumption that individuals are intentionally or consciously maximizing expected fitness—they just tend to function *as if* they were attempting to do so.

Inclusive Fitness. The basic account of adaptation given in the preceding paragraphs has an important limit: it utterly fails to explain altruistic traits—that is, physical and behavioral traits that reduce an individual's reproductive success while increasing that of another individual. However, altruism is widespread in nature, as strikingly illustrated by the sterile castes found in eusocial insects such as ants, bees, and wasps. To solve this puzzle, William Hamilton (1964) developed *inclusive fitness theory*, also known (somewhat improperly) as *kin selection theory*. Inclusive fitness theory started a revolution in evolutionary biology, and provided the first unified explanation of social behavior—from parental care and family dynamics to altruism and self-sacrifice in groups. Today, inclusive fitness theory is the bedrock of the study of social evolution, from bacteria to humans (see Grafen, 2009; West, Griffin & Gardner, 2007).

In a nutshell, the theory shows that what is maximized by natural selection is not individual fitness, but a different quantity termed *inclusive fitness*. Inclusive fitness is the sum of (1) an individual's contribution to its own reproductive success, and (2) the individual's contribution to the reproductive success of other individuals, weighted by a coefficient of relatedness. Relatedness is an index of genetic similarity, ranging from $r = 1$ between two genetic clones (e.g., identical twins) and $r = 0$ between two unrelated individuals. In simplified terms, the relatedness between parent and child ($r = 0.5$) is the same as that between two full siblings; while that between grandparent and grandchild ($r = 0.25$) is the same as that between two half-siblings; and so on.[1] Inclusive fitness theory is encapsulated by Hamilton's rule:

$$rb > c$$

The rule states that an actor's behavior (or any other phenotypic trait with social effects) will be selected for if the fitness benefit b enjoyed by the recipient, weighted by the relatedness r between actor and recipient, is larger than the cost c incurred by the actor. Thus, costly altruistic behavior can evolve provided that the relatedness between actors and recipients is sufficiently high. The implications of inclusive fitness are not limited to altruism, and Hamilton's rule can be applied to a broad range of social dynamics, including competition and mutually beneficial cooperation (as distinct from purely altruistic behavior). Inclusive fitness theory leads to an updated version of the individual-as-maximizing agent analogy: when social interactions are involved, individuals will tend to behave as if they were maximizing their expected *inclusive* fitness (Grafen, 2006, 2009). Unlike individual fitness, maximizing one's inclusive fitness is equivalent to maximizing the replication of one's genes in future generations, since—by definition—related recipients (those for which $r > 0$) are carrying copies of the actor's own genes.[2] For this reason, inclusive fitness theory has sometimes been presented as a theory of the "selfish gene" (Dawkins, 1976)—a potentially misleading label, given its original focus on the evolution of altruism.

Inclusive fitness theory is also equivalent to *multilevel selection theory*, an approach to social evolution that focuses on group rather than individual dynamics (e.g., Sober & Wilson, 1998). While multilevel selection has often been viewed as alternative to inclusive fitness, it has since become clear that the two theories are mathematically interchangeable (see Marshall, 2011; West et al., 2007), and differ only in how they partition the costs and benefits of social traits. Whereas inclusive fitness partitions fitness

[1] More precisely, relatedness is a regression coefficient that predicts the recipient's genotype from the actor's genotype. Relatedness can become negative if two individuals can be expected to be genetically less similar than two randomly selected members of the population (see Grafen, 2009; West et al., 2007).

[2] The existence of epigenetic inheritance does not fundamentally change this picture. If epigenetic markings are reliably transmitted across generations, they are equivalent to genetic alleles from the standpoint of natural selection. If epigenetic markings are reversible and environmentally induced, they mediate short-term developmental plasticity and are irrelevant to inclusive fitness computations (see Shea, Pen, & Uller, 2011).

effects between actors and recipients, multilevel selection partitions them between individuals and their broader social groups. Thus, in a multilevel framework, altruism toward group members (to the point of self-sacrifice or sterility) can be selected for if it is counterbalanced by an appropriate benefit to the group as a whole. The equivalent explanation in terms of inclusive fitness is that group formation mechanisms typically increase relatedness within groups relative to that between groups. Thus, helping group members leads to an indirect fitness benefit that can be so strong as to override large individual costs.

Special Metatheoretical Assumptions

Psychological Mechanisms. Psychological adaptations, which govern mental and behavioral processes, are referred to by evolutionary psychologists as *psychological mechanisms*. Most research in evolutionary psychology focuses on identifying evolved psychological mechanisms because it is at this level where invariances occur. Indeed, evolutionary psychologists assert that there is a core set of universal psychological mechanisms that comprise our shared human nature (see Buss, 2005). The move to the level of psychological mechanisms is important to avoid a common fallacy—that of assuming that human behavior (1) has the conscious goal of maximizing inclusive fitness, and (2) actually maximizes inclusive fitness in current environments. At a very general level, natural selection does tend to produce organisms that behave as if they were trying to maximize their expected fitness (see above). However, actual behavior is ultimately mediated by a host of psychological mechanisms with local and sometimes conflicting goals (e.g., learning a language, finding and attracting mates, choosing food, avoiding diseases). There is no general "fitness maximization mechanism" anywhere in the brain. Each mechanism works and evolves within constraints (e.g., information availability, time constraints, coordination and conflict with other mechanisms, previous evolutionary history); as a result, the overall structure of the mind–brain is more akin to a gerrymandered contraption than an optimal, omniscient decision maker.

Even more importantly, the fact that a given adaptation was produced through differential reproduction does not imply that either (1) selection is *currently* favoring that adaptation or (2) variation in the expression of that adaptation will be associated with *current* reproductive success. For example, the dopamine-mediated reward mechanisms found in the mesolimbic system in the brain appear to have evolved to provide a pleasurable reward in the presence of adaptively relevant stimuli such as food or sex. In contemporary environments, however, these same mechanisms are subverted by the use of psychoactive drugs such as cocaine and amphetamines, which deliver huge dollops of pleasurable reward in the absence of the adaptively relevant stimuli, often to the user's detriment (Durrant & Ellis, 2003).

The concept of a psychological mechanism was updated by Bjorklund and colleagues (2007) to make it more consistent with EDP's metatheoretical assumption of probabilistic epigenesis. These authors proposed a definition of *evolved probabilistic cognitive mechanisms* (p. 22):

> [Psychological] mechanisms that are functionally organized to solve recurrent problems faced by ancestral populations, are highly probable when species-typical environments are encountered (i.e., when the developmentally relevant features of the environment are in the range typically encountered during a species' evolution), and are products of emerging developmental systems that have evolved over the course of the ontogenies of our ancestors.

This definition stresses the probabilistic nature of the ontogenetic processes responsible for building psychological mechanisms; it also makes it clear that, while evolved mechanisms prepare an organism for life in a species-typical environment, they are not preformed or specified in advance by a rigid genetic program.

Domain Specificity. As is apparent from the preceding paragraphs, evolutionary psychology views psychological mechanisms as having some degree of functional specialization. More specifically, psychological mechanisms are composed of structures that (1) exist in the form they do because they recurrently solved specific problems of survival and reproduction over evolutionary history; (2) are designed to take only certain kinds of information from the world as input; (3) process that information according to a specific set of rules and procedures; (4) generate output in terms of information to other psychological mechanisms and physiological activity or manifest behavior that is directed at solving specific adaptive problems (see Buss, 2012). In short, psychological mechanisms are designed by selection to address specific *domains* of the physical and social world. Although evolutionary psychologists assert that the mind is not comprised primarily of content-free (domain-general) psychological mechanisms, it is likely that different mechanisms differ in their levels of specificity, and that there are some higher level mechanisms that function to integrate information across more specific lower level mechanisms. In addition, some general-purpose abilities (e.g., associative learning) may be co-opted in the context of different specialized functions. It is important to stress that functional specialization of a psychological

mechanism does not imply clear-cut anatomical localization in the brain, nor complete functional independence from other mechanisms. Indeed, psychological mechanisms are expected to show a considerable degree of integration and reciprocal interaction.

The rationale behind the domain specificity argument is fairly straightforward: What counts as adaptive behavior differs markedly from domain to domain. The sort of adaptive problems posed by food choice, mate choice, and social exchange often require different kinds of solutions. A clear analogy can be drawn with the functional division of labor in human physiology. Different organs have evolved to serve different functions and possess properties that allow them to fulfill those functions efficiently, reliably, and economically: the heart pumps blood, the kidneys excrete urine, and so on. A super, all-purpose, domain-general internal organ faces the impossible task of serving multiple, incompatible functions. Analogously, a super, all-purpose, domain-general mind/brain mechanism faces the impossible task of efficiently and reliably solving the plethora of behavioral problems encountered by humans in ancestral environments. Thus, neither an all-purpose physiological organ nor an all-purpose psychological mechanism is likely to evolve.

Environment of Evolutionary Adaptedness. Biological adaptation is necessarily a historical concept, and all claims about adaptation are claims about the past. The environment in which a given trait evolved is termed its *environment of evolutionary adaptedness* (EEA). When we claim that the thick insulating coat of the polar bear is as an adaptation, we are claiming that possession of that trait advanced reproductive success in ancestral environments. However, traits that served adaptive functions and thus were selected for in past environments may not still be adaptive in present or future environments. In a globally warmed world, for example, the polar bear's pelt may become a handicap that reduces the fitness of its owner. While natural selection is expected—all else being equal—to weed out traits that have become detrimental to fitness, the process may often take a long time. This generates the potential for mismatch between an organism's adaptations and its present environment.

The possibility of mismatch raises a subtle but crucial point regarding the meaning of *adaptive*. Broadly speaking, psychological and physiological processes can be described as adaptive if they result from the unimpaired functioning of adaptations. Thus, adaptive in the broad sense is a shorthand to describe the functioning of naturally selected processes and mechanisms, regardless of whether they are *currently* promoting reproductive success (i.e., adaptive in the narrow sense). For example, pursuit of mating relationships with fertile partners is guided by adaptive psychological processes, regardless of whether contraceptive technology prevents reproduction in present-day societies.

Within the same organism, different adaptations will often have different EEAs (for extended discussion see Durrant & Ellis, 2003). Consider the human adaptations of language and infant attachment. While the origin of language is firmly anchored in approximately the last 2 million years, infant attachment reflects a much lengthier evolutionary history and a shared heritage with other mammalian and primate species. While evolutionary timing helps define the EEA of a trait, the EEA itself is not a specific time or place; rather, EEAs capture the statistical regularities of the environment in which the trait evolved (Tooby & Cosmides, 1990). Environmental variation itself can be part of an EEA; for example, metabolic processes can evolve so as to maximize survival in an unpredictable environment, whereby food abundance is suddenly followed by starvation. In this case, metabolic adaptations evolve in an EEA characterized by a consistent pattern of unpredictable variation.

Over the last few millennia—the span of a few hundred generations—humans have experienced rapid and constantly accelerating rate of change in health, nutritional, social, and technological conditions. While genetic evolution has been accelerating as well (e.g., Hawks, Wang, Cochran, Harpending, & Moyzis, 2007), many of our evolved adaptations can be expected to be at least partly mismatched to modern lifestyles. At the same time, many adaptation-relevant aspects of our environment have probably remained the same: humans everywhere, for example, still find and attract mates, have sex, raise families, make friends, compete for status, and gossip (Crawford, 1998). Most important is that current and ancestral environments do not have to be identical in every respect to sustain the normal development and expression of evolved psychological mechanisms.

Probabilistic Epigenesis. The concept of probabilistic epigenesis has a long history in embryology and is one of the central assumptions of DST (see Gottlieb, 2007). Probabilistic epigenesis holds that development involves continuous bidirectional influences between genetic activity, neural activity, behavior, and the physical and social environment (similar interactions take place in the development of non-neural mechanisms). In this view, neural structures begin to function when they are still developing, and their activity—both spontaneous and evoked by the

environment—plays an important role in the ontogenetic process. This is contrasted with predetermined models in which genetic programs build neural structures, that begin to function and interact with the environment only when they are mature. The reciprocal, bidirectional interaction between multiple levels introduces a probabilistic element in the outcomes of developmental processes.

A key implication of probabilistic epigenesis is that genetic activity is influenced and regulated by neural, behavioral, and external events. Gene–environment (GxE) interactions in development, whereby the effects of an allelic variant are contingent on contextual variables, are prime examples of probabilistic epigenesis (Gottlieb, 2007). Probabilistic epigenesis provides reasons for expecting widespread plasticity in the outcomes of developmental processes; however, it is not sufficient to explain *adaptive* plasticity and phenotype-environment matching (Bjorklund et al., 2007). Understanding adaptive plasticity requires a synthesis between the proximate and ultimate level of analysis—where development meets adaptation.

Developmental Systems Theory: An Alternative Metatheory?

Researchers in developmental psychopathology often refer to developmental systems theory (DST) as a metatheoretical framework for the discipline. DST is a general approach to development and evolution rooted in the organismic concepts of embryology and developmental psychobiology. The major themes of DST are probabilistic epigenesis and developmental plasticity, with a strong emphasis on bidirectional interplay between genes and environment; an extended view of inheritance that goes beyond DNA to include epigenetic processes, cellular structures, scaffolded developmental environments (e.g., nests), and culturally transmitted information; and a view of the developing organism as actively involved in shaping its environment (see Griffiths & Gray, 2004; Oyama et al., 2001). Consistent with the metatheoretical framework we have presented, DST emphasizes the multiplicity of factors that jointly determine phenotypic outcomes and stresses the contextual, contingent nature of development.

Soft Versus Hard DST

Much of the difficulty in discussing the role of DST stems from the fact that DST is not a single, unified theory; in fact, it is possible to recognize at least two versions of DST—a "soft" version and a "hard" version—with vastly different implications for developmental science (Frankenhuis et al., 2013; Robert et al., 2001). Soft DST is essentially a theory of development; in this view, a developmental system comprises all the resources (e.g., genes, cellular structures, sensory experiences, physical parameters of the environment) that contribute to the ontogeny of the individual organism. However, the organism remains the main biological entity, and evolutionary processes acts on populations of organisms. In other words, soft DST reconceptualizes the causal structure of development—for example by placing genetic inheritance in a broader perspective and emphasizing bidirectional effects—but is otherwise consistent with inclusive fitness theory and the logic of individual adaptation (Pradeu, 2010). Indeed, many developmentally oriented extensions of evolutionary biology already incorporate the main tenets of soft DST (e.g., West-Eberhard, 2003).

In contrast, hard DST is not so much a theory of development as a radical alternative to mainstream evolutionary theory. In hard DST, a developmental system comprises all the resources that produce the developmental outcomes that are *stably replicated* in that lineage. As a consequence, it is impossible to meaningfully distinguish between organism and environment, and what evolves are not populations of organisms but populations of replicating organism–environment systems. Such holistic reconceptualization of natural selection breaks down the individual-as-maximizing agent analogy and makes adaptationist analysis all but impossible (Pradeu, 2010). This is because hard DST is inconsistent with inclusive fitness theory: selection is no longer assumed to act on individuals that can be more or less genetically related with one another, but on whole developmental systems (comprising every recurring influence on development, including social and biogeographical factors) for which there is no meaningful definition of reproductive success or relatedness. In addition, hard DST not only objects to the concept of genetic programs, but—in a further break from mainstream biology—also rejects the very idea that genes store *information* as unacceptable preformationism (Oyama et al., 2001).

In summary, DST comprises two related but partially distinct approaches. Soft DST is a developmentally oriented extension of mainstream evolutionary theory, and is fully consistent with the metatheoretical framework of EDP. In contrast, hard DST advances a radically novel theory of evolution, and constitutes an alternative metatheoretical framework with little overlap with that of EDP. Embracing soft DST does not commit one to also adopt the assumptions of hard DST. Unfortunately, the distinction between the soft and hard version of DST is often obscured in the literature, leaving many researchers

confused as to the exact implications of the theory (see Frankenhuis et al., 2013; Pradeu, 2010).

Implications for Developmental Science

The distinction between soft and hard DST provides insight in the current theoretical status of developmental psychology and psychopathology. We surmise that, when developmental scientists embrace a DST perspective, they usually reason in terms of soft DST. However—and possibly without realizing it—they end up adopting the whole metatheoretical package of hard DST, with the added baggage of antiadaptationism and a priori rejection of mainstream evolutionary thinking. As a result, developmental science is deprived of some of the most powerful tools in biology, such as inclusive fitness theory and the concept of adaptation. By contrast, we contend that the metatheoretical framework of EDP—a synthesis of adaptationism and soft DST—provides a suitable evolutionary foundation for developmental psychopathology. In the remainder of the chapter we demonstrate the heuristic and integrative power of this approach.

BEYOND PATHOLOGY: ADAPTATION, MALADAPTATION, AND DISORDERS

In an evolutionary framework, the terms *adaptive* and *maladaptive* denote the effect of a trait or behavior on biological fitness. From the standpoint of the individual organism, adaptive traits are those that enhance inclusive fitness compared with potential alternatives. However, all adaptations have fitness costs as well as benefits; to be adaptive a trait does not have to be cost free but it only needs to yield a positive overall contribution to the organism's fitness. This notion of adaptation and maladaptation contrasts sharply with how the same terms are usually employed in developmental psychology and psychopathology. In these disciplines, adaptive traits and behaviors are those that promote health, safety, subjective well-being, and mutually rewarding social relations. Socially undesirable, aversive, or health-damaging traits are viewed as maladaptive. These definitions of adaptation and maladaptation are conceptually orthogonal and ought to be carefully differentiated. In this chapter we always refer to adaptation and maladaptation in the biological sense, and employ the terms *desirable* and *undesirable* to denote the implications of a trait for health, safety, well-being, and social values.

Unsettling as it may be, the logic of natural selection promotes reproductive success, not happiness or health (see Cosmides & Tooby, 1999; Gluckman et al., 2011; Nesse, 2004a). Thus, biologically adaptive traits may or may not be socially desirable or conducive to health and well-being; conversely, a trait is not maladaptive just because it has negative effects on an individual's welfare. Traits that consistently reduce well-being and adversely impact an individual's health can be selected for as long as they result in enhanced reproduction—a highly counterintuitive notion in mainstream psychology. At the same time, adaptiveness and desirability—though conceptually distinct—are functionally connected to some degree. This is because positive emotions such as joy, excitement, and pride and are generally aroused by the fulfillment of fitness-enhancing goals, while threats to fitness are generally met with negative feelings such as sadness, anger, and shame (Nesse, 2004a).

The functional connection between threats to fitness and negative emotions lends intuitive plausibility to the implicit assumption—firmly entrenched in psychopathology and psychiatry—that aversive traits are by default pathological or "maladaptive" (see Nesse & Jackson, 2006). The evolutionary approach challenges this assumption, and unpacks the intuitive concept of disorder by separating adaptation from health and desirability. The result is a general framework for thinking about pathology that can be applied to both medical and psychopathological conditions.

What Is a Disorder?

Mental disorder is a central concept of psychopathology, yet a satisfactory definition of disorder is notoriously difficult to achieve. In an influential paper, Jerome Wakefield (1992) built on previous biologically informed approaches to advance a definition of disorder as a *harmful dysfunction*. According to this definition, conditions are recognized as disorders when they (1) are caused by the failure of a biological mechanism to perform its evolved function, and (2) inflict some harm or damage on the affected person, as judged by sociocultural standards. This is a hybrid definition that combines the objective dysfunction criterion with the subjective, culturally bound harm criterion. In Wakefield's account, people evaluate a condition as a disorder when the subjective perception of harm or undesirability is coupled with the idea that something in the body or mind is not working properly. In line with an evolutionary approach, what constitutes proper functioning of a biological mechanism can be correctly evaluated only by considering the evolved functions of that mechanism. To understand pathology, one needs to understand the function of the relevant biological mechanisms, as well as

the structure of the environment in which they evolved (Nesse, 2001; Troisi & McGuire, 2002).

We believe that, correctly understood, the harmful dysfunction analysis is a useful heuristic for reasoning about pathology and disorders. Although Wakefield's proposal has been hotly debated, its core propositions have withstood criticism (see Wakefield, 1999, 2011). To avoid common misgivings, the following points should be kept in mind. First, evolved mechanisms are defined broadly; major organs like the heart are mechanisms, but so are specialized brain areas, microscopic cellular structures, and biochemical pathways. Accordingly, dysfunctions can occur in many ways and for a wide variety of causes (e.g., deleterious genetic mutations, pathogen infections, injuries and wounds, side effects of evolved defenses). Second, *dysfunctional* is not synonymous with *maladaptive*. Since dysfunctions interfere with evolved design, they can often be expected to reduce an individual's fitness; however, a reduction in fitness is not required to identify a dysfunction. It is quite possible for a dysfunction to be selectively neutral—for example, because it occurs too late in life to impact an individual's reproductive success, or because changes in the environment reduce its damaging effects. This is why myopia—a failure of the crystalline lens to project a focused image on the retina—remains a dysfunction even if glasses and contact lenses eliminate its negative effects on survival. Third, the concept of dysfunction is a fuzzy one rather than all-or-none, and evolved mechanisms can show varying degrees of functionality (Wakefield, 1999). Thus, obvious instances of dysfunction are going to be surrounded by borderline cases for which there is no clear-cut demarcating criterion—as for example in the case of hypertension, extreme variation in height, and personality disorders.

A Taxonomy of Undesirable Conditions

Despite their theoretical significance, harmful dysfunctions are only a fraction of what people regard as diagnosable problems or seek treatment for (Cosmides & Tooby, 1999; Lilienfeld & Marino, 1999). Fever is an evolved defense against pathogens; with rare exceptions, it reflects a well-functioning system rather than a dysfunction—yet it is often treated with drugs. More generally, conditions that are not harmful dysfunctions in Wakefield's sense may nevertheless be labeled and treated as disorders, especially if their etiology and functional implications are incompletely understood. For example, it has been hypothesized that some forms of psychopathy are adaptive behavioral phenotypes that exist at a low frequency and thrive by exploiting others (e.g., Mealey, 1995). If this hypothesis were correct, a number of apparent dysfunctions (e.g., reduced empathy, lack of guilt, impulsivity) would be better understood as design features of the psychopathic strategy. Still, psychopathy is a source of trouble for society at large, and would be legitimately regarded as a condition in need of treatment even if it were established as a biologically adaptive variant rather than a disorder in the strict sense. This example also illustrates how conflicts of interest between social actors modulate the perception and definition of a problematic condition; obsessional jealousy may appear desirable and useful to the affected individual, but harmful and undesirable to his/her partners (for a detailed analysis of this issue see Cosmides & Tooby, 1999).

We now take a wider perspective and consider the many ways evolutionary and developmental processes may result in undesirable conditions, including—but not limited to—harmful dysfunctions in the narrow sense (see Cosmides & Tooby, 1999; Gluckman et al., 2011). The taxonomy we present combines Wakefield's dysfunction criterion with the effects of a given condition on biological fitness (Figure 1.1). When considering the adaptiveness of a condition, we further distinguish between the fitness contribution of a *trait* or *mechanism*—averaged across all the individuals who express it—and the fitness of a *particular individual*. The distinction is useful because a mechanism may be fitness-enhancing *on average*, while imposing fitness costs on some individuals (e.g., Cosmides & Tooby, 1999). Distinguishing between individual and average fitness permits a fine-grained analysis of the interplay between adaptation and maladaptation in psychopathology (Frankenhuis & Del Giudice, 2012). Although we discuss them separately, the following categories are not mutually exclusive; a given condition or class of conditions may well reflect the interplay of multiple factors and require overlapping evolutionary explanations.

Harmful Dysfunctions

All biological and artificial mechanisms—no matter how well designed—are vulnerable to malfunctions, failures, and breakdowns. Developmental pathways typically evolve canalization properties (e.g., biochemical buffering mechanisms) that confer them robustness against accidents and perturbations. However, the accumulation of such events over time can affect development, resulting in random deviations from the target phenotype (*developmental instability*). More dramatically, an evolved mechanism may cease to perform its functions because of accidents or environmental insults beyond its regulatory

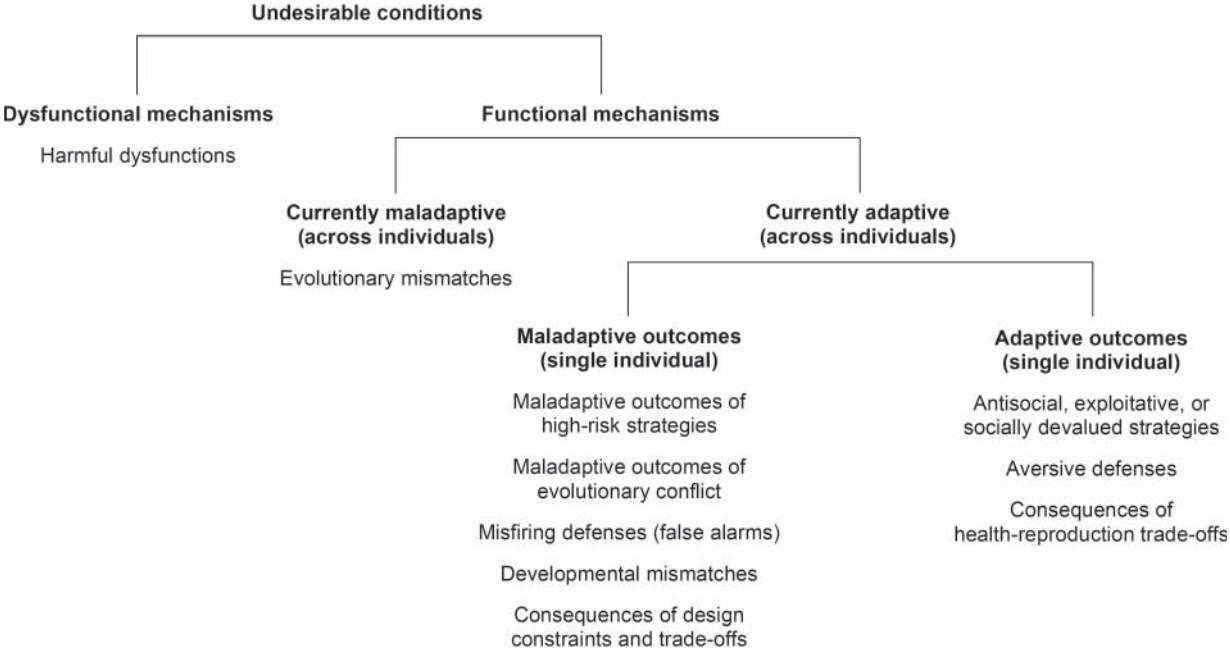


Figure 1.1 An evolutionary taxonomy of undesirable conditions.

capacity (e.g., brain injury, exposure to toxins), deleterious genetic/epigenetic changes (e.g., mutations and deletions), and attacks or manipulations by pathogens (see Crespi, 2000, 2010).

New deleterious mutations arise at every generation and they may be passed down to descendants, persisting for some time in a population until they are weeded out by natural selection. Harmful variants may be especially difficult to eliminate if they have recessive effects (i.e., they are expressed only when an individual inherits two copies of the same allele). The continuous process of creation and elimination of deleterious mutations is called *mutation–selection balance*; its dynamics determine the frequency and persistence of harmful variants in a population. Sometimes, a single mutation in a critical pathway is sufficient to cause a disorder; more often, disorders may result from the cumulative effect of many slightly deleterious mutations (*mutation load*), each with a small impact on phenotypic function. Mutation–selection balance has been proposed as a likely explanation for the persistence of common, heritable, and harmful mental disorders like autism, schizophrenia, bipolar disorder, and mental retardation (Keller & Miller, 2006). Since a large proportion of human genes are expressed in brain development, the likelihood that mutation load will have negative consequences on mental functioning is especially high. The role of mutation load in autism and schizophrenia is consistent with the high rate of new mutations in people with these disorders (e.g., Sanders et al., 2012).

Exposure to pathogens (harmful viruses, bacteria, and other parasites) is another common cause of biological dysfunction. Infectious diseases—especially when they occur in early development—have been associated with increased risk for a number of mental disorders including autism, schizophrenia, and depression (see Patterson, 2011; Benros, Mortensen, & Eaton, 2012). The role of pathogens in the etiology of mental disorders does not contradict that of genetic mutations. Infections, like mutations, can perturb developmental processes at critical stages; accordingly, mutation load and pathogen load may ultimately converge on the same neurobiological pathways and exert a cumulative effect on the risk for psychopathology. In addition to their direct effects on individual organisms, pathogens may indirectly contribute to the risk of harmful dysfunctions through their effect on the evolution of defenses. Pathogens and hosts are constantly involved in coevolutionary arms races, so that for every improvement in defensive mechanisms, new means of offense are going to be selected for on the other side (and vice versa). Coevolutionary arms races tend to produce increasingly complex offense/defense mechanisms (consider the intricacy of the immune system); in turn, increased complexity may render those mechanisms more vulnerable to failures and dysfunctions (Nesse, 2001).

Evolutionary Mismatches

Because of natural selection, evolving organisms tend to become progressively more successful at surviving and reproducing in their environment, broadly conceived to include not only physical factors but also social relations with conspecifics as well as interactions with other species (predators, prey, pathogens, and so forth). The environment, however, is not a static background: environments change all the time because of external events (e.g., geological change), social evolution within a species (e.g., increased population density), and coevolutionary processes between species (e.g., new pathogens). When environmental changes are rapid and extensive, previously adaptive mechanisms may suddenly become maladaptive and generate all sorts of unintended and/or undesirable consequences. Thanks to cultural and technological evolution, humans have gained an unprecedented power to alter their social and physical environment, and in so doing have created enormous opportunity for evolutionary mismatch.

Evolutionary mismatch occurs when an organism encounters a *novel environmental context* (outside of the range that was recurrently encountered over its evolutionary history) that disrupts normal development or impairs adult functioning. Evolutionary mismatches are likely to be implicated—to various degrees—in the etiology of mental disorders. In modern societies, for example, the media expose girls and women to a relentless stream of images of unrealistically attractive "competitors"—an artificial, evolutionarily novel kind of social stimulus. It has been hypothesized that such exposure hyperactivates the evolved mechanisms that regulate female competition for attractiveness and status, contributing to the rising incidence of eating disorders (e.g., Abed, 1998). Other instances of potential mismatch are less obvious. For example, sanitation in developed countries determines a lack of exposure to common microorganisms ("old friends") during development. These novel hygienic conditions appear to interfere with the early ontogenetic processes that train the immune system and set its overall functioning parameters. The resulting states of chronic inflammation may increase the risk for a range of physical and mental disorders, especially depression (Raison, Lowry & Rook, 2010).

Although we have emphasized its negative consequences, evolutionary mismatch is an unavoidable and often vital aspect of evolution. By definition, all evolving organisms exhibit some degree of mismatch to their present environment—otherwise they would stop evolving altogether. The very process of adaptation generates subtle forms of mismatch that may contribute to the etiology of undesirable conditions. When a trait has been subjected to strong recent selection, the resulting adaptive changes may co-occur with maladaptive side effects on other traits that are genetically and/or developmentally linked to the selected trait. Similarly, recently evolved adaptations are likely to show increased scope for dysregulation because they have yet to be fine-tuned by natural selection (see Crespi, 2010).

Maladaptive Outcomes of Adaptive Mechanisms

So far, we have reviewed case in which undesirable conditions are caused by failures of evolved design. Harmful dysfunctions occur when a biological mechanism fails to perform its evolved functions; conversely, evolutionary mismatches occur when an intact mechanism becomes maladaptive because of novel environmental conditions. However, maladaptive outcomes at the individual level may systematically occur even when adaptive mechanisms perform their evolved functions in an environment that matches the EEA on the relevant dimensions. This is one of the central insights of evolutionary psychopathology: observing maladaptive outcomes at the individual level is not sufficient to infer maladaptation at the level of evolved mechanisms. We now review some important reasons why adaptive mechanisms may systematically yield maladaptive outcomes (for in-depth discussion see Cosmides & Tooby, 1999; Crespi, 2010; Frankenhuis & Del Giudice, 2012).

Maladaptive Outcomes of High-Risk Strategies. An important source of maladaptation at the individual level is the evolution of risky adaptive strategies[3]. Risky behavior is part and parcel of daily life: many activities that contribute to survival and reproduction also increase the probability of harm, injury, loss, or death. Searching for food and competing for mates are both fraught with danger, but potential dangers are compensated by the potential fitness advantages of these activities. From an evolutionary perspective, we would expect natural selection to favor mechanisms that produce risk taking when the fitness benefits outweigh the costs. Further insight in the dynamics of risky strategies can be gained by defining risk in its technical sense of unpredictable variation in

[3]In an evolutionary framework, the term *strategy* denotes an organism's realized phenotype among a set of possible phenotypes. Adoption of a given strategy can depend on both environmental and genetic factors. It should be stressed that the term does not imply conscious planning, deliberation, or even awareness; an organism's choice between alternative strategies can be implemented by low-level physiological means, such as a hormonal switch or a change in genetic expression.

outcomes (see Frankenhuis & Del Giudice, 2012; Ellis et al., 2012). Whereas some behavioral decisions offer a narrow range of possible outcomes (low-risk), others entail widely variable outcomes (high-risk), with the potential for large gains as well as large losses. Consider a predator that can choose between two types of prey: larger and hard-to-catch animals versus smaller and easily caught ones. Imagine also that the expected energetic returns associated with hunting each prey type are identical: one results in a high reward with a low probability, the other in a low reward with a high probability. In this scenario, hunting larger prey qualifies as more risky, because it entails more variable outcomes.

Broadly speaking, natural selection favors risk aversion when the relationship between behavioral outcomes and fitness is characterized by diminishing returns. For instance, a well-fed animal should look for low-risk food items (or not forage at all) when additional calories only slightly improve its condition. Conversely, when better outcomes yield increasing fitness returns, organisms may become risk-prone. For example, an animal on the brink of starvation may choose to forage in a nutrient-rich habitat, even if it is infested with predators, because it has so much to gain from additional calories (discussed in Frankenhuis & Del Giudice, 2012). An analogous logic applies to competition for reproduction. In some mating systems, reproductive benefits are highly skewed towards top-ranking individuals (i.e., winner-takes-all systems). In such conditions, males are intensely selected to compete for top rank, even if this implies a greater risk of injury; for instance, male elephant seals engage in ferocious fights that often cause harm and sometimes result in death. Still, males benefit—on average—from participating in fights because not participating implies being shut out from reproduction.

The logic of risky strategies can shed light on the interplay between adaptation and maladaptation in development and psychopathology. For example, externalizing behavior can be interpreted as a high-risk tactic of social competition (Del Giudice et al., 2011; Ellis et al., 2012; Martel, 2013). In some cases, aggressive children and adolescents become dominant, respected, and popular leaders in their peer groups; in other cases, they do not succeed and become unpopular or rejected, incurring physical and psychological harm. These outcomes can be individually maladaptive even if they result from an adaptive strategy designed to achieve dominance and social status. A similar logic may apply to schizotypal personality traits (e.g., the tendency to experience unusual perceptions, bizarre ideation, and reference thoughts). While schizotypal traits increase the risk of schizophrenia (a severe, harmful disorder), when schizotypal individuals do not develop a disorder, their enhanced creativity may facilitate high mating success (e.g., Nettle, 2001; reviewed in Del Giudice, Angeleri, Brizio, & Elena, 2010); this would amount to a high-risk strategy with widely variable outcomes.

Maladaptive Outcomes of Evolutionary Conflict. Conflicts of interest between individuals abound in nature—for example between mating rivals, or between dominants and subordinates in a hierarchy. While cooperation and even altruism can be favored by natural selection, it is often the case that a given individual can maximize its own fitness only at the expense of another individual's reproduction. An especially intriguing kind of evolutionary conflict is that between parents and their offspring (Trivers, 1974; see Schlomer, Del Giudice, & Ellis, 2011). While a parent is equally related to all its offspring ($r = 0.5$), each offspring is more related to itself ($r = 1$) than to any of its present or future siblings ($r = 0.5$ in the case of full siblings). Offspring are thus selected to demand more than their "fair share" of their parent's investment in time, food, protection; conversely, parents are selected to resist such attempts, setting the stage for *parent–offspring conflict* over the distribution of parental investment. Of course, parents and offspring also have a lot of evolutionary interests in common, so conflict is tempered with a substantial amount of cooperation and altruism.

Although parent–offspring conflict is not maladaptive in itself—parents and offspring are both acting so as to maximize their own fitness—the dynamics of conflict often result in nontrivial costs for both parties. Furthermore, conflict may occasionally escalate to dangerous levels, yielding maladaptive outcomes for the parent, the offspring, or both. A dramatic example is provided by prenatal conflicts about fetal nutrition (Haig, 1993; reviewed in Schlomer et al., 2011). During pregnancy, the placenta—a fetal organ that only expresses the fetal DNA—releases massive amounts of hormones in the maternal bloodstream. These hormones affect maternal metabolism so as raise the nutrient content of maternal blood and increase the supply of blood to fetal circulation. The interplay between fetal hormones and maternal countermeasures may produce a range of undesirable side effects, including gestational hypertension and gestational diabetes. In rare cases, the physiological tug-of-war between mother and fetus may become dysregulated and result in life-threatening conditions such as preeclampsia (severe maternal hypertension). In a recent paper, one of us (Del Giudice, 2012) speculated that a similar

conflict may arise about fetal exposure to maternal stress hormones, with mothers favoring higher levels of exposure than fetuses. Indeed, several puzzling features of stress regulation in pregnancy could be explained by the interplay between fetal attempts at manipulation and maternal countermeasures (for a detailed exposition see Del Giudice, 2012). Elevated prenatal stress has been associated with increased risk for a broad range of psychopathological outcomes in children—including anxiety, hyperactivity, autism, and schizophrenia (reviewed in Glover, 2011). To some extent, these undesirable outcomes may arise as maladaptive side effects of parent–offspring conflict in pregnancy.

Evolutionary conflict usually takes place between different individuals, but this is not always the case. Indeed, conflicts of interest can also arise between different genes within the same individual (*intragenomic conflict*; for a thorough review see Burt & Trivers, 2006). Intragenomic conflicts may involve sexual chromosomes, mitochondrial genes, or "selfish" strands of DNA that—for various reasons—follow inheritance rules that differ from those of the rest of the genome. Most relevant to the present discussion, the maternally and paternally inherited halves of an individual's genome may have divergent fitness interests when parental investment is involved. In species that are not perfectly monogamous—that is, most sexually reproducing species including humans—the occurrence of multiple paternity increases the chance that siblings in the same family have the same mother but different fathers. As a result, the genes inherited from the father are—on average—less strongly related to those of one's siblings than the genes inherited from the mother. This generates complex dynamics in which maternal and paternal genes may favor opposite traits in the offspring (e.g., maternal genes may benefit from less demanding offspring, while paternal genes may benefit from *more* demanding offspring; see Schlomer et al., 2011). This latent conflict between the paternal and maternal genome is played out by *imprinted genes*, that is, genes that are differentially expressed depending on whether they were inherited from the mother or from the father (see Burt & Trivers, 2006; Schlomer et al., 2011; Wilkins & Haig, 2003).

Not surprisingly, imprinted genes have been found to be involved in prenatal conflicts about fetal nutrition (reviewed in Schlomer et al., 2011). In addition, many imprinted genes are expressed in the brain, and parent-of-origin effects have been detected in the key signaling pathways that mediate social behavior—including the dopaminergic, serotonergic, and oxytocinergic pathways (see e.g., Davies, Lynn, Relkovic, & Wilkinson, 2008). It is quite possible that intragenomic conflict between imprinted genes may contribute to the development of psychopathology. For example, Crespi and Badcock (2008) hypothesized that autistic spectrum conditions are characterized by overexpression of paternal genes, whereas psychosis spectrum conditions are characterized by overexpression of maternal genes. This diametrical model of autism and psychosis was revised and extended by Del Giudice and colleagues (2010) to account for nonclinical variation in autistic-like and schizotypal personality traits.

Misfiring Defenses. Adaptive defenses are mechanisms designed to protect individuals from physical and/or social harm. Most negative emotions—including fear, anxiety, disgust, and shame—can be conceptualized as defensive mechanisms, as they play crucial protective roles against physical danger, contamination by pathogens, social exclusion, and so forth (see Nesse, 2004a; Nesse & Jackson, 2006). The calibration of defenses involves a trade-off between the rate of false negatives (failing to activate a defense mechanism when a threat is present) and that of false positives (mistakenly activating the mechanism when no threat is present). Defensive mechanisms are usually designed by natural selection to accept a high rate of false positives so as to avoid catastrophic false negatives; this is known as the *smoke detector principle* (Nesse, 2005).

The smoke detector principle suggests that defensive mechanisms will often misfire or activate with excessive intensity, even when no actual threat is present. Adaptive defenses—like fever, cough, and anxiety—are usually aversive and often disabling; occasionally, inappropriate activation of a defensive mechanism may cause serious harm to the individual. For this reason, misfiring defenses are a likely source of undesirable conditions, ranging from benign "false alarms" to dangerous overreactions. The crucial point is that inappropriate activation of a defensive mechanism does not necessarily imply that the mechanism is dysfunctional or dysregulated—even optimally functional defenses may be designed to misfire from time to time. The logic of the smoke detector principle can be employed to shed light on the etiology of emotional symptoms such as panic attacks, anxiety, and phobic symptoms (Nesse, 2005; Nesse & Jackson, 2006).

Developmental Mismatches. Conditional adaptation is the process by which developing organisms make use of contextual cues to direct their developmental trajectory, so as to increase the likelihood that their future phenotype will match the state of the environment. Conditional adaptation is a manifestation of adaptive plasticity, and—when successful—it can dramatically increase the reproductive

success of an organism across a broad range of environments. However, the predictive accuracy (i.e., validity) of contextual cues is usually far from perfect; even when accuracy can be improved by sampling the environment more thoroughly, the potential benefit must be balanced against the required investment of time and effort. For these reasons, conditional adaptation is a fallible process, and a proportion of individuals end up developing a mismatched phenotype. Natural selection can favor conditional adaptation even if the fitness costs of mismatch are high, as long as the average benefits of plasticity are larger than the average costs across individuals. We will deal more extensively with the costs and benefits of developmental plasticity in a later section.

Constraints and Trade-offs. The design of an organism is always shaped by countless physical constraints that limit the range of phenotypic change and burden evolved adaptations with undesirable side effects. For example, the erect posture of humans necessarily increases the impact of falling; a larger body size makes organisms more vulnerable to starvation, and so forth. Physical constraints are compounded by the legacy of previous evolutionary history: natural selection builds incrementally on previous designs, and its inability to start from scratch introduces further constraints on adaptive design (*path dependence*). For example, the fact that human babies are delivered through the pelvic canal poses severe constraints on head size at birth; conversely, selection for larger head size at birth is the biggest ultimate source of maladaptive obstetrical complications. Equally important is the ubiquity of design trade-offs: increasing the functionality of one system may interfere with the functionality of another; increasing the efficiency of a system early in life may lead to decreased efficiency when the organism gets older; enhanced defenses against a given disease may increase vulnerability to another; and so forth. Specifically, a "risk factor" for disorder A may often protect the individual from disorder B. For example, it has been suggested that the long allele of the serotonin transporter gene promoter (5-HTTLPR) may offer protection against depression but increase the risk for psychopathy (Glenn, 2011).

Undesirable Adaptations

The last category in this taxonomy is also the most intriguing from an evolutionary standpoint. As we just discussed, undesirable conditions often reflect the individually maladaptive outcomes of otherwise adaptive mechanisms. However, it may also be the case that *adaptive* outcomes are perceived as undesirable conditions, or even classified as bona fide disorders (Nesse, 2004a; Nesse & Jackson, 2006). Distinguishing undesirable adaptations from maladaptive outcomes can be theoretically and empirically challenging (see Nesse, 2011), but is an essential step to correctly understand the meaning and etiology of the relevant conditions.

Antisocial, Exploitative, or Socially Devalued Strategies. In complex social species like ours there are many potential routes to reproductive success, and not all of them involve cooperation and prosociality. Individuals who develop antisocial, exploitative behavioral strategies may often reap considerable rewards—especially in harsh and unpredictable social contexts. Of course, the enhanced reproductive success of (some) antisocial individuals may come at a cost to their own emotional well-being as well as the welfare of their victims. We already mentioned the hypothesis that some types of psychopathy represent an adaptive strategy of this kind; the hypothesis is supported by the robust association between psychopathic traits and a pattern of precocious sexuality, promiscuity, and sexual coercion (see Barr & Quinsey, 2004; Del Giudice, 2014a; Glenn, Kurzban, & Raine, 2011; Mealey, 1995). A similar case has been made for borderline personality disorder, a pervasive pattern of impulsivity and emotional, affective, and relational instability that is more common in females (Brüne, Ghiassi, & Ribbert, 2010). The heterogeneous category of personality disorders is likely to include other biologically adaptive behavioral variants that are treated as problematic, for example because they cause harm or distress to an individual's social partners.

Aversive Defenses. When defenses activate inappropriately or respond with excessive intensity, the outcome may be correctly recognized as maladaptive. However, many protective mechanisms have strongly aversive effects (e.g., vomiting, panic); for this reason, they may give rise to undesirable conditions not only when they misfire but also when they respond appropriately in presence of actual threats. Sometimes, defensive processes can be altogether mistaken for disorders, especially if their logic is incompletely understood and if the correspondence between threat and response is imperfect (because of the smoke detector principle). Indeed, the "fallacy of mistaking defenses for diseases" is a pervasive feature of current psychopathological approaches (Nesse & Jackson, 2006). Many diagnosable instances of emotional disorders—involving low mood, anxiety, and so forth—may be better understood as unpleasant but adaptive responses to contextual factors.

As already noted, distinguishing adaptive defensive reactions from maladaptive outcomes or dysfunctional

responses is not an easy task (Nesse, 2011). This is exemplified by the debate on evolutionary models of depression. Some authors have argued that major depression can be adaptive as a mechanism of motivational disengagement from unproductive goals, signaling of social submission, and solicitation of help from family and friends (e.g., Sloman & Price, 1987; Watson & Andrews, 2002). However, while low mood has a number of crucial adaptive functions, the available evidence is more consistent with the idea that major depression usually reflects a maladaptive dysfunction of the systems involved in mood regulation (e.g., Nesse, 2006; Nettle, 2004).

Health–Reproduction Trade-Offs. Antisocial strategies and aversive defenses do not exhaust the potential range of undesirable adaptations. The more general point is that, since natural selection maximizes fitness rather than health, traits that increase reproductive success may often have substantial health costs. For example, many health problems associated with aging are the price we pay for more efficient functioning earlier in life (see Nesse, 2001). In developmental psychology, risk taking and impulsivity in adolescence are often viewed as dysfunctional; however, they are better explained as behavioral adaptations to the stronger mating competition faced by human males (e.g., Ellis et al., 2012; Nesse, 2001).

Implications for the Core Points of Developmental Psychopathology

The mutual interplay between *normal and pathological development* is one of the core points of developmental psychopathology. An evolutionary perspective offers a deeper understanding of how "normality" and "pathology" can be defined in the first place and provides researchers with a conceptual toolkit for analyzing the full spectrum of undesirable conditions—from harmful and/or maladaptive dysfunctions to adaptive but undesirable mechanisms that may be erroneously mistaken for disorders. In between lies a range of explanatory categories in which adaptation and maladaptation coexist to various degrees. All too often, models in developmental psychopathology converge on dysregulation as the default explanation of undesirable conditions (see the next section). As we have shown here, dysregulation is only one of many potential explanations of psychopathological outcomes; a biologically informed taxonomy like the one we presented (see also Cosmides & Tooby, 1999; Nesse, 2001, 2011) can be a useful guide to formulate alternative hypotheses and build more sophisticated explanatory models.

An especially intriguing case is that of high-risk strategies characterized by unpredictable outcomes. Strategic risk provides a powerful explanation of *multifinality*, since—by definition—individual variables associated with risky strategies can be expected to predict positive outcomes in some individuals *and* negative outcomes in others. Furthermore, the outcomes of high-risk strategies are often determined in large part by chance factors, highlighting the connection between multifinality and *probabilistic causality* in developmental trajectories. A similar picture emerges if one considers the calibration of adaptive defenses and the probabilistic trade-offs involved in the balance between misfiring and appropriate responding.

An evolutionary approach also provides a nuanced view of the interplay between *risk and protective factors*—another defining point of developmental psychopathology. In particular, the logic of constraints and trade-offs suggests that some putative "risk factors" for a given condition may actually protect individuals from other (and perhaps more severe) conditions. Similarly, the logic of adaptive defenses should alert researchers to the possibility that some putative "protective factors" involving defense downregulation may actually interfere with an individual's ability to protect itself from rare but potentially severe threats. In sum, the approach we advocate goes beyond intuitive notions of risk and resilience and contributes to draw a more realistic picture of the complex, layered relations between health and pathology.

BEYOND MENTAL HEALTH: CONDITIONAL ADAPTATION AND LIFE HISTORY THEORY

A widespread set of assumptions in developmental psychology is that children raised in supportive and well-resourced environments (e.g., who live in communities with social networks and resources for young people; who have strong ties to schools and teachers; who benefit from nurturing and supportive parenting; who are exposed to prosocial peers) tend to develop normally and express optimal trajectories and outcomes. By contrast, developmental processes among children raised in high-stress environments (e.g., who experience poverty, discrimination, low neighborhood attachment, and community disorganization; who feel disconnected from teachers and schools; who experience high levels of family conflict and negative relationships with parents; who are exposed to delinquent peers) put them at risk for dysregulation, leading to impaired functioning and problem behaviors that are destructive to themselves and others. This set of assumptions is powerful and pervasive, if usually implicit,

and underlies what we call the *mental health model* of developmental psychopathology.

In contrast with the mental health model, theory and research in evolutionary biology have come to acknowledge that, in most species, single best strategies for survival and reproduction are unlikely to evolve. Instead, the locally optimal strategy normally varies as a function of three overarching parameters. First, the costs and benefits of different strategies depend on the physical, economic, and social parameters of an organism's environment (e.g., food availability, mortality rates, quality of parental investment, social competition). This context-dependency means that a strategy that promotes success in some environmental contexts may lead to failure in others. Second, the success and failure of different strategies depends on an organism's condition or relative competitive abilities in the population (e.g., age, body size, health, history of wins and losses in agonistic encounters); that is, the cost–benefit trade-offs of different strategies varies depending on an organism's internal condition and competitive status. Third, an organism's sex often has important implications for the range of available strategies and their relative costs and benefits.

In this section we discuss how developmental processes increase adaptation by matching an organism's phenotype to local environmental conditions and individual characteristics. We begin by reviewing the general concepts of plasticity and conditional adaptation. We then introduce evolutionary life history theory and show how it provides a general framework for adaptive plasticity, as well as an integrative understanding of the development of individual differences in physiology, growth, and behavior.

Developmental Plasticity and Conditional Adaptation

Because the viability of different survival and reproductive strategies is so context- and condition–dependent, natural selection tends to maintain *adaptive developmental plasticity*: biological systems that reliably guide the development of alternative phenotypes (including anatomy, physiology, and behavior) to match an organism's internal condition and external environments (see West-Eberhard, 2003). Developmental plasticity involves "durable biological change in the structure or function of a tissue, organ, or biological system" (Kuzawa & Quinn, 2009, p. 132). Importantly, adaptive developmental plasticity is a nonrandom process; it is the outcome of structured interplay between the organism and its environment, shaped by natural selection to increase the capacity and tendency of individuals to track both their internal condition and external environments and adjust the development of their phenotypes accordingly. Developmental plasticity is ubiquitous throughout the animal world (see extensive reviews in DeWitt & Scheiner, 2004; West-Eberhard, 2003).

Developmental plasticity is critically important for enabling organisms to adapt to stress, which has always been part of the human experience. Indeed, almost half of children in hunter–gatherer societies—the best model for human demographics before the agricultural revolution—die before reaching adulthood (e.g., Volk & Atkinson, 2013). Thus, from an evolutionary-developmental perspective, stressful rearing conditions, even if those conditions engender sustained stress responses that must be maintained over time, should not so much impair neurobiological systems as direct or regulate them toward patterns of functioning that are adaptive under stressful conditions (see Ellis et al., 2012; Frankenhuis & de Weerth, 2013).

Because developmental plasticity involves durable change, it is inherently forward-looking; that is, it involves predicting—and preparing—for future environments. Boyce and Ellis (2005) make this explicit in their definition of *conditional adaptation*: "Evolved mechanisms that detect and respond to specific features of childhood environments, features that have proven reliable over evolutionary time in predicting the nature of the social and physical world into which children will mature, and entrain developmental pathways that reliably matched those features during a species' natural selective history" (p. 290). During fetal development and infancy, important features of the environment are communicated to the child via the placenta and lactation in nutrients, metabolites, hormones, growth factors, and immune factors that reflect the mother's current and past experiences (Kuzawa & Quinn, 2009). Beyond these molecular signals from the mother, relevant features of the environment are detected and encoded through the child's ongoing experiences.

Developmental plasticity necessitates developmental trade-offs. For example, tadpoles (*rana sylvatica*) alter their size and shape based on the presence of dragonfly larvae in their rearing environment (Van Buskirk & Relyea, 1998). These alterations involve development of smaller and shorter bodies and deep tail fins. Although tadpoles that do not undergo these morphological changes are highly vulnerable to predation by dragonflies, those that do but end up inhabiting environments that are not shared with dragonflies have relatively poor developmental and survival outcomes. In short, the predator-induced phenotype is only conditionally adaptive. This process highlights that in many cases, natural selection favors a primary phenotype that yields high payoffs under favorable

circumstances and a secondary phenotype that "makes the best of a bad situation" (West-Eberhard, 2003).

The Role of Genotypic Variation

As should be clear from the tadpole example, in addition to the apparent benefits of developmental plasticity, there can be substantial costs. On the one hand, there is the cost of producing and maintaining the appropriate regulatory and assessment mechanisms to support alternative patterns of development. On the other hand, environmental cues may have limited validity, and thus developmental plasticity in response to current conditions may fail to correctly predict future environmental conditions. Consequently, while adaptive developmental plasticity is widespread, it is not always be the best or only option. As an alternative to adaptive developmental plasticity, or in conjunction with it, natural selection may also maintain genetic variation as a solution to the critical adaptive problem of matching phenotypes to heterogeneous environments.

There are a variety of circumstances in which genetic contributions to alternative phenotypes are likely to be favored by natural selection. When individuals inhabit multi-niche environments, and they are able to choose the niche that best fits their phenotype, it may partly or fully obviate the need for developmental plasticity. Instead, a diversity of genetically regulated phenotypes that are specialized to the different social or physical niches can thrive in this context (see Wilson & Yoshimura, 1994). In addition, genetic variation can be maintained through *balancing selection,* whereby selection for alternative phenotypes systematically changes across time, space, population states, and so forth. A common type of balancing selection is *frequency-dependent selection*, which occurs when the fitness of different phenotypes changes as a function of their frequency in a population. The most viable form of frequency-dependent selection is negative, selecting against a given phenotype as it becomes more common. For example, aggressive individuals may be very successful when they are surrounded by tame individuals; however, as they multiply and begin to "invade" the population, their reproductive success may drop as they now compete mainly with other aggressive individuals. Balancing selection can also result from *heterozygote advantage* (when individuals who are heterozygous at a certain locus have higher fitness than either of the homozygous types) or from changes in selection pressures over time and space (*fluctuating selection*). Fluctuating selection pressures, by definition, weaken directional selection and therefore enable higher rates of genetically-regulated phenotypic variation (including neutral and deleterious forms of variation).

A crucial question is, to what degree should phenotypic variation be more developmentally contingent and plastic versus more strongly regulated by genotypic variation? The answer is not simple; indeed, what is typically found in organisms is a mixture of the two. Theoretical models suggest that one should often expect a balance between genetic and environmental determination of phenotypic individual differences. Depending on the structure of environmental variation, the costs and benefits of plasticity, and the life history of an organism, a given selection regime—for example one of temporally fluctuating selection—may maintain different proportions of developmental plasticity and genotypic variation.

The reproductive strategies of the male swordtail fish provide an example of this complexity, demonstrating the importance of adaptive genetic variation, adaptive developmental plasticity, and their interplay (reviewed in Ellis, Jackson, & Boyce, 2006). In the swordtail, three alleles at the *P* locus on the Y chromosome correspond to three modes in size distribution of mature males (small, intermediate, and large). Although all three genotypes perform the range of species-typical mating strategies, they do so at different size-related frequencies. Specifically, small, intermediate, and large males generally sneak, sneak and court, and court females, respectively. Size is the primary mediating mechanism in this species through which allelic variations influence mating strategies.

In determining alternative mating strategies, the key developmental event in male swordtail fish is gonadarche (maturation of the gonads). Specifically, the three alleles at the *P* locus differentially influence timing of gonadarche, which occurs earlier in genotypically small than in genotypically large males. In addition to these genetic influences, timing of gonadarche is also sensitive to a number of environmental factors, such as temperature and agonistic interactions with other males. These environmental influences can result in genotypically small males that are larger than genotypically intermediate males, and alternative mating strategies correlate more strongly with size than with genotype. In addition, mating strategies of male swordtail fish are competition-dependent in relation to interaction with other males. For example, males of intermediate size will sneak and chase females rather than court when in the presence of larger males.

In sum, both genomic and environmental factors influence timing of gonadarche, which in turn coordinates patterns of gene expression involved in the developmental cascade that induces sexual maturation and halts or dramatically reduces growth. Timing of gonadarche strongly influences size, and size is a major developmental

factor in entrainment of alternative mating strategies. At the same time, mating strategies are conditionally adjusted in response to current physical and social dimensions of the environment. Thus, although there are strong genotypic influences on size and developmentally-linked mating strategies, the development of the alternative phenotypes in fact emerges through a complex series of gene-environment interplay. Importantly, these developmental interactions occur through integrated effects of gene products and environmental conditions on the developing phenotype.

Reaction Norms

A useful tool for thinking about developmental plasticity is the concept of a *reaction norm*. A reaction norm is a function describing how a single individual may express different phenotypes in response to a range of environmental conditions. While reaction norms are often treated as a property of genotypes (see Schlichting & Pigliucci, 1998), genotypic effects on development—including individual differences in plasticity—are always mediated by the preexisting phenotype. Moreover, genetically different individuals may develop the same phenotype following different developmental trajectories. Thus, reaction norms may be legitimately employed to map phenotypic change on preexisting phenotypic (rather than genotypic) differences.

Figure 1.2 illustrates individual differences in developmental plasticity in the simple case of linear reaction norms. As can be seen in the figure, individuals may differ in the *elevation* and/or *slope* of their reaction norms. A steeper slope indicates higher susceptibility to environmental factors, as the same amount of variation in environmental conditions results in a larger change in the expressed phenotype. The *reaction range* of an individual is the difference between the minimum and maximum phenotypic score over a fixed range of the environmental variable, and denotes the individual's overall potential for plasticity. When the reaction norms of different individuals are not parallel (different slopes; Figures 1.2b and 1.2c), the result is a statistical genotype × environment (GxE) or phenotype–environment (PxE) interaction, whereby the effect of the environment is moderated by an individual's genotype/phenotype (and vice versa).

Adaptive Plasticity in the Development of Life History Strategies

From Life History Trade-offs to Life History Strategies

A major framework in evolutionary biology for explaining patterns of developmental plasticity and individual differences is life history theory (see Kaplan & Gangestad, 2005; Stearns, 1992). All organisms live in a world of limited resources; for example, the energy that can be extracted from the environment in a given amount of time is intrinsically limited. Time itself is a limited good; the time spent by an organism looking for mates cannot be used to search for food or care for extant offspring. Due to these structural and resource limitations, organisms cannot maximize all components of fitness simultaneously and instead are selected to make trade-offs that prioritize resource expenditures so that greater investment of time and/or resources in one domain occurs at the expense of investment in competing domains.

For example, resources spent on mounting a robust inflammatory response to fight infection cannot be spent on reproductive effort. Thus, the benefits of inflammatory response are traded off against the costs of lower ovarian function in women and reduced musculoskeletal function in men (Clancy et al., 2013; Muehlenbein & Bribiescas, 2005). Trade-offs between reproductive effort and health go in the opposite direction as well, as early reproductive maturation is linked to more physical health problems in

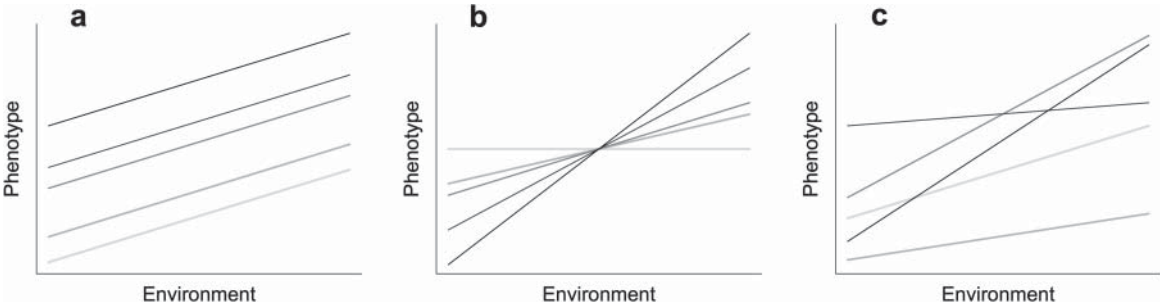


Figure 1.2 (1) Individual differences in phenotypic elevation but not in slope and reaction range; all genotypes have the same plasticity. (2) Individual differences in slope and reaction range (differential plasticity); all genotypes have the same elevation at the environmental mean. (3) Individual differences in elevation, slope, and reaction range.

adulthood (e.g., Allsworth, Weitzen, & Boardman, 2005). Each trade-off constitutes a decision node in allocation of resources, and each decision node influences the next decision node (opening up some options, foreclosing others) in an unending chain over the life course (Ellis, Figueredo, Brumbach, & Schlomer, 2009). This chain of resource-allocation decisions—expressed in the development of a coherent, integrated suite of physiological and behavioral traits—constitutes the individual's life history strategy.

Life history strategies are adaptive solutions to fitness trade-offs within the constraints imposed by social conditions, physical laws, phylogenetic history, and developmental mechanisms. An organism's life history strategy coordinates morphology, physiology, and behavior in a way that maximizes expected fitness in a given environment (Braendle, Heyland, & Flatt, 2011; Réale et al., 2010). At the most basic level, the resources of an organism must be distributed between *somatic effort* and *reproductive effort*. Somatic effort can be further subdivided into growth, survival and body maintenance, and developmental activity (Geary, 2002). Developmental activity includes play, learning, exercise, and other activities that contribute to building and accumulating *embodied capital*—strength, coordination, skills, knowledge, and so forth (Kaplan & Gangestad, 2005; Kaplan, Hill, Lancaster, & Hurtado, 2000). Reproductive effort can be subdivided into *mating effort* (finding and attracting mates, conceiving offspring), *parenting effort* (investing resources in already conceived offspring), and *nepotistic effort* (investing in other relatives, for example siblings and grandoffspring).

The critical decisions involved in a life history strategy can be summarized by the fundamental trade-offs between current and future reproduction, between quality and quantity of offspring, and—in sexually reproducing species—between mating and parenting effort (see Ellis et al., 2009). By delaying reproduction, an organism can accumulate resources and/or embodied capital, thus increasing the quality and fitness of future offspring; however, the risk of dying before reproducing increases concomitantly. When reproduction occurs, the choice is between many offspring of lower quality and fewer offspring of higher quality. Although intensive parental investment is a powerful way to increase the embodied capital (and long-term prospects) of one's descendants, the fitness gains accrued through parenting must be weighed against the corresponding reduction in mating opportunities. Different life history strategies solve these problems in different ways by determining how organisms allocate effort among fitness-relevant traits. The same basic framework can be used to describe differences between species, as well as differences between individuals of the same species.

At the broadest level of analysis, life history traits covary along a dimension of *slow* versus *fast* life history strategies. Variation along the slow-fast continuum is observed both between related species and between individuals of the same species (see Ellis et al., 2009; Réale et al., 2010). Slow growth and late reproduction correlate with long life span, high parental investment, fewer offspring of higher quality, and low juvenile mortality. Conversely, fast growth and early reproduction correlate with high juvenile mortality, short life span, larger numbers of offspring, and reduced parental investment in each (Figure 1.3). Fast life history strategies are comparatively high risk, focusing on mating opportunities (which typically involves more risky and aggressive behavior), reproducing at younger ages, and producing a greater number of offspring with more variable outcomes.

Sex Differences in Life History Trade-offs

The asymmetries introduced by sexual reproduction have important implications for the life histories of males and females. For example, in most species males tend to engage

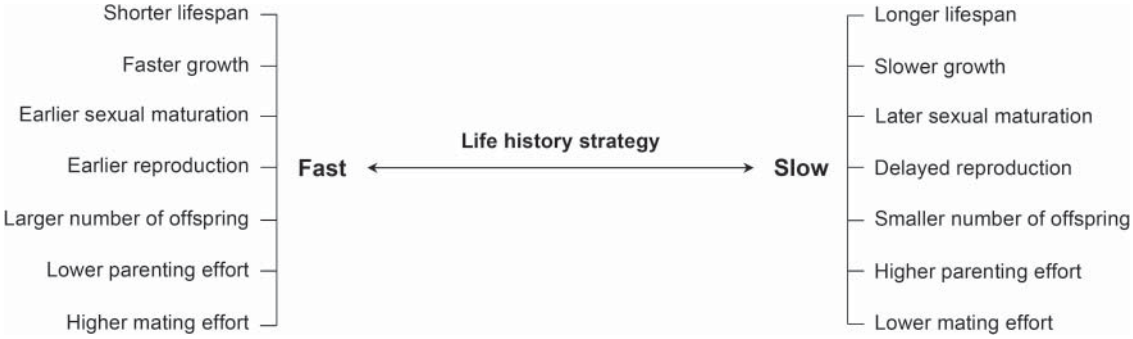


Figure 1.3 The fast–slow continuum of life history variation.

in higher mating effort and lower parental effort than females (Geary, 2002; Trivers, 1972). In addition, males usually undergo stronger sexual selection, that is, their reproductive success is more variable than that of females; they also tend to mature more slowly, in order to gain the competitive abilities and qualities needed for successful competition for mates. Sexual asymmetries in life history strategies can be attenuated in species with monogamous mating systems and when both parents contribute to offspring care. Compared with other mammals, humans show an unusually high degree of paternal investment; we are clearly adapted for the possibility of monogamous, long-term relationships. However, human paternal care is also highly variable and facultative (e.g., Geary, 2005; Quinlan, 2008), and strict monogamy is rarely if ever found. Overall, human mating is best characterized as strategically flexible (Gangestad & Simpson, 2000), with a widely documented tendency for men to engage in higher mating effort than women.

As a result, the trade-off between current and future reproduction is more pressing for women than for men: women's reproductive rate is limited by the long duration of gestation and the considerable energetic investment of pregnancy and lactation, and their window for successful reproduction necessarily ends with menopause. In contrast, men can potentially sire many offspring in a very short time, as well as for a more extended period of their lives. Men's crucial trade-off is the one between mating and parenting: the payoffs of high mating effort are potentially much larger for males, who can benefit directly from having access to a large number of partners; women can usually have only one child at a time, and thus benefit comparatively less from mating with multiple partners.

Environmental Determinants of Life History Strategy

Developmental calibration of slow versus fast life history strategies is a prototypical case of developmental plasticity. Key dimensions of the environment that regulate the development of life history strategies include energy availability, extrinsic morbidity–mortality, and predictability of environmental change (Ellis et al., 2009; Kuzawa & Bragg, 2012). Energetic resources—caloric intake, energy expenditures, and related health conditions—set the baseline for many developmental processes. Energy scarcity slows growth and delays sexual maturation and reproduction, resulting in a "slow" life history strategy. However, when bioenergetic resources are adequate to support growth and development, then proximal cues to extrinsic morbidity–mortality and unpredictability generally promote faster life history strategies.

Extrinsic morbidity–mortality refers to external sources of disability and death that are relatively insensitive to the adaptive decisions of the organism. Environmental cues indicating high levels of extrinsic morbidity–mortality cause individuals to develop faster life history strategies. Faster strategies in this context—a context that devalues future reproduction—function to reduce the risk of disability or death prior to reproduction. Moreover, high extrinsic morbidity–mortality means that investing in parental care has quickly diminishing returns, which favors reduced parental investment and offspring quantity over quality. Accordingly, exposure to environmental cues indicating extrinsic morbidity–mortality (i.e., observable cues that reliably covaried with morbidity–mortality risks during evolutionary history) can be expected to shift life history strategies toward current reproduction by anticipating maturation and onset of sexual activity. In humans, these cues may include exposure to violence, harsh childrearing practices, premature disability and death of other individuals in one's local ecology, and so forth.

In addition to extrinsic morbidity–mortality, environmental unpredictability—stochastic changes in ecological and familial conditions also regulates development of life history strategies (Ellis et al., 2009). In environments that fluctuate unpredictably (e.g., changing randomly between Conditions A and B, so exposure by parents or their young offspring to Condition A does not reliably forecast whether offspring will mature into Condition A or B), long-term investment in a development of a slow life history strategy does not optimize fitness; all of the energy invested in the future is wasted if the individual matures into an environment where life expectancy is short. Instead, individuals should detect and respond to signals of environmental unpredictability by adopting faster life history strategies. In humans, cues of unpredictability may include erratic neighborhood conditions, frequent residential changes, fluctuating economic conditions, changes in family composition, and so forth.

Belsky and colleagues (1991) were the first to hypothesize that harsh parenting, conflictual family relations, and insecure attachment would predict early sexual maturation, impulsivity, reduced cooperation, and exploitative interpersonal styles—the expected correlates of a fast life history strategy in humans. Empirical studies have confirmed these associations and detailed how harsh family relations, insecure attachment, and high levels of mortality in the immediate environment predict early puberty (in females), precocious sexuality, unstable couple relationships, and promiscuous mating styles (see special section of *Developmental Psychology*; Ellis & Bjorklund, 2012).

Key psychological mediators of fast life history strategies include insecure attachment styles, impulsivity, present orientation (the inability to delay gratification and/or wait for larger rewards in the future), and a short subjective life expectancy. These variables are reliably associated with earlier onset of sexual activity, unrestricted sociosexuality (a desire for short-term, promiscuous sexual relationships), larger number of sexual partners, earlier age at first birth in women, increased risk taking, reduced cooperation, and antisocial behavior (reviewed in Belsky, 2012; Chisholm, 1999; Del Giudice, 2009; Del Giudice, 2014a; Figueredo & Jacobs, 2010; Figueredo et al., 2006). At the level of personality traits, slow life history strategies are robustly associated with agreeableness and conscientiousness (Del Giudice, 2014a). Taken together, these results strongly support the existence of a fast-slow dimension underlying a broad spectrum of individual differences in humans.

Because extrinsic morbidity–mortality and unpredictability are distinct, developmental exposures to each of these environmental factors should uniquely contribute to variation in life history strategy (Ellis et al., 2009). Longitudinal analyses of the National Longitudinal Study of Adolescent Health, the National Institute of Child Health and Human Development (NICHD) Study of Early Child Care and Youth Development, and the Minnesota Longitudinal Study of Risk and Adaptation (MLSRA) support this prediction (Belsky, Schlomer, & Ellis, 2012; Brumbach, Figueredo, & Ellis, 2009; Simpson, Griskevicius, Kuo, Sung, & Collins, 2012). For example, in the NICHD and MLSRA studies, exposures to environmental unpredictability in the first 5 years of life (e.g., parental changes, residential changes) uniquely predicted faster life history strategies in adolescence and emerging adulthood, independent of the effects of unpredictability in later childhood and indicators of extrinsic morbidity–mortality.

The Centrality of the Phenotype

All developmental processes are ultimately the product of structured organism–environment interplay. Development is always modulated by the organized phenotype, which is initially provided by the parents in the form of a zygote and then changes during ontogeny in response to both genetic and environmental influences.

Consider a central life history trait: timing of sexual maturation. As discussed above, sexual maturation is regulated by energetic conditions, so that—on average—individuals in well fed populations experience early puberty and poorly fed populations experience late puberty. The effects of energetic conditions, however, are modulated by the organized phenotype. For example, food-getting ability (a behavioral phenotype), metabolic efficiency (a physiological phenotype), and energy stores in the form of body fat (a morphological phenotype) all contribute to regulation of puberty; that is, these phenotypic traits modulate the effects of the critical environmental factor (energy availability) on maturation and functioning of the reproductive axis. The same logic applies to genetic effects: genes provide templates for the production of particular molecules that become incorporated into the phenotype, depending on the responsivity of the phenotype to those molecules and the presence of the necessary environmental building blocks (substances from outside the organism) to support gene expression (West-Eberhard, 2003). The effects of genes, environments, and phenotypes are hierarchically organized: The preexisting phenotype is the transducer of both genetic and environmental sources of information. Specifically, genetic and environmental effects depend on the phenotype being organized to accept them, and the modified phenotype retains these effects as development proceeds. In this sense, the phenotype embodies one's own particular history of genetic and environmental effects.

The organizational role of the phenotype is critical to understanding the development of life history strategies. As we will discuss in detail in the next section, Del Giudice and colleagues (2011) proposed that one of the key functions of the stress response system is to regulate an organism's life history strategy. According to the adaptive calibration model (ACM; Del Giudice et al., 2011; Ellis, Del Giudice, & Shirtcliff, 2013), the stress response system coordinates the development of alternative life history strategies by affecting a broad suite of physiological and psychological traits, including growth and maturation, sexual and reproductive functioning, social learning, aggression, competition and risk taking, pair bonding, and related factors. This occurs in part through extensive physiological linkages between the stress response system and the reproductive axis (Ellis, 2004). The key idea is that activation of stress, metabolic, and immune system responses during childhood provides crucial *information* about threats and opportunities in the environment, their type, and their severity. Over time, this information becomes biologically embedded in the parameters—recurring set points and reactivity patterns—of these systems. These parameters provide the developing person with statistical summaries of key dimensions of the environment. An alternative pathway for the effects of stress may revolve around somatic damage: if early stress causes permanent damage to the organism and thus reliably reduces life expectancy, it may be adaptive for individuals exposed to stress early in life to engage in faster

life history strategies even if the environment improves later on (Nettle, Frankenhuis, & Rickard, 2013). In total, the stress response system operates as a mechanism of conditional adaptation: it collects and biologically embeds information from the environment, and makes use of that information to match the developing phenotype to local environmental conditions. In this manner, the environment becomes instantiated in the phenotype.

At the same time, the phenotype modulates environmental effects at all points in development. As a result of differences in extant phenotypes, individuals differ in their reaction norms (Schlichting & Pigliucci, 1998). Because reaction norms differ in slope across individuals, some people are more likely than others to experience sustained developmental change in response to environmental exposures, including change in the physiological parameters that mediate development of alternative life history strategies. Moreover, as a result of differences in the organized phenotype, life history-relevant physiological parameters already differ across individuals at birth (cf. temperament). Stated differently, people differ in the elevation of their reaction norms. This means that developmental change in the physiological bases of life history strategies and their behavioral outcomes are likely to occur around different points on the life history spectrum (i.e., around the faster range of life history in some individuals and the slower range in others).

In total, the organized phenotype is present from conception and can be described in terms of the steepness and location of its reaction norms along various dimensions. These reaction norms, which have already undergone significant development by the time a child is born, are both regulated by and constrain the effects of environmental and genetic factors. The organized phenotype incorporates and biologically embeds environmental and genetic inputs throughout the life course. This ongoing process translates into individual differences in such critical traits as body size, energy reserves, metabolic efficiency, susceptibility to environmental influence, immune function, fecundity, mate value, and fighting ability. Differences between individuals in these phenotypic traits influence the cost–benefit trade-offs of different life history strategies and thus play a central role in regulating the development of these strategies.

Consider the trade-off between mating effort and parenting effort in men. Sexual selection models, such as Gangestad and Simpson's (2000) *strategic pluralism theory*, emphasize social and sexual competition as important factors shaping adaptive variation in reproductive strategies. According to this perspective, individuals who are competitively advantaged relative to peers (i.e., who possess social and physical attributes that make them successful in same-sex competition and targets of choice by the other sex) have more mating opportunities. These enhanced opportunities tend to bias resource allocations toward more mating effort at the expense of parental effort. Because male reproductive success is ultimately constrained by the ability to access, attract, and retain mates, alternative male mating strategies should be especially attuned to the demands and desires of women and the ability of men to successfully engage in intrasexual competition. To a large extent, this variable success arises from phenotypic traits that facilitate gaining status and attracting mates (e.g., size, aggressiveness, physical attractiveness, social relations with others). This leads to the hypothesis that intrasexual competitive abilities in men will regulate life history strategies, especially the mating-parenting trade-off.

This hypothesis has been supported by a large empirical literature showing that men who achieve high social status or who possess honest indicators of genetic quality (e.g., physical attractiveness, bilateral symmetry of body parts) engage in more mating effort. For example, anthropological evidence indicates that social status is directly related to male reproductive success in horticultural, agricultural, and pastoral societies (see Pérusse, 1993, for an extensive review). Men with higher status in industrial societies, as measured by education, occupation, and income, also report a greater number of sex partners than men of lower social status (Pérusse, 1993). In addition, men who report that they are more attractive to the opposite sex also report having sex at an earlier age, a greater number of sex partners, and an unrestricted sociosexual orientation (reviewed in James & Ellis, 2013). Finally, men who are more symmetrical in bilateral traits have been found to have more lifetime sexual partners as well as more extrapair sexual encounters during ongoing relationships (controlling for physical attractiveness). In contrast, no consistent relations have been found between women's symmetry and number of lifetime sexual partners or extrapair sexual relationships (reviewed in Thornhill & Gangestad, 2004).

Another critical life history trade-off that is regulated by phenotypic condition is current versus future reproduction. Effort put into reproducing now will use energy or resources that cannot be used or saved for future reproduction. The costs of current reproduction may be paid in terms of reduced number, quality, or survival of future offspring, as well as reduced growth and survival of the parent. This decision whether to pay these costs critically

depends of the physical condition of the individual. If either external conditions (e.g., infectious diseases, warfare) or internal state (e.g., poor health, oxidative stress) indicate a heightened probability of premature disability or death, then individuals should shift resource allocations toward current reproduction (presuming adequate bioenergetic resources to support a fast strategy).

Research examining relations between exposures to stress, biological aging or health, and reproductive strategies has provided preliminary support for this hypothesis. For example, Bleil and colleagues (2013) found that heightened psychosocial stress was associated not only with ovarian reserve depletion in older women but also with earlier puberty and higher antral follicle count in younger women, indicating a faster life history strategy. Likewise, women who were exposed *in utero* to the Dutch famine of 1944–1945 not only had increased risk of chronic degenerative disease but also started reproducing at a younger age, had more offspring, had more twins, and were less likely to remain childless (Painter et al., 2008), again indicating a faster life history strategy. An important qualification to these findings is that individuals with life-expectancy-reducing chronic disease diagnosed during childhood also shift toward current reproduction (e.g., early age at first reproduction), even though the incidence of serious chronic disease was uncorrelated with family and ecological stressors (Waynforth, 2012). These data indicate that internal factors, such as compromised phenotypic condition (i.e., damage), in and of itself, can contribute to accelerate life history strategies. Once again, this underscores the centrality of the phenotype in organizing adaptive plasticity through the reciprocal interplay of environmental and genetic factors, either of which can have more decisive effects in different developmental contexts (see extended discussion in West-Eberhard, 2003).

Implications for the Core Points of Developmental Psychopathology

While the mental health model of developmental processes resonates with the intuitions of many researchers, its narrow view of adaptation and maladaptation is an obstacle toward the goal of synthesizing *normal and pathological development* in a single framework. The concepts of adaptive plasticity and conditional adaptation offer a better appreciation of the logic of individual differences and that of gene-environment interplay in development. The crucial idea is that adverse environmental conditions often direct developmental processes along alternative adaptive pathways, rather than simply impair or dysregulate them.

The framework of life history theory adds a layer of specificity to this general picture. Life history concepts can be employed to make remarkably accurate predictions about the structure of individual differences in physiology, growth, and behavior, and the environmental factors that shift development along alternative trajectories. In particular, life history theory delineates basic dimensions of environmental stress and support that underlie the multitude of *risk and protective factors* described in developmental psychopathology—resource availability, morbidity/mortality risk, and unpredictability. This is especially useful given the confusing abundance of environmental/contextual variables that might be measured and correlated with developmental outcomes. It is also important to stress how adaptive plasticity and life history theory offer a thoroughly *contextualist* view of development, though one that is compatible with a major role of genetic factors and genotype × environment interactions.

Finally, the centrality of the phenotype in enabling and structuring adaptive plasticity has a number of implications for the prospect of integrating developmental psychopathology and EDP. First of all, it does away with the notion that EDP is wedded to any sort of genetic determinism and shows how it is possible to integrate a sophisticated view of developmental mechanisms within an explicitly evolutionary framework. Second, it suggests a deep theoretical rationale for the prevalence of *probabilistic causality* in development. Third, it affords a principled way to investigate the connection between behavioral strategies and *brain and neurobiological factors*, thanks to the concept of biological embedding. In the next section we will further illustrate this point by reviewing the role of the stress response system in collecting environmental information and regulating physical and behavioral development.

BEYOND ALLOSTATIC LOAD: THE STRESS RESPONSE SYSTEM AS A MECHANISM OF CONDITIONAL ADAPTATION

How does repeated or chronic childhood adversity shape biobehavioral development and, through it, mental and physical health? Consistent with the mental health model, there is a widely accepted answer to this question in the field of developmental psychopathology. Instantiated in models of "toxic stress" (Shonkoff et al., 2012) and "allostatic load" (Lupien et al., 2006; McEwen & Stellar, 1993), that answer posits a striking duality: biological responses to stress are usually adaptive in the short term, but protracted activation of stress response systems is

maladaptive and toxic in the long term. Toxic stress causes disruptions of brain structure and function, resulting in dysregulation of physiological mediators—autonomic, neuroendocrine, metabolic, and immune—"that are the precursors of later impairments in learning and behavior as well as the roots of chronic, stress-related physical and mental illness" (Shonkoff et al., 2012, p. e236). As eloquently stated by Juster and colleagues (2011), the wear and tear of toxic stress and altered stress hormone functioning "inexorably strains interconnected biomarkers that eventually collapse like domino pieces trailing toward stress-related endpoints" (p. 725).

These models of toxic stress and allostatic load, however, only tell half of the story. The other half is the central role of the stress response system (SRS) in orchestrating physical and psychosocial development of both humans and nonhuman species (Ellis et al., 2006; Korte, Koolhaas, Wingfield, & McEwen, 2005), both in terms of species-typical development and individual differences. One of the most remarkable features of the SRS is the wide range of individual variation in its physiological parameters. Some individuals respond quickly and strongly even to minor events, whereas others show flat response profiles across most situations. Furthermore, the balance of activation among primary SRS subsystems—the sympathetic nervous system (SNS), the parasympathetic nervous system (PNS), and hypothalamus-pituitary-adrenal (HPA) axis—can vary considerably across individuals.

In developmental psychopathology, the standard framework for understanding the development and meaning of individual differences in stress responsivity is that of the *allostatic load model* (ALM; see Juster et al., 2011; Lupien et al., 2006; McEwen & Stellar, 1993). A guiding assumption of the ALM is that there is an optimal level of stress responsivity; accordingly, both "hyperarousal" and "hypoarousal"—recurring over or under activity of physiological mediators—are routinely described as dysfunctional deviations from the norm, usually caused by a combination of excessive stress exposure and genetic or epigenetic vulnerability. In this framework, environmental stress is treated as a risk factor for all kinds of symptoms and disorders (Compas & Andreotti, 2013). While some authors have argued that optimal adaptation is fostered by environments that contain *moderate* amounts of stressors (e.g., Rutter, 1993; Seery, 2011), the underlying assumption remains that a single best environment exists, and that deviations from that optimum cause dysregulation and pathology.

In this section we argue that acceptance of these assumptions, without placing them in a larger evolutionary-developmental framework, has impeded our understanding of the role of stress response systems in adaptively regulating development (for a detailed exposition see Ellis & Del Giudice, 2014). Specifically, models of allostatic load focus on the long-term *costs* of childhood stress and adversity—the "wear and tear" on multiple organ systems induced by chronic stress—but do not address the *benefits* of calibrating autonomic, neuroendocrine, metabolic, and immune systems to match current and future environments. We argue that this overemphasis on costs misses something fundamental and thus weakens the conceptual power of the ALM perspective. The result has been an imbalanced approach to research that has yielded dramatically more empirical knowledge about dysfunction than adaptive function, making it difficult to gain a coherent big picture of the subject matter.

A promising alternative to the ALM is provided by the *adaptive calibration model* (ACM; Del Giudice et al., 2011), a theory of individual differences in stress responsivity that builds on the concepts of life history theory and developmental plasticity. The ACM supplements the ALM and revises some of its key assumptions, thus laying the foundation for a broad theory of individual differences in stress responsivity. In this section we summarize the key tenets of the ACM, explicitly compare the ACM with the ALM, and discuss the implications of the two models for understanding adaptive and maladaptive developmental responses to stress (for more extended discussion, see Ellis & Del Giudice, 2014). Besides offering a broader perspective on the role of stress in development, the ACM exemplifies how the principles of EDP can be leveraged to achieve theoretical integration across multiple levels of analysis, from social behavior to neurobiology.

The Adaptive Calibration Model

The ACM is a theory of developmental programing focusing on calibration of the SRS and associated life history strategies to local environmental conditions. The ACM has its main theoretical foundations in life history theory and the theory of adaptive developmental plasticity (West-Eberhard 2003); it integrates and extends previous evolutionary models of stress (e.g., Boyce & Ellis 2005; Flinn, 2006; Korte et al., 2005; Porges, 2007) into a coherent theoretical framework. For a detailed presentation of the model, see Del Giudice and colleagues (2011).

The central tenet of the ACM is that the SRS operates as a mechanism of conditional adaptation, with a key role in

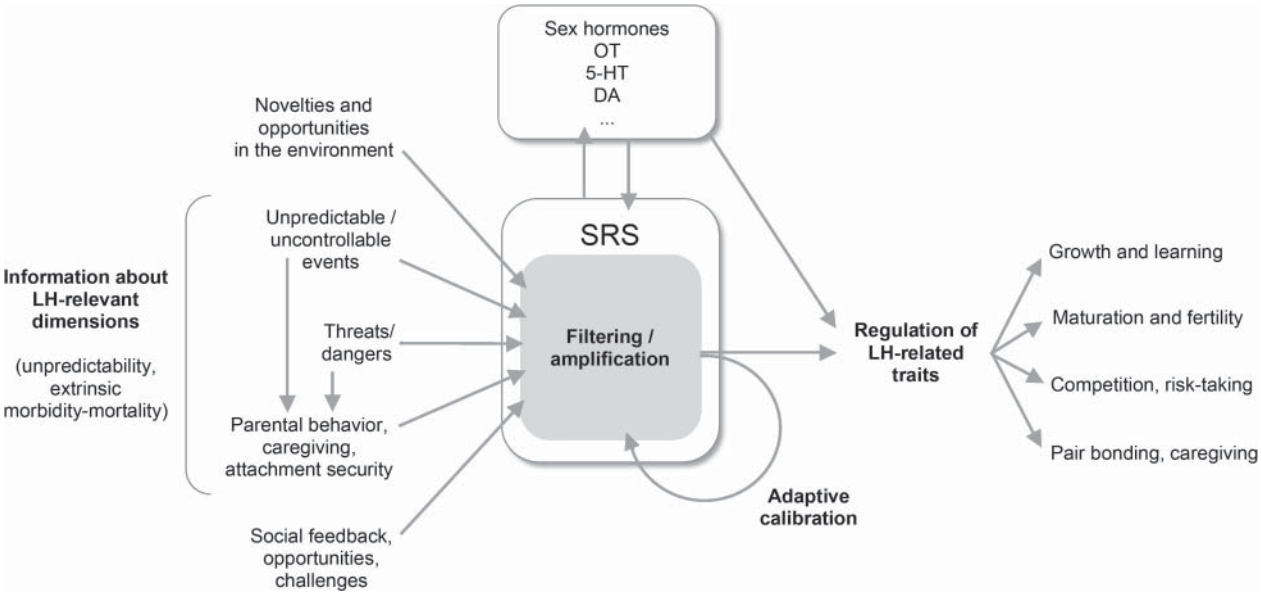


Figure 1.4 Core theoretical structure of the adaptive calibration model. SRS: stress response system; LH: life history; OT: oxytocin; 5-HT: serotonin, DA: dopamine. *Source:* Reprinted from M. Del Giudice, B. J. Ellis, & E. A. Shirtcliff, The adaptive calibration model of stress responsivity, *Neuroscience & Biobehavioral Reviews*, *35*, 1564, 2011.

regulating the development of individual life history strategies (Figure 1.4). In the ACM, the activation of autonomic, neuroendocrine, metabolic, and immune system responses during childhood provides crucial information about threats and opportunities in the environment, their type, and their severity. Over time, this information becomes embedded in the parameters—recurring set points and reactivity patterns—of these systems. These parameters provide the developing person with statistical summaries of key dimensions of the environment. For example, sustained activation of the HPA axis is generated by exposures to danger, unpredictable or uncontrollable contexts, and social evaluation, as well as energetic stress (see Dickerson & Kemeny, 2004; Gunnar et al., 2009); thus, the HPA axis tracks the key environmental variables involved in regulation of alternative life history strategies. Analogous arguments have been made regarding mesolimbic dopamine (Gatzke-Kopp, 2011). In turn, individual differences in SRS functioning regulate the coordinated development of a broad cluster of life history-relevant traits (Figure 1.4).

Although the ACM focuses on developmental plasticity, all developmental processes are the product of systematic organism–environment interplay. Because some individuals have steeper reaction norms than others, some individuals are more likely than others to experience sustained developmental change in response to environmental exposures. Further, as a result of differences in the organized phenotype, SRS parameter values already differ across individuals at birth. Consequently, individuals differ in the location of their reaction norms along SRS dimensions (Boyce & Ellis, 2005), with change more likely to occur for different individuals around higher versus lower ends of responsivity. Within these reaction norm constraints, the ACM articulates a theory of environmental regulation.

In total, the SRS (1) collects and biologically embeds information from the environment and (2) makes use of that information to match the developing phenotype to local environmental conditions. A crucial aspect of this matching process is the (iterative) calibration of the SRS itself in the service of life history goals (curved arrow in Figure 1.4). SRS activity also feeds back on the system itself, resulting in responsivity patterns that are adaptively calibrated to current environmental conditions and the individual's overall strategy. This underscores the fact that responsivity patterns develop over time, and may change—within limits—if the local environment undergoes prolonged changes in safety or predictability (i.e., recalibration). Changes in responsivity are also expected to occur in tandem with key hormonal switches such as adrenarche, gonadarche, childbirth, and menopause. More details on pathways and transitions in development of responsivity patterns can be found in Del Giudice and colleagues (2011).

The Role of the SRS in Allostasis and in Transduction of Environmental Information

Environmental events signaling threats to survival or well-being produce a set of complex, highly orchestrated responses within the neural circuitry of the brain and peripheral neuroendocrine pathways regulating metabolic, immunologic, and other physiological functions. The SRS comprises primarily three anatomically distinct yet integrated and cross-regulated circuits: the PNS, SNS, and HPA axis. The general function of the PNS is to promote vegetative functions in the absence of stress (i.e., rest and restorative behavior) and reduce or downregulate cardiac activity. When a stressor is encountered, the PNS responds quickly by withdrawing this inhibitory influence (i.e., *vagal withdrawal*), allowing the SNS to operate unopposed and thus causing rapid increases in physiological arousal. The PNS promotes flexible responding to stress, sustained attention, and coping with mild to moderate stressors (such as solving a difficult puzzle). More extreme defense reactions associated with freeze/hide behaviors also involve PNS activation, albeit via different efferent fibers (Porges, 2007).

If parasympathetic deactivation is not sufficient to cope with the present challenge, activation of the SNS occurs within seconds, providing a second layer of response in this hierarchy. Sympathetic activation mediates fight–flight responses following a fast, direct pathway via the noradrenergic innervation of visceral organs and a slower, hormonal pathway through innervation of the adrenal medulla (e.g., Gunnar & Vazquez, 2006). Following SNS activation, the adrenal medulla secretes epinephrine (E) and norepinephrine (NE) to increase heart rate, respiration, blood supply to skeletal muscles, and glucose release in the bloodstream.

The third component of the SRS is the HPA axis, which mounts more delayed, long-term responses to environmental challenge. The end point of the HPA response is cortisol release by the adrenal cortex, typically within 5 minutes after the triggering event, with a cortisol peak between 10 and 30 minutes (Gunnar & Vazquez, 2006). The main effects of cortisol are to (1) mobilize physiological and psychological resources (e.g., energy release, alertness and vigilance, memory sensitization), and (2) counter-regulate physiological effects of SNS activation, facilitating stress recovery.

The process by which the regulatory parameters of the SRS (as well as other neurobiological systems) are modified in the face of challenge is termed *allostasis* (i.e., "stability through change"). Allostasis refers to the moment to moment process of increasing or decreasing vital functions (i.e., adaptively adjusting physiological parameters within the organism's operating range) to new steady states in response to the demands of the environment and the organism's resources (McEwen & Stellar, 1993; see also Lupien et al., 2006). Allostasis functions to help the organism cope with challenging events or *stressors*, enabling short-term adaptation to environmental perturbations. However, the term allostasis is not always used consistently; for example, some authors restrict the meaning of allostasis to long-term, potentially permanent changes in the system's parameters in contexts of protracted stress (what McEwen and Wingfield [2003] labeled *allostatic states* and is now more commonly referred to as *biological embedding*).

The SRS orchestrates whole-organism reactions to challenge through a suite of coordinated responses (i.e., allostatic adjustments). Depending on the intensity and duration of a stressor, SRS activation can reorient attentional focus, increase the organism's readiness for action (e.g., by increased heart/respiratory rate and changes in blood flow to various organs), shift the balance between different memory- and learning-related processes, release glucose into the bloodstream, suppress (or enhance) reproductive functioning, regulate immune function, and so on. The concept of allostasis represents a significant point of convergence between the ACM and the ALM. The ACM explicitly embraces the concept of allostasis and describes the coordination of allostatic responses as one of the main biological functions of the SRS.

The SRS responds not only to threats and challenges in the environment but also to novelties and positive social opportunities (e.g., unexpected or exciting rewards, opportunities for status enhancement, potential sexual partners). More generally, the SRS appears to mediate susceptibility to both cost-inflicting and benefit-conferring features of the environment, operating as an amplifier (when highly responsive) or filter (when unresponsive) of various types of contextual information (see extended discussion in Ellis, Del Giudice, & Shirtcliff, 2013). As we will discuss in the next section, this dual function of the SRS is captured by the concept of biological sensitivity to context (Boyce & Ellis, 2005), which posits that a highly responsive SRS increases the organism's openness to environmental influence.

The Role of the SRS in Regulating Development of Life History Strategies

The ACM proposes that, across development, the environmental information collected by the SRS (in interaction with the child's genotype) canalizes physiological and

behavioral phenotypes to match local ecological contexts (Figure 1.3). The SRS coordinates the development of alternative life history strategies by affecting a broad suite of life history-related physiological and psychological traits, including growth and maturation, sexual and reproductive functioning, social learning, aggression, competition and risk taking, pair bonding, and related factors. The assumption is that these traits and trade-offs are regulated in ways that once—even if possibly no longer—reliably enhanced fitness across different environmental contexts.

First of all, the SRS is crucially involved in the regulation of growth and metabolism, and chronic stress has been linked to individual differences in physical growth patterns. The SRS also modulates learning in a number of different ways: HPA and autonomic profiles have been associated with individual differences in cognitive functioning, memory, and self-regulation. Second, the SRS is functionally implicated in all the components of mating and parenting, beginning with sexual maturation. The autonomic systems, HPA, and gonadal axes are connected by extensive functional cross-talk, and HPA activity is linked to variation in pubertal maturation and fecundity. Variation in SRS functioning is also associated with romantic attachment styles. In turn, attachment styles predict relationship stability, commitment, and investment—all key determinants of parenting effort in humans. More directly, SRS functioning affects parenting behavior, including controlling and intrusive parenting practices, inconsistent discipline, and parental sensitivity to children's needs and demands. In men, cortisol and testosterone work together to direct somatic and behavioral effort toward mating or parenting. Finally, sexual competition is a crucial aspect of mating effort. Dominance-seeking, aggression, and risk taking are all functionally connected to mating competition, and all are associated with SRS functioning in synergy and interaction with testosterone, serotonin, and dopamine. Furthermore, stress exposure regulates mating behavior by altering mate preferences and affecting the perceived attractiveness of potential sexual partners (reviewed in Del Giudice et al., 2011; Ellis & Del Giudice, 2014).

In summary, the SRS not only collects and encodes crucial life history-relevant information but is also involved in the regulation of all the major aspects of human life history strategies. Other systems that contribute to life history regulation include the hypothalamic-pituitary-gonadal axis, the serotonergic, dopaminergic, and oxytocinergic systems, and the immune system. Not coincidentally, all of these systems engage in extensive bidirectional cross-talk with the SRS (see e.g., Gatzke-Kopp, 2011; Miller, Chen, & Parker, 2011; van Goozen, Fairchild, Snoek, & Harold, 2007).

Patterns of Responsivity

Del Giudice and colleagues (2011) provide an extended theoretical and empirical treatment of the logic underlying the development of alternative responsivity patterns in the ACM (see Figure 1.5), including predicted relations between SRS physiology and serotonergic, dopaminergic, and oxytocinergic functioning. Here we briefly summarize this logic. In safe, low-stress environments, a highly responsive SRS enhances social learning and engagement with the external world, allowing the child to benefit more fully from social resources and opportunities (Boyce & Ellis, 2005), thus favoring development of a *sensitive* phenotype (pattern I). The association between high parental sensitivity, positive family relations, and the development of a highly responsive SRS is supported by a number of studies (e.g., Ellis et al., 2005; Evans et al. 2013; Hackman et al., 2013). According to the ACM, sensitive patterns should be characterized by moderate HPA/SNS responsivity and high PNS responsivity. A sensitive phenotype makes children better at detecting positive opportunities and learning to capitalize on them. For example, high PNS responsivity has been linked to socio-emotional competence, engagement, and self-regulation (e.g., Stifter & Corey, 2001). Social learning and sensitivity to context are especially adaptive in the context of slow life history strategies, as a form of protracted somatic investment (Kaplan & Gangestad, 2005). In very safe and protected settings, sensitive individuals will rarely experience strong, sustained activation of the SNS and HPA systems; thus, the individual enjoys the benefits of responsivity without paying significant health costs (e.g., immune, energetic).

At moderate levels of environmental stress, the cost–benefit balance begins to shift as the potential advantages of high sensitivity decrease and the physiological and health costs of maintaining a hyper-responsive SRS increase. The optimal level of SRS responsivity is predicted to fall downward, favoring development of *buffered* phenotypes (pattern II) characterized by moderately low reactivity and a slow life history strategy. Buffered responsivity is expected to be the modal pattern in most populations (with most SRS parameters set around the mean), particularly in the low-risk, middle-class populations that provide a majority of research participants in psychology and neuroscience. The emergence of buffered responsivity patterns under conditions of moderate environmental stress is empirically consistent with the *stress inoculation hypothesis*, the idea that early exposure to

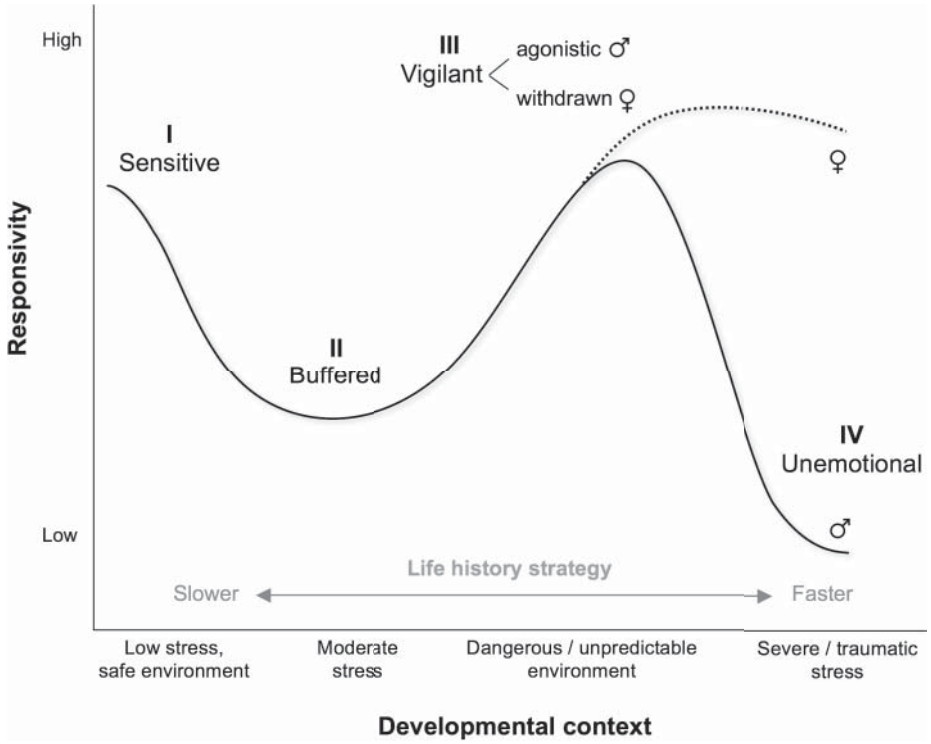


Figure 1.5 Predicted curvilinear relation between developmental context and optimal levels of stress responsivity. The figure does not imply that all components of the SRS will show identical responsivity profiles, nor that they will activate at the same time or over the same time course (see Del Giudice et al., 2011). Male and female symbols indicate sex-typical patterns of responsivity, but the model also predicts substantial within-sex variation. *Source:* Adapted from M. Del Giudice, B. J. Ellis, & E. A. Shirtcliff, The adaptive calibration model of stress responsivity, *Neuroscience & Biobehavioral Reviews*, *35*, 1577, 2011.

repeated mild stressors downregulates the SRS and leads to increased resistance to stress later on (e.g., Rutter, 1993). However, the ACM places stress inoculation in a broader theoretical perspective, in which moderate responsivity is only one out of many locally adaptive patterns of SRS functioning.

The benefits of increased responsivity rise again when the environment is perceived as dangerous and/or unpredictable. A responsive SRS enhances the individual's ability to react appropriately to dangers and threats while maintaining a high level of engagement with the social and physical environment. Moreover, engaging in fast life history strategies should lead the individual to allocate resources in a manner that discounts the long-term physiological costs of the stress response in favor of more immediate advantages. In this context, the benefits of successful defensive strategies outweigh the costs of frequent, sustained HPA and SNS activation, leading to *vigilant* phenotypes (pattern III). The predicted profile of vigilant individuals includes high HPA/SNS responsivity and low PNS responsivity (see Del Giudice et al. 2011). In turn, this physiological profile should be associated with fast life history-related traits such as fast maturation and high mating effort. Increased SRS responsivity in dangerous environments can be expected to go together with increased responsivity in other neurobiological systems; for example, hyper-dopaminergic function may contribute to the vigilant phenotype by boosting attention to threat-related cues and fast associative learning (Gatzke-Kopp, 2011).

Compared with their sensitive counterparts, vigilant individuals may show slower HPA recovery (i.e., they may take longer to return to baseline) and slower habituation (see Gunnar & Vazquez, 2006). For this reason, they are also likely to show stronger hypocortisolism following prolonged periods of stress. Although we argue that vigilant phenotypes represent biologically adaptive responses to early stress, their "hair trigger" regulation may render them especially vulnerable to breakdown or persistent dysregulation following extreme stressors. On average, males and females are expected to differ in the predominant behavioral correlates of vigilant patterns—aggressive and agonistic behavior versus anxiety and withdrawal—because of the different costs and benefits of aggression, impulsivity, and risk taking in the two sexes

(Archer, 2009; see also Martel, 2013). Indeed, several studies suggest that acute HPA activation—typical of vigilant patterns—tends to promote risk taking in males and risk aversion in females (see Mather & Lighthall, 2012; Starcke & Brand, 2012). Accordingly, high SRS responsivity can be associated with both internalizing and externalizing symptoms, especially in younger children (see Alink et al., 2008; Gunnar & Vazquez, 2006; van Goozen et al., 2007).

In very dangerous environments characterized by severe or traumatic stress, the balance shifts again toward low responsivity, especially for males who adopt a fast, mating-oriented life history strategy characterized by antagonistic competition and extreme risk taking. Such a strategy requires outright insensitivity to threats, dangers, social feedback and the social context. For an extreme risk-taker, informational insulation from environmental signals of threat is an asset, not a weakness (see also Korte et al., 2005). In particular, adopting an exploitative/antisocial interpersonal style requires one to be shielded from social rejection, disapproval, and feelings of shame (all amplified by heightened HPA responsivity; reviewed in Del Giudice et al., 2011). An *unemotional* pattern of generalized low responsivity (pattern IV) can be evolutionarily adaptive at the high-risk end of the environmental spectrum – especially in males – despite its possible negative consequences for the social group and for the individual's subjective well-being. This type of chronic low responsivity should be carefully distinguished from temporary exhaustion periods, usually arising after prolonged SRS activation in highly responsive individuals exposed to enduring stressors. The association of risk taking with low levels of SRS responsivity and basal activity is well documented, especially in males (e.g., Bubier & Drabick 2008; Halpern et al. 2002).

Unemotional profiles should be associated with high mating effort and early sexual maturation; this is consistent with the robust association between low SRS responsivity, externalizing behaviors (especially in male adolescents and adults), and callous-unemotional traits. As we discuss in a later section, this constellation of traits is associated with early maturation, precocious sexuality, and sexual promiscuity. Finally, the ACM hypothesizes two developmental pathways leading to unemotional responsivity patterns. In the first pathway, an initially responsive phenotype shifts toward unresponsivity following chronic severe stress. In particular, some children are expected to shift from pattern III to pattern IV during middle childhood or adolescence (Del Giudice et al. 2011). This prediction is consistent with the finding that associations between HPA activity and aggressive/externalizing behavior tend to be positive in preschoolers but negative in middle childhood and adulthood (Alink et al., 2008). In the second pathway, unresponsivity may develop even in low-stress environments because of strong genetic predispositions, and may be apparent already in early childhood.

The logic of sex differences in responsivity patterns is based on sexual selection theory informed by life history considerations. At the slow end of the life history continuum, both sexes engage in high parental investment, and male and female interests largely converge on long-term, committed pair bonds; sex differences in behavior are thus expected to be relatively small. As environmental danger and unpredictability increase, males benefit by shifting to low-investment, high-mating strategies; females, however, do not have the same flexibility since they benefit much less from mating with multiple partners and incur higher fixed costs through childbearing. Thus, male and female strategies should increasingly diverge at moderate to high levels of environmental danger/unpredictability. In addition, sexual competition takes different forms in males and females, with males engaging in more physical aggression and substantially higher levels of risk taking (e.g., Archer, 2009; Wilson, Daly, & Pound, 2002). As mating effort increases, sexual competition becomes stronger and sex differences in competitive strategies become more apparent. For these reasons, sex differences in responsivity patterns and in the associated behavioral phenotypes should be relatively small at low to moderate levels of environmental stress (patterns I and II) and increase in stressful environments (pattern III). Finally, we expect males to be overrepresented as high-risk, low-investment strategists (pattern IV).

The shifting equilibrium between costs and benefits of responsivity is predicted to result in a complex curvilinear relation between environmental stress and SRS responsivity (Figure 1.5). The ACM taxonomy of responsivity patterns is supported by preliminary empirical evidence on autonomic responsivity in middle childhood (Del Giudice, Hinnant, Ellis, & El-Sheikh, 2012). While the SRS has a crucial role in directing the development of alternative life history strategies, it does so in interaction with other neurobiological systems. Accordingly, the four responsivity patterns described in the ACM are characterized not just by different profiles of SRS functioning, but also by functionally organized individual differences in behavior, in the physiology of the hypothalamic-pituitary-gonadal axis, in serotonergic and dopaminergic pathways, and other systems (Del Giudice et al., 2011). Each pattern reflects a unique combination of costs, benefits, and specific vulnerabilities to pathology. Finally, it should be noted that

Figure 1.5 depicts an idealized, population-level reaction norm. In practice, different individuals may respond differently to the same level of environmental stress and show different degrees of plasticity—owing to different environmental sampling histories and the effects of genetic, epigenetic, and endophenotypic variation—as discussed in the section on differential susceptibility.

ALM and ACM: A Comparison

Allostatic load is a label for the long-term costs of allostasis; it is often described as the "wear and tear" that results from repeated allostatic adjustments (i.e., adaptation to stressors), exposing the organism to adverse health consequences. The ALM emphasizes that biological responses to threat, while essential for survival, have negative long-term effects that promote illness. The *benefits* of mounting biological responses to threat are traded off against *costs* to mental and physical health, and these costs (allostatic load) increase as the organism ages.

Basic tenets of the ACM an ALM are compared in detail in Ellis and Del Giudice (2014) and juxtaposed in Table 1.1. Both the ACM and ALM emphasize the adaptive nature of short-term physiological responses to stress (Table 1.1, row labeled *Activation of autonomic, neuroendocrine, metabolic, and immune systems*). Further, the ACM concurs with the ALM regarding the effects of childhood stress and adversity on regulation of allostatic mechanisms. Indeed, a substantial body of research has now documented biological embedding of early life stress in SRS parameter values (Table 1.1, row labeled *Changes in allostatic mechanisms*). In the ALM, however, this biological embedding is construed negatively, as the result of cumulative stress exposures that predispose the individual to morbidities and premature mortality. As shown in Table 1.1 (row labeled *Cognitive, behavioral, and emotional impairments in children*), some of these outcomes include lower performance on standard tests of intelligence and executive functions and increased mental health problems (reviewed in Ellis & Del Giudice, 2014). The ACM also acknowledges that chronic SRS activation carries substantial costs, in terms of biological fitness as well as health and well-being. While the ACM stresses conditional adaptation, it leaves open the possibility that, for a number of reasons, some developmental outcomes are biologically maladaptive. In terms of proximal responses

TABLE 1.1 Comparison of Adaptive Calibration Model and Allostatic Load Model[1]

Responses to psychosocial stress/ unpredictability	Examples of response	ACM	ALM
Activation of autonomic, neuroendocrine, metabolic, and immune systems	• Acute SNS and HPA responses mobilize energy reserves; protect against septic shock and nutrient deprivation; permit fight or flight responses that are normally protective against danger. • Inflammation accelerates the healing of wounds.	Central to theory	Central to theory
Changes in allostatic mechanisms	• Increased inflammatory tone • Elevated cortisol and catecholamines • Muted cardiovascular responses to stress	Central to theory	Central to theory
Cognitive, behavioral, and emotional impairments in children	• *Reduced scores on standard tests of intelligence, language, memory, and other abilities* • *Early onset and increased prevalence of psychopathology*	*Not inconsistent with theory*	*Central to theory*
Cognitive, behavioral, and emotional adaptations to stress in children	• *Tailoring of emotion systems, arousal responses, and perceptual abilities to the detection and monitoring of danger* • *Development of insecure attachments, mistrustful internal working models, opportunistic interpersonal orientations, oppositional-aggressive behavior*	*Central to theory*	*Not inconsistent with theory*
Long-term deleterious outcomes	• *Cognitive and physical impairments* • *Depression* • *Increased risk of cardiovascular disease and all-cause mortality*	*Not inconsistent with theory*	*Central to theory*
Long-term adaptive changes in biobehavioral systems	• **Adaptive calibration of autonomic, neuroendocrine, metabolic, and immunological systems** • **Regulation of alternative life history strategies to match ecological conditions**	**Central to theory**	**Beyond the scope of the theory**

[1] *Light shading* indicates a difference in emphasis between the ACM and ALM. **Dark shading** indicates a qualitative divergence between the two theories. Reprinted from B. J. Ellis & M. Del Giudice, Beyond allostatic load: Rethinking the role of stress in regulating human development, *Development and Psychopathology*, *20,* 9, 2014.

to childhood adversity, The ACM and ALM mainly differ in their emphasis on the benefits (ACM) versus the costs (ALM) of allostatic adjustments (shown in italics in Table 1.1).

Cost–Benefit Trade-Offs in the Development of Alternative Phenotypes.

The ACM and ALM diverge considerably in how they deal with cost–benefit trade-offs, individual differences, and long-term developmental changes. From an evolutionary standpoint, the ALM makes no distinction between the two meanings of *adaptive* and *maladaptive*, as conceptualized from a mental health versus evolutionary perspective. Indeed, maladaptation is typically inferred whenever there are substantial costs to the organism. For example, if elevated cortisol levels in adolescents are associated with an undesirable outcome, such as reduced working memory, then elevated cortisol is classified as a marker of allostatic load (see Juster et al., 2011). This reasoning ignores the crucial fact that biological processes are maintained by natural selection when their fitness benefits outweigh the costs, not when they are cost-free; indeed, even large costs can be offset by large enough expected benefits. Although there are practical reasons for identifying allostatic load biomarkers, this approach alone is incomplete because it only specifies dysfunction and not the adaptive functions of developmentally calibrated biological parameters.

Because of the failure to distinguish between (mal)-adaptive and (un)desirable outcomes, most applications of the ALM do not adequately address the trade-offs involved in the development of physiological and behavioral phenotypes; as a consequence, the ALM literature often lacks a theory of adaptive individual variation in stress responsivity (see Korte et al., 2005, for a notable exception). Instead the ALM focuses on optimal SRS parameter values, as defined by covariation with desirable health outcomes; deviations from these optimal settings form the basis of dysregulation. The applied goal of the ALM is to identify nonoptimal autonomic, neuroendocrine, metabolic, and immune profiles that predict psychiatric and biomedical disorder (Table 1.1).

In contrast, the ACM emphasizes adaptation in context and posits that optimal SRS parameter values vary as a function of environmental conditions. From this perspective, the notion of globally optimal baseline or responsivity levels for SRS parameters is highly problematic; indeed, the entire literature on biological sensitivity to context demonstrates that the value of hypo-responsivity versus hyper-responsivity is context dependent (see extended discussion that follows). The ACM gives full consideration to the costs and benefits of SRS responsivity. For example, consider heightened stress responsivity in a dangerous, unpredictable environment. In the ACM, it is hypothesized that the costs of repeated SRS activation are offset by improved management of danger. Although the system is on a hair trigger, with a resulting increase in anxiety and/or aggression, few instances of actual danger will be missed. In addition, engaging in a fast, present-oriented life history strategy makes it optimal to discount the long-term health costs of chronic SRS activation if the immediate benefits are large enough (for in-depth discussion, see Del Giudice et al., 2011).

In the ALM framework, the same pattern of responsivity would be treated as dysfunctional because the stress response is deployed even in absence of true dangers (e.g., "excessive" response, "unnecessary" triggering; e.g., Lupien et al., 2006) and because of the associated undesirable states and health risks (e.g., interpersonal distress). However, this approach fails to consider that biological defenses are usually designed by natural selection to accept a high rate of false positives. In most instances, unnecessary responding is an adaptive feature of the system—though a costly one—rather than a sign of dysregulation or malfunction.

Long-Term Adaptations to Stress: The Developmental Regulation of Alternative Life History Strategies

According to the ACM, childhood adaptations to stress may eventuate in long-term adaptive changes in biobehavioral systems. Herein lies the key difference between the ACM and ALM (shown in bold in Table 1.1). In the ALM, energy devoted to mounting autonomic, neuroendocrine, metabolic, and immune responses to threat is traded off against wear and tear on multiple organ systems. The ACM extends this logic by conceptualizing these trade-offs as decision nodes in allocation of resources. It is through this chain of resource-allocation decisions—instantiated in the regulatory parameters of the SRS and related biological systems—that the developing organism adapts to local conditions. Thus, the ACM shifts the emphasis from dysregulation to conditional adaptation (Table 1.1).

From an evolutionary perspective, increased wear and tear is a cost of pursuing a fast life history strategy. The fast strategy is instantiated in a chain of resource allocation decisions over the life course that "make the best of a bad situation" by trading off survival for reproduction. Thus, many biologically embedded changes that the ALM conceptualizes as costs (e.g., heightened HPA reactivity)

the ACM views as decision nodes in development of a faster strategy. Conversely, slower life history strategies involve greater allocation of resources toward enhancing growth, vitality, and long-term survival (e.g., DNA repair). Development of a fast life history strategy in dangerous and unpredictable contexts is not impairment or dysfunction; it is a coherent, organized response to stress that has been shaped by a natural selective history of recurring exposures to harsh and unpredictable environments.

Implications for the Core Points of Developmental Psychopathology

The integrative perspective on stress responsivity presented in this section touches on many core points of developmental psychopathology. First of all, the ACM illustrates that evolutionary principles are not just relevant to the behavioral level of analysis. On the contrary, they can be fruitfully applied to understand the role of *brain and neurobiological factors* in development, and employed to craft detailed models of neurobiological functioning. Like the ALM, the ACM helps synthesize *normal and pathological development* in a single framework; however, the ACM goes beyond the ALM with a broader view of costs and benefits and a detailed theory of adaptive matching between environment and phenotype. The ACM fully incorporates the *contextualism* of life history theory; in this perspective there is no single optimal phenotype or developmental trajectory—only locally adaptive, contextually sensitive strategies with their baggage of costs and trade-offs.

An important feature of the logic of responsivity patterns is that it invites—indeed, virtually requires—a *person-centered approach* to individual differences in stress physiology and neurobiology (e.g., Del Giudice et al., 2012). Even the schematic model depicted in Figure 1.5 shows that causal relations between environmental variables and developmental outcomes are predicted to be highly *nonlinear;* if the model is correct, attempts to model stress responsivity with standard linear models are doomed to yield inconsistent and misleading results. Responsivity patterns also provide a striking illustration of *equifinality* and *multifinality* in the interplay between environment, neurobiology, and behavior. In the ACM, dramatically different environments may entrain the development of similar responsivity profiles; for example, sensitive and vigilant patterns are both hypothesized to imply high HPA responsivity. In turn, similar responsivity profiles may predict remarkably different behavioral correlates—for example low impulsivity in sensitive patterns versus high impulsivity in vigilant patterns. While the resulting developmental trajectories may look empirically baffling, they become tractable when they are framed in the appropriate functional perspective.

Finally, the ACM potentially explains why, in the empirical literature, heightened and dampened stress responsivity seem to work as *risk factors* in some studies and as *protective factors* in others. Both sensitive and buffered phenotypes are associated with lower levels of psychosocial stress and concomitant development of slower life history strategies, whereas both vigilant phenotypes and unemotional phenotypes are associated with higher levels of psychosocial stress and concomitant development of faster life history strategies (Figure 1.5). Depending on the specific outcomes under investigation, heightened reactivity may look like a protective factor in sensitive phenotypes and a risk factor in vigilant phenotypes, while dampened reactivity may look like a protective factor in buffered phenotypes and a risk factor in unemotional phenotypes. As we discuss in a later section, the picture is further complicated by the possibility that some disorders are actually more likely to occur at the *slow* end of the life history continuum. Taming this complex interplay of cause and effect will only be possible with the help of a detailed theory of biological and developmental trade-offs.

BEYOND DIATHESIS-STRESS: DIFFERENTIAL SUSCEPTIBILITY TO ENVIRONMENTAL INFLUENCES

As discussed in the preceding sections, early experiences can have profound and lasting effects on psychological development. Nevertheless, people vary dramatically in the extent to which they respond to their social and physical environment. Similar developmental experiences may have profound effects on some individuals and slight or even negligible effects on others. The idea that some individuals are more susceptible than others to environmental adversity has a long history in psychology, and is captured by the complementary concepts of *vulnerability* and *resilience* (for a recent review see Compas & Andreotti, 2013). Individual differences in vulnerability may be determined by a combination of genetic factors and previous experiences, and explain why, for example, only some children develop such undesirable outcomes as aggression, insecure attachment, and cognitive difficulties in response to stressful or impoverished rearing experiences. The concept of vulnerability lies at the heart of the diathesis-stress model of psychopathology, which is arguably the dominant paradigm in the field.

Against this background, recent empirical and theoretical advances have brought about a conceptual revolution in the study of organism × environment interactions. As has become increasingly apparent, many of the same factors that determine increased vulnerability to stress and adversity also confer enhanced responsivity to the *positive*, supportive aspects of the environment (Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Boyce & Ellis, 2005). No longer confined to vulnerability, susceptibility to environmental influence can be understood as a generalized trait that increases the range of potential developmental outcomes in a bivalent fashion. While some individuals are disproportionately likely to suffer damage if exposed to harshness and adversity, they are also disproportionately likely to benefit from nurturance and support. Here we introduce the concept of *differential susceptibility*, discuss its importance for developmental processes, and review the models that have been proposed to explain the evolution of systematic individual differences in susceptibility to the environment. For further discussion see Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn (2011a).

Differential Susceptibility: Orchids and Dandelions

In the differential susceptibility literature, highly susceptible children are referred to by the shorthand designation of *orchid children*, signifying their special sensitivity to both highly stressful and highly nurturing environments. For example, highly irritable infants tend to become less sociable than moderately irritable infants when they are insecurely attached, but *more* sociable if they experience secure attachment relationships (Stupica, Sherman, & Cassidy, 2011). Similarly, children with difficult temperament develop more behavior problems when they experience low-quality care, but *fewer* behavior problems when reared in a high-quality context (Pluess & Belsky, 2009). Children who are low in susceptibility to environmental influence, on the other hand, are designated as *dandelion children*, reflecting their relative ability to function adequately in species-typical circumstances of all varieties (Boyce & Ellis, 2005). Differential susceptibility can be distinguished from both vulnerability (specific sensitivity to negative environmental factors) and the more recent concept of *vantage sensitivity* (specific sensitivity to positive environmental factors; see Pluess & Belsky, 2013).

Converging evidence from different areas of research indicates that highly susceptible children share a cluster of interrelated traits including high physiological reactivity across multiple systems (including the SRS), negative emotionality, and difficult temperament (reviewed in Belsky et al., 2007; Boyce & Ellis, 2005; Ellis et al., 2011a). While the genetics of susceptibility is still incompletely understood, genes involved in serotonergic and dopaminergic pathways appear to play a central role (e.g., Bakermans-Kranenburg & Van IJzendoorn, 2011; Belsky & Beaver, 2011; Heiming & Sachser, 2011); as discussed above, serotonergic and dopaminergic pathways interact bidirectionally with the SRS. Together, these interconnected systems contribute to a general phenotypic dimension of *neurobiological susceptibility* to the environment (see Boyce & Ellis, 2005; Ellis et al., 2011a).

Figure 1.6 illustrates the concept of differential susceptibility by showing the reaction norms of high susceptibility and low susceptibility individuals in a population. Differential susceptibility requires that reaction norms cross somewhere in the middle range of environmental variation. Figure 1.6 may represent either a genotype × environment (GxE) or phenotype × environment (PxE) interaction, depending on whether individuals are distinguished by their genotype (e.g., variants of the serotonin transporter gene) or phenotype (e.g., high stress responsivity, negative emotionality).

In summary, differential susceptibility is a special case of developmental plasticity; its defining characteristics are (1) a crossover interaction in which more susceptible individuals have a broader reaction range and steeper reaction norms (compare with Figure 1.2b), and (2) a clear positive–negative polarity of the relevant environmental dimension. These two factors together result in systematic variation in the strength of relations between environmental exposures and developmental outcomes that maps on to the orchid–dandelion distinction. Whether environmental conditions can be labeled as "positive" or "negative" in a biological sense depends on their likely effects on an individual's fitness. As we discussed in the section on life history theory, many of the negative environmental factors investigated by developmental psychologists are ultimately correlated with danger, unpredictability, and resource scarcity.

Differential susceptibility has far-reaching implications for developmental psychology and psychopathology; it moderates the effects of environmental exposures on developmental and life outcomes. Ultimately, this means that the development of some individuals, more than others, will be influenced by their experiences and environments—even if these were exactly the same. Differential susceptibility to the environment, therefore, constitutes a central mechanism in the regulation of alternative patterns of human development. Over the last few years, the concept

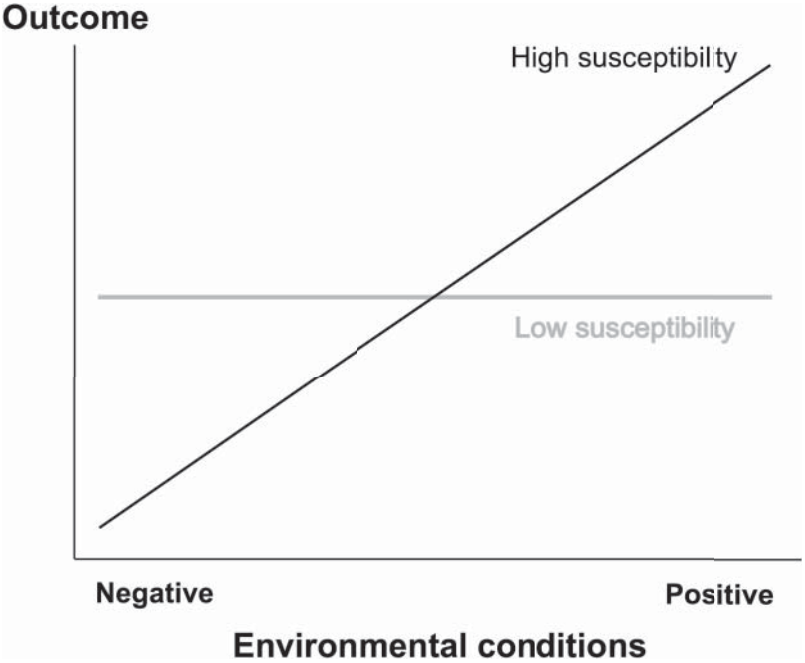


Figure 1.6 Reaction norms showing differential susceptibility. More susceptible individuals are disproportionally affected by both negative and positive environments.

of differential susceptibility has generated considerable enthusiasm in developmental psychology and has rapidly become the foundation of an expanding empirical literature. Evidence of differential susceptibility exists for a number of traits and outcomes including prosociality, sociability, externalizing and internalizing symptoms, depression, and timing of puberty (see Ellis & Boyce, 2011, and other papers in that special issue).

Evolutionary Models of Differential Susceptibility

Individual differences in neurobiological susceptibility to the environment raise many important questions. Why do they exist in the first place? Are they adaptive—and if so, what evolutionary processes are responsible for their maintenance in human populations? When do they emerge in development, and by what interplay of genetic and environmental factors? Evolutionary models of differential susceptibility (Belsky, 1997, 2005; Boyce & Ellis, 2005; Ellis et al., 2006) have explored different explanations for the maintenance of individual differences—balancing selection, selection for conditional adaptation, and selection for diversified bet-hedging. These explanations are not mutually exclusive, and indeed they can potentially be integrated within a single theoretical framework.We now briefly review each in turn.

Maintenance of Differential Susceptibility Through Balancing Selection

There is considerable evidence that individual differences in susceptibility can be attributed—at least in part—to individual differences in genotype. The best examples include allelic variation in the serotonin-transporter gene promoter (5-HTTPLR) and the dopamine D4 receptor gene (DRD4). Recent meta-analyses have demonstrated that these polymorphisms moderate environmental effects in a "for better *and* for worse" manner; that is, different variants of these genes are generally associated with differential susceptibility to both stressful and nurturing environmental conditions (Bakermans-Kranenburg & van IJzendoorn, 2011; van IJzendoorn, Belsky, & Bakermans-Kranenburg, 2012). Other genetic variants involved in differential susceptibility have been identified, not only in dopaminergic and serotonergic pathways but also in the oxytocinergic system and the HPA axis (see Cicchetti & Rogosch, 2012; Ellis et al., 2011a).

As discussed in a previous section, adaptive genotypic differences in a population may be maintained by various forms of balancing selection, including negative frequency-dependent selection. Building on the work of Wilson and Yoshimura (1994), Ellis and colleagues (2006) proposed a negative frequency-dependent model of the maintenance of genetically regulated variation

in differential susceptibility to the environment. In this model, developmental specialists are defined by relatively flat reaction norms, such that phenotypic development is minimally sensitive to normal environmental variation. Different developmental specialists are instead characterized by different genetically regulated behavioral types (e.g., shy vs. bold, slow vs. fast life history strategy). Although developmental specialists lack plasticity, their specialized personalities enable them to thrive in the niche that they are specialized to exploit. Developmental generalists, by contrast, are defined by relatively steep reaction norms, such that phenotypic development is highly context-dependent. Different developmental generalists thus experience different developmental outcomes based on their rearing experiences. All else being equal, the presence of multiple niches in a single environment will favor developmental specialists over developmental generalists when individuals can evaluate and select niches that increase their fitness. This is because specialists outperform generalists in their preferred niche. However, multi-niche environments are often characterized by negative density-dependence, meaning that as a given niche becomes more crowded (i.e., overexploited relative to its size), the fitness benefits of specializing in that niche decrease. This is the cost of specialization.

Models of genotypic variation in susceptibility are still in the formative stages. The general hypothesis that frequency-dependent selection can maintain individual variation in susceptibility or responsiveness to the environment is well supported by mathematical models (Wilson & Yoshimura, 1994; see also Wolf, van Doorn, & Weissing, 2008) but has not yet generated empirical work in humans. Another plausible but less explored possibility is that other types of balancing selection—for example spatially and temporally fluctuating selection—may coexist with frequency-dependent selection and contribute to maintain genotypic variation in human populations (see Ellis et al., 2011a).

Development of Differential Susceptibility Through Conditional Adaptation

Depending on the structure of the environment and of an organism's life cycle, conditional adaptation can be maintained alongside genetic variation by spatially and temporally fluctuating selection pressures (see Del Giudice, 2012, under review). The theory of Biological Sensitivity to Context (Boyce & Ellis, 2005) posits a *nonrandom distribution* of neurobiological susceptibility to the environment within populations that emerges through conditional adaptation to variable environmental conditions. From this perspective, differential susceptibility results, in part, from individuals tracking different environmental conditions and altering their development to match those conditions. The assumption is that this matching process promoted fitness across heterogeneous environmental contexts over human evolution.

Biological sensitivity to context theory identified physiological mechanisms of differential susceptibility—autonomic, adrenocortical, and immune reactivity to psychosocial stressors—and proposed that this psychobiologic reactivity moderated the effects of early environmental exposures on physical and mental health outcomes in the bivalent manner discussed above (reviewed in Pluess & Belsky, 2009; Ellis et al., 2011a). This dual function signified the need to conceptualize stress reactivity more broadly as biological sensitivity to context, which Boyce and Ellis (2005) defined as neurobiological susceptibility to both cost-inflicting and benefit-conferring features of the environment and operationalized as heightened reactivity in one or more of the stress response systems. In total, biological sensitivity to context theory proposed that individual differences in the magnitude of biological stress responses function to regulate openness or susceptibility to environmental influences, ranging from harmful to protective.

As discussed in the previous section, the ACM explicitly builds on the logic of biological sensitivity to context. In a nutshell, the theory of biological sensitivity to context proposes that heightened susceptibility is adaptive at both ends of the environmental continuum—in both highly stressful and highly protected environments. This results in a U-shaped curvilinear relation between early stress/adversity and susceptibility to later environmental effects (Boyce & Ellis, 2005). Consistent with the focus of biological sensitivity to context on adaptive plasticity, the ACM views early experience as a crucial determinant of individual differences in neurobiological susceptibility to the environment. Potential cues of danger and adversity versus safety and support include prenatal stress (e.g., fetal exposure to stress hormones), parenting quality, family stability and conflict, attachment security, and neighborhood quality.

These contextual factors are hypothesized to affect development mainly by upregulating or downregulating the activity of infants' and children's stress response systems, as shown in Figure 1.5. Whereas the original conceptualization of biological sensitivity context focused primarily on the functions of high stress responsivity, the ACM expanded this conceptualization to encompass the functions of low stress responsivity—and thus added

the unemotional pattern shown in Figure 1.5. This addition turned the original U-shaped curve into a more complex function (see discussion of the ACM responsivity patterns in the previous section). Like the theory of biological sensitivity to context, the ACM conceptualizes variation in neurobiological susceptibility to the environment as part of a conditional adaptation process that matches stress response profiles to local conditions. This conceptualization is supported by a large empirical literature demonstrating changes in SNS, PNS, and HPA parameter values over development in response to different developmental experiences (reviewed in Boyce & Ellis, 2005; Del Giudice et al., 2011), including prenatal experiences such as infections, fetal undernutrition, and exposure to maternal stress hormones (Pluess & Belsky, 2011).

Differential Susceptibility as Adaptive Stochastic Variation

According to the theory of differential susceptibility advanced by Belsky (1997, 2005), the main adaptive function of differential susceptibility is spreading the risk of mismatch by making some individuals resistant to environmental influences, including—but not limited to—the influences of parental behavior on children's development. When early cues correctly predict future states of the environment, susceptible individuals benefit from enhanced phenotype-environment matching; but when prediction fails (for example because the environment undergoes sudden and unpredictable changes), they end up developing a mismatched phenotype and potentially suffering large fitness costs as a result. Individuals who follow a fixed developmental trajectory may avoid the fate of their more susceptible counterparts when ecological cues fail to predict later environmental states. Thus, for a parent, producing offspring with varying degrees of susceptibility works as an insurance against future unpredictability.

In evolutionary terms, this is an example of reproductive *bet-hedging*—a strategy that reduces average individual fitness in the short term, but enhances the long-term reproductive success of the genetic lineage by decreasing fitness variance across generations (Bull, 1987; Seger & Brockmann, 1987; Starrfelt & Kokko, 2012). More specifically, differential susceptibility is conceptualized as an instance of *diversified* bet-hedging, that is, a strategy that reduces fitness variance between generations by increasing phenotypic variability among offspring (Philippi & Seger, 1989). Such a strategy could be maintained by an evolutionary history of exposure to environments that fluctuated unpredictably over time. Bet-hedging strategies increase the probability of achieving some reproductive success in every generation while limiting success in good conditions and shielding against total failure in bad (for a detailed treatment see Starrfelt & Kokko, 2012).

Theory and data from evolutionary biology indicate that fluctuating selection pressures, if sufficiently strong, can support variable or random generation of offspring phenotypes ("adaptive coin-flipping") arising from a monomorphic genetic structure. This strategy can be implemented through a stochastic developmental switch (presumably instantiated by epigenetic mechanisms), which generates one of several alternative phenotypes according to a probabilistic rule. For example, in a range of animal species, when mothers cannot forecast the likely environment of their offspring, or environmental cues in the maternal generation suggest that the offspring environment is likely to vary unpredictably, mothers hedge their bets by increasing variation in offspring phenotypes (Crean & Marshall, 2009). Although temporally fluctuating selection pressures can select for stochastic phenotypic variation, diversified bet-hedging cannot be instantiated through *genetic* polymorphisms because the resulting phenotypes do not all have the same average fitness (Bull, 1987; Philippi & Seger, 1989). Thus, the bet-hedging hypothesis can explain adaptive stochastic variation in susceptibility but not genotypic variation, in contrast with early formulations of the theory (Belsky, 1997). More recent formulations of the theory (e.g., Belsky, 2005; Pluess & Belsky, 2011) also acknowledge the role of early environmental influences—especially prenatal exposure to stress—in shaping individual levels of susceptibility.

In total, the bet-hedging hypothesis of differential susceptibility is valuable in that it provides a plausible adaptive explanation for stochastic variation in susceptibility to environmental influence. More generally, the larger framework advanced by Belsky (2005) emphasizes the potential adaptive significance of unsystematic within-family variability in susceptibility to the environment. However, adaptive stochastic variation coexists with many sources of neutral or maladaptive unsystematic variation, which result from the random effects of sexual recombination, nonadaptive phenotypic plasticity, random perturbations in developmental processes, harmful genetic and epigenetic mutations, and so forth. The empirical challenge for the theory advanced by Belsky (1997, 2005) is that it may be extremely difficult to distinguish between adaptive within-family variation that has been shaped by natural selection and within-family variation that is truly random and non-adaptive (see Ellis et al., 2011a).

Differential Susceptibility as a Model of Organism–Environment Interplay: The Case of Pubertal Development

The differential susceptibility framework returns us to the centrality of the phenotype and the complexity of organism–environment interplay. Susceptibility to the environment is instantiated in the biology of the nervous system; it is *neurobiological* susceptibility. Genetic susceptibility factors operate through neurobiological processes, and behavioral indicators of susceptibility are grounded in neurobiology. Neurobiological susceptibility itself is not a static trait; it develops and changes in response to genetic and environmental influences, which become incorporated into the phenotype over time. Genetic factors, environmental factors, and the extant phenotype all interact in intricate ways that are not yet entirely understood, including both systematic effects and stochastic processes.

A good demonstration of the real-life complexity of differential susceptibility is the interplay of early life stress, stress responsivity, and polymorphic variation in the estrogen receptor α gene (*ESR1*) in the regulation of pubertal development. The timing of pubertal development is a central life history trait; as discussed in a previous section, Belsky and colleagues (1991) first predicted that early stress would entrain fast life history strategies, leading to accelerated puberty timing (the *psychosocial acceleration theory*; see Ellis, 2004). Specifically, the theory posits that ecological stressors in and around the family create conditions that undermine parental functioning and lower the quality of parental investment—such as by escalating marital conflict, increasing negativity and coercion in parent–child relationships, and reducing positivity and support in parent–child relationships. According to the theory, children respond to these familial and ecological conditions (particularly those experienced in the first 5–7 years of life) by developing in a manner that speeds up pubertal maturation, anticipates the onset of sexual activity, and promotes the development of a cluster of behavioral traits associated with fast life histories, including impulsivity and unstable pair bonds.

A study by Ellis and Essex (2007) investigated the psychosocial acceleration theory in the Wisconsin Study of Families and Work. Consistent with predictions, higher quality parent–child relationships in preschool—more parental warmth and family positivity, less parent–child stress and conflict—forecast slower pubertal maturation in daughters. Although this association proved robust, the unique effect of parent–child relationships on puberty was relatively small. However, theories of differential susceptibility suggest that the weak main effects of environmental variables on many developmental outcomes may often reflect the fact the children differ in whether, how, and how much they are affected by rearing experiences. As articulated by Belsky (2000), the weak main effects of parenting variables on pubertal timing may overestimate the impact of family environments in some children (dandelions, more fixed reproductive development) and underestimate it in others (orchids, more plastic reproductive development).

This hypothesis was supported in a later study of the same data set (Ellis, Shirtcliff, Boyce, Deadorff, & Essex, 2011b). Specifically, higher SRS responsivity in first grade—a key facet of neurobiological susceptibility—moderated the effects of parental behavior on maturation: lower quality parent–child relationships forecast faster initial tempo of puberty and earlier pubertal timing, but only among children showing heightened SNS/HPA reactivity. In other words, the data revealed a clear PxE interaction between parent–child relationships and SRS responsivity, consistent with the biological sensitivity to context account of differential susceptibility (Boyce & Ellis, 2005).

This, however, is only part of the story. Neurobiological susceptibility is not a fixed trait but develops over time through the interplay of various causal factors—including genetic variation and early environmental effects. In the same dataset, growing up in either highly supportive or highly stressful home environments predicted development of high SNS reactivity (consistent with the U-shaped curve predicted by biological sensitivity to context theory; see previous discussion), whereas growing up in a highly stressful home environment predicted heightened HPA activation (Ellis, Essex, & Boyce, 2005). Thus, under conditions of early environmental stress and uncertainty, indexed by coercive and unsupportive family relationships, individuals developed heightened neurobiological susceptibility to the environment (as indexed by SNS and HPA activation) and subsequently accelerated pubertal maturation in early adolescence, with family stress and neurobiological susceptibility acting synergistically in this process. Heightened neurobiological susceptibility thus enabled a stronger pubertal response to adversity. According to psychosocial acceleration theory, this response may represent a strategic—that is, functional—way of developing under stress.

The other side of the coin is that under conditions of early environmental protection and stability, indexed by positive and supportive family relationships, individuals also developed heightened neurobiological susceptibility,

which in combination with high-quality parent–child relationships forecast slower initial pubertal tempo and later pubertal timing (Ellis et al., 2011b). In this case, heightened neurobiological susceptibility enhanced responsiveness to environmental resources and support. As suggested by life history models, the resulting pattern of late sexual maturation may also constitute adaptive variation. Specifically, Ellis (2004) hypothesized that children have been selected to capitalize on the benefits of high quality parental investment and reduce the costs of low quality parental investment by contingently altering the length of childhood. Given high family resources and support and biological sensitivity to these development-enhancing contexts, extending childhood by delaying onset of puberty or slowing pubertal tempo may function to improve socio-competitive competencies (i.e., embodied capital) that ultimately increase reproductive potential.

Timing of puberty depends not only on the environment; indeed, all measures of pubertal development also show heritability values indicative of robust genotypic effects (see Ellis, 2004). As can be expected from the vantage point of differential susceptibility theory, recent evidence indicates that GxE interactions are also involved in the regulation of pubertal development (Manuck, Craig, Flory, Halder, & Ferrell, 2011). Consistent with past research (reviewed in Ellis, 2004), Manuck and colleagues (2011) found that women who reported being raised in families characterized by distant interpersonal relationships and high levels of conflict tended to reach menarche earlier than women raised in close families with little discord. However, this effect was moderated by variation in the gene coding for estrogen receptor α (*ESR1*). Among women who were homozygous for minor alleles of the two *ESR1* polymorphisms examined in the study, a childhood history of low-quality family relationships was associated with earlier age of menarche compared with a childhood history of high-quality family relationships; no such effect was found among women with other *ESR1* genotypes. Intriguingly, estrogen receptor α is highly expressed in the hypothalamus, where it regulates the activity of the HPA axis (Bao, Meynen, & Swaab, 2008). Thus, among its other possible effects, variation in *ESR1* may affect pubertal development by contributing to the development of higher or lower levels of neurobiological susceptibility.

In summary, regulation of pubertal development depends on genetic factors and GxE interactions, such as between *ESR1* variation and family stress; on environmental factors, such as energetics and psychosocial stress; on interactions between these environmental factors and extant phenotypic characteristics that modulate neurobiological susceptibility to the environment, such as SRS responsivity; on the developmental calibration of these stress response systems, which filter and embed information about environmental stress and support, mediating the organism's openness to environmental inputs; and on genetic influences and GxE interactions in the regulation of neurobiological susceptibility to the environment (see extended discussion in Ellis, 2013). At the nexus of all of these processes is the organized phenotype, which exists from conception; modulates, integrates, and retains genetic and environmental effects; and is the basis of differential susceptibility. Yet even if all of these factors are taken into account, there is still be much unexplained variation due to stochastic developmental processes.

This is the tangled web of development. Theoretical models propose that differential susceptibility develops through a mixture of genetic regulation—maintained by balancing selection—and environmental regulation that enables conditional adaptation. Whereas balancing selection and conditional adaptation result in systematic variation in neurobiological susceptibility to the environment, unsystematic variation may also be maintained by natural selection as an insurance policy against unpredictably changing environments (diversified bet-hedging). Taken together, these evolutionary processes may result in large individual differences in whether, how, and how much people are affected by their experiences. Differential susceptibility, therefore, can be expected to play a key role in moderating the effects of environmental conditions on developmental outcomes, including the development of life history strategies.

Implications for the Core Points of Developmental Psychopathology

The theory of differential susceptibility brings about a fundamental change in the way one thinks about *risk* and *resilience* in development. First, the same genetic or phenotypic factor can behave as *both* a risk and a protective factor depending on the ecological context. Second, the very children whose heightened responsivity appears to make them vulnerable to developing psychopathology (orchid children) may also be most able to benefit from positive, supportive environments and interventions. The divergent outcomes associated with highly susceptible phenotypes also set the stage for pervasive, systematic manifestations of *multifinality* in development.

As we have seen, the development of susceptibility is itself a dynamic process, taking place through an intricate interplay of genetic, environmental, and stochastic

effects. This perspective combines the *contextualism* of conditional adaptation with new and potentially fruitful explanations of *probabilistic causality*. Whereas standard approaches tend to see probabilistic causality as opposed to biological adaptation, the theory of bet-hedging shows how natural selection can make adaptive use of developmental randomness as a response to unpredictable environmental change.

Still other implications for developmental psychopathology stem from the centrality of the phenotype in regulating differential susceptibility. First, a view of the phenotype as the result of sequential organism–environment interplay blurs the distinction between variable-centered and *person-centered approaches*. Second, the concept of neurobiological susceptibility is a powerful reminder that genetic, epigenetic, and environmental effects must ultimately be understood in terms of their influence on *brain and neurobiological* pathways; it also illustrates how multiple pathways and molecules—for example serotonin, dopamine, cortisol, and sex hormones—may exert synergistic effects by converging on general, adaptive dimensions of phenotypic variation.

BEYOND THE DSM: A LIFE HISTORY FRAMEWORK FOR MENTAL DISORDERS

In the preceding sections we showed that EDP provides an integrative biological perspective on human development, and sheds light on the origin and function of individual differences in life history strategy, developmental plasticity, and physiological responsivity to stress. We now take this approach one step further and show how the principles of life history theory can be employed to outline a unifying framework for the analysis and classification of mental disorders (for a detailed exposition see Del Giudice, 2014a, 2014b). For the sake of simplicity and consistency with standard usage, in this section we employ the term *disorder* as a synonym for diagnosable condition—regardless of whether the condition represents a harmful dysfunction in the narrow sense (Wakefield, 1992).

Limitations of Current Taxonomic Approaches

The dominant approach to the classification of mental disorders is that of the Diagnostic and Statistical Manual (*DSM*) of the American Psychiatric Association (2013). In the *DSM*, disorders are defined by lists of symptoms, and grouped together mainly on the basis of symptom similarity—in keeping with the atheoretical stance embodied by the Manual. Thus, *DSM-5* categories include, for example, anxiety disorders; disruptive, impulse-control, and related disorders; depressive disorders; obsessive-compulsive and related disorders; and feeding and eating disorders (American Psychiatric Association, 2013).

While the *DSM* system has many undisputable qualities—diagnostic reliability above all—it also has a number of significant problems (see, e.g., Beauchaine, Klein, Erickson, & Norris, 2013; Nesse & Jackson, 2006). The main limitation of the *DSM* is also its defining feature: the deliberate absence of a theoretical model of mental disorders. Since disorders and disorder categories are primarily defined by symptom similarity, many diagnostic classes are likely to include a heterogeneous mix of conditions with different etiological, developmental, and functional characteristics. More troubling, the *DSM* lacks a theory of normative mental functioning, and is therefore ill equipped to discriminate between adaptive defensive responses and disordered functioning (Nesse & Jackson, 2006).

The main alternative to the *DSM* system comes from a family of empirical approaches based on patterns of genetic and phenotypic correlations between disorders (e.g., Kendler, Prescott, Myers, & Neale, 2003; Lahey, Van Hulle, Singh, Waldman, & Rathouz, 2011; Lahey et al., 2008; Watson, 2005). Empirical taxonomic studies suggest the existence of broad, hierarchically organized clusters of disorders that overlap only in part with *DSM* categories. The fundamental distinction in empirical taxonomies is that between *internalizing* and *externalizing* disorders. Externalizing disorders are characterized by impulsivity, disinhibition, and high levels of aggressive, antisocial, and/or disruptive behavior. Internalizing disorders are marked by high levels of anxiety and negative emotionality. The internalizing spectrum comprises a cluster of *distress disorders* (depression, generalized anxiety disorder [GAD], post-traumatic stress disorder [PTSD]) and a cluster of *fear disorders* (panic disorder, agoraphobia, social phobia, and specific phobias; Clark & Watson, 2006). Obsessive-compulsive spectrum disorders are typically treated as a separate internalizing cluster; other disorders that are usually included in the internalizing spectrum are bipolar disorders and borderline personality disorder (BPD), although their exact placement is more problematic (see Beauchaine & Hinshaw, 2013; Lahey et al., 2008; Watson, 2005). A recent factor-analytic study by Caspi and colleagues (2014) supplemented the internalizing and externalizing categories with a *thought disorder* factor comprising schizophrenia, mania (bipolar spectrum), and obsessive-compulsive disorder (OCD). Moreover,

the authors identified a general, higher-order factor of psychopathological risk they labeled the *p factor* (see Caspi et al., 2014).

The internalizing–externalizing distinction has received considerable empirical support, and has become a standard tool in developmental psychopathology (Beauchaine & Hinshaw, 2013). In the latest edition of the *DSM*, the authors explicitly recognized the usefulness of the broad distinction between internalizing and externalizing disorders (American Psychiatric Association, 2013, p. 13). However, this approach also has a number of important limitations. First of all, disorders are grouped based on their emotional and affective characteristics; however, emotions can serve multiple motivational goals, and associations between emotions and motivational processes are often remarkably nonspecific (see Nesse, 2004a). For example, anger can be triggered by aggressive competition, by threats to one's dominance or status, by suffering or witnessing acts of injustice, by separation from an attachment figure, and so forth. Anxiety, shame, and sadness are prominently associated with psychopathology, but their motivational specificity is also extremely low. Thus, classifications of disorders based on emotion and affect are unlikely to reliably capture the underlying motivational structure.

Moving to the empirical level, there is mounting evidence that the interalizing–externalizing dichotomy is riddled with ambiguities and inconsistencies. To begin with, depression and GAD—often regarded as prototypical internalizing disorders—are in fact bridge diagnoses that overlap with both internalizing and externalizing disorders at the phenotypic, genetic, and developmental level (e.g., Lahey et al., 2008, 2011). Also, some disorders that are usually considered part of the internalizing spectrum—such as obsessive-compulsive disorder (OCD) and BPD—show atypically large correlations with externalizing disorders (Crowell, Kaufman, & Lenzenweger, 2013; Lahey et al., 2008). Finally, the interalizing–externalizing taxonomy excludes many important pathological conditions—notably schizophrenia, autism, and most personality disorders—because they are not primarily characterized by mood/emotional alterations and do not fit the conceptual distinction between internalization and externalization (the recent analysis by Caspi and colleagues [2014] is a partial exception).

A Life History Framework for Psychopathology

In the preceding sections we discussed how life history strategies play a central role in the organization of physiology and behavior. They define an organism's priorities and determine the allocation of effort and resources toward competing biological goals. Differences in life history strategy are the joint product of genetic and environmental influences on development, and are reflected in organized patterns of individual differences in motivation, affect, self-regulation, and personality. By organizing individual differences on such a broad scale, life history strategies set the stage for the development of psychopathology. More precisely, individual differences in life history strategy can be expected to determine individual differences in risk profiles for a broad range of mental disorders. As one moves along the fast–slow continuum of life history variation, some disorders and symptoms should become more frequent, while others should become less likely to occur.

The predictable association between life history strategy and risk for psychopathology offers a high-level functional criterion for the classification of mental conditions. This leads to the novel distinction between *fast spectrum* and *slow spectrum* disorders—that is, disorders that cluster at the fast or slow end of the life history continuum (Del Giudice, 2014a, 2014b). Until recently, life history approaches to psychopathology have focused almost exclusively on the fast end of the fast-slow continuum. As widely recognized in the literature, fast life history strategies can predispose individuals to a variety of disorders, either as maladaptive outcomes of life history-related traits or potentially adaptive but undesirable behavioral strategies (e.g., Belsky et al., 1991; Brüne et al., 2010; Figueredo & Jacobs, 2010; Jonason, Li, Webster, & Schmitt, 2009; Salmon, Figueredo, & Woodburn, 2009). The framework advanced by Del Giudice (2014a) extends this approach by addressing the role of *slow* strategies in setting the stage for the development of mental disorders.

It is important to stress that the functional connection between life history strategy and psychopathology is usually an *indirect* one. Causal pathways to psychopathology involve a multiplicity of traits and mechanisms—including temperament and personality, self-regulatory processes, and so forth. The general idea is that an individual's configuration of life history-related traits may increase the likelihood of developing a certain disorder or cluster of disorders—often in interaction with other causal factors including developmental insults, deleterious genetic or epigenetic mutations, infections, nutritional deficits, and psychosocial stressors. The power of life history theory lies in the ability to integrate these diverse etiological processes within a common frame of reference. The result is a large-scale map of the psychopathological landscape

organized along the fast-slow axis of life history variation. Such a map is an invaluable guide in understanding comorbidity patterns, since functionally related disorders—for example different disorders in the slow spectrum—can be expected to co-occur more frequently in the same individual. At the same time, the fast-slow distinction can be used to tease apart functionally distinct conditions that coexist within the same descriptive category because of their phenotypic similarity.

In total, a functional analysis based on life history principles helps to "carve nature at its joints" by revealing commonalities between separate categories and suggesting important distinctions between phenotypically similar disorders (Keller & Nesse, 2006). Of course, mental disorders are complex biosocial phenomena, and as such they can be analyzed at many different levels. A life history analysis is only the first step toward a comprehensive functional account of psychopathology: the broad perspective afforded by the fast–slow distinction should be complemented by narrower accounts focusing on specific motivational/behavioral systems, cognitive mechanisms, genetic pathways, and so forth.

Four Pathways From Life History Strategy to Psychopathology

The general statement that life history strategies set the stage for the development of psychopathology can be supplemented by a finer-grained analysis of the causal pathways that lead to the onset of mental disorders. First of all, some *adaptive life history-related traits may be regarded as symptoms*. This is most likely to happen with fast life history strategies characterized by impulsive, exploitative, or aggressive tendencies. The resulting phenotype may be classified as a disorder, even if it does not reflect maladaptive or dysfunctional processes. Even if they are biologically adaptive, or used to be adaptive in ancestral environments, such strategies may often involve substantial costs in terms of health and emotional well-being. Another important category of adaptive traits that may be diagnosed as symptoms of a disorder is that of aversive defenses. When defenses activate inappropriately or respond with excessive intensity, the outcome may be correctly recognized as maladaptive. However, many protective mechanisms have strongly aversive effects, and can be occasionally harmful to the individual. For this reason, they may give rise to undesirable conditions not only when they misfire but also when they respond appropriately in presence of actual threats.

The correlates of life history strategies often include upregulation or downregulation of psychological and physiological defensive mechanisms. Upregulated defenses have a lower threshold for activation and/or respond with higher intensity when they activate. Defense upregulation can be associated with both fast and slow strategies, although the specific type of mechanism involved is likely to differ between the two. In the context of fast life histories, upregulated defenses help protect the individual from immediate danger in risky, unpredictable environments. In the context of slow strategies, upregulated defenses may help the individual prevent dangerous events and avoid potentially risky situations, even if the current environment is reasonably safe. Moreover, protecting oneself from even minor damages and losses contributes to the long-term maintenance of the soma (i.e., somatic effort)—a key priority for slow life history individuals. In contrast, downregulation of defenses is most likely in the context of fast life history strategies, especially those involving a high degree of risk taking. As discussed in a previous section, the underlying logic is that, to fulfill their purpose, such strategies require insensitivity to threats, dangers, and so forth.

The second pathway from life history strategy to psychopathology derives from the fact that *life history-related traits may be expressed at maladaptive levels*. Even phenotypic traits that are biologically adaptive within a certain range may become maladaptive if they exceed that range. Sometimes, the expected fitness associated with a trait may slowly increase up to an optimal level, then decrease abruptly following a "cliff-edged" function. In such cases, selection for optimal trait levels may result in a high frequency of maladaptive phenotypes that overshoot the fitness optimum (Nesse, 2004b). A trait can reach maladaptive expression levels owing to a combination of genetic, epigenetic, and environmental factors that contribute to push the phenotype in the same direction. In the simplest case, extreme levels of a trait may appear in the offspring of two individuals who are both high on that trait, yet still within the adaptive range. Thus, assortative mating—the tendency for sexual partners to be more similar than average on a certain trait—can increase the risk for psychopathology due to extreme trait values. Parent–offspring conflict and intragenomic conflict are other likely causes of maladaptive trait expression. When conflict is present, phenotypic development can be conceptualized as the result of opposing forces, much like a game of tug-of-war. If for any reason this dynamic equilibrium is broken (for example, a mutation in the offspring may make it unable to counteract parental manipulation), the resulting imbalance may easily determine dysregulated or pathological outcomes.

In principle, the pathway leading from maladaptive trait expression levels to psychopathology may involve traits associated with both fast and slow life histories. However, there is some evidence that assortative mating on life history-related traits in humans tends to become stronger toward the slow end of the continuum (Figueredo & Wolf, 2009). If so, disorders that involve maladaptive expression levels of adaptive traits should occur more frequently in association with slow strategies, as similarity between parents increases the likelihood that offspring will inherit extreme genotypic combinations.

Third, as noted in a previous section, even *adaptive strategies may yield individually maladaptive outcomes*. Risky strategies are a prime candidate as a systematic source of individually maladaptive outcomes. Life history-related traits can steer individuals on high-risk pathways, thus increasing the likelihood of maladaptive and/or undesirable outcomes in case of strategy failure—even when the strategy is adaptive on average. This is more likely to happen in the context of fast life history strategies, which tend to promote risk taking and favor the pursuit of large, immediate returns regardless of the potential costs. While some individuals engaging in high-risk strategies may end up developing mental disorders, other individuals expressing the same traits may enjoy desirable or biologically adaptive outcomes, often depending on chance and unpredictable contextual factors. Another important category of adaptive traits that systematically produce maladaptive outcomes is that of defensive mechanisms. Following the logic of the smoke detector principle, defensive mechanisms are usually designed to misfire occasionally, even in absence of threats. Individual differences in life history strategy are reflected in the calibration of behavioral and physiological defenses (see earlier discussion of the ACM), and indirectly affect the risk of inappropriate defense activation.

Fourth and last, *adaptive life history-related traits may increase vulnerability to dysfunction*. While life history traits are designed to promote adaptation, they can nevertheless increase vulnerability to some types of dysfunction as a side effect. For example, some configurations of personality traits within the adaptive range (for example schizotypy or autistic-like personality) may become especially conducive to psychopathology when they are coupled with high mutation load or brain-damaging infections (see Del Giudice, 2010). Also, fast life history-related traits such as risk proneness and future discounting may indirectly increase an individual's exposure to environmental factors such as pathogens. Finally, upregulated defensive systems are not only more prone to misfiring but also more vulnerable to actual instances of malfunction and dysregulation (Nesse, 2001). These four pathways from life history strategy to psychopathology are logically distinct but not mutually exclusive and may coexist in the etiology of any given disorder.

Correlates of Fast and Slow Spectrum Psychopathology

The conceptual distinction between fast and slow spectrum pathology provides a powerful heuristic criterion for the functional classification of mental disorders. Whatever the specific causal pathway (or combination of pathways) that determine the onset of a given disorder, fast spectrum conditions will be associated with traits such as low agreeableness and conscientiousness, impulsivity, disinhibition, and early sexual maturation (especially in females). Conversely, slow spectrum conditions will exhibit a signature of slow life history-related traits in the areas of motivation, self-regulation, personality, and sexual maturation. Correlations between life history–related traits and specific disorders may or may not imply a *causal* role of those traits in the etiology of the disorders. However, regardless of their role in the etiology of a given disorder, life history correlates can be employed as convergent *markers* of the underlying life history strategy. In principle, this approach can be extended to include genetic, epigenetic, and neurobiological markers (e.g., Del Giudice et al., 2011; Figueredo et al., 2004, 2006). A nonexhaustive list of markers of fast and slow spectrum psychopathology is presented in Table 1.2.

A life history perspective yields novel predictions about the environmental correlates of mental disorders. Ecological harshness and unpredictability tend to entrain development of fast life history strategies, while slow strategies are favored in safe and predictable contexts. As a result, many classic risk factors for psychopathology—such as stressful life events, low socioeconomic status, negative family relationships, trauma, and abuse—are predicted to increase the occurrence of fast spectrum disorders, but not that of slow spectrum disorders. On the contrary, slow spectrum disorders should be associated—at least on average—with safe, predictable environments, higher socioeconomic status, and *reduced* exposure to ecological and family stressors.

Sex Differences

If life history strategies set the stage for psychopathology, sexual asymmetries in life history trade-offs should produce consistent patterns of sex differences in the epidemiology of mental disorders. The first key asymmetry concerns the mating versus parenting trade-off. On average, human males invest more in mating effort and less in parenting effort than females. The intensity

TABLE 1.2 Correlates of fast and slow spectrum psychopathology

	Fast spectrum psychopathology	Slow spectrum psychopathology
Motivation	Social antagonism	Social compliance, conformity
	Unstable attachments	Stable attachments
	Precocious sexuality	Delayed sexuality
	Sexual promiscuity, high sex drive	Sexual restraint, low sex drive
	Sensation/novelty seeking	Preference for routines
	Risk taking	Risk aversion, harm prevention
Self-regulation	Disinhibition, impulsivity	Inhibition, restraint
	Discounting of future rewards	Discounting of immediate rewards
Personality traits	Low conscientiousness	High conscientiousness
	Low agreeableness	High agreeableness
Sexual maturation	Early, fast maturation	Late, slow maturation
Environment	Harsh, unpredictable	Safe, predictable
	High exposure to stressors	Low exposure to stressors

Source: Reprinted from M. Del Giudice, An evolutionary life history framework for psychopatholgy, Psychological inquiry, 25, 274, 2014a.

of mating effort increases sexual selection for competitive traits such as risk taking, dominance-seeking, and physical aggression (see Archer, 2009; Wilson et al., 2002). In total, higher mating effort in males should predispose them to fast spectrum disorders characterized by high levels of risk taking, such as those in the externalizing cluster (Martel, 2013). In contrast, females have generally less to gain and more to lose from high-risk strategies than males and can be expected to invest more effort in somatic maintenance and protection. As a consequence, they should be more prone to develop disorders that involve the upregulation of protective defenses, and to exhibit more psychological and physiological symptoms reflecting defense upregulation. This prediction applies to disorders across the fast-slow continuum, since upregulated defenses can be functionally associated with both fast and slow life history strategies. The higher incidence of anxiety disorders in females (see Martel, 2013) is consistent with this prediction.

Another important asymmetry in life history strategy concerns the trade-off between current and future reproduction. As already discussed in the section on life history theory, this trade-off plays a more critical role in the organization of female life history strategies, since decisions concerning reproductive timing are more critical for females than for males. As a consequence, the timing of sexual maturation in females should be more sensitive to cues of danger and unpredictability (James et al., 2012). Indeed, the available data suggest that ecological stress in the first years of life anticipates gonadal puberty in girls, but not in boys (reviewed in Belsky, 2012). In addition, indices of sexual maturation in females can be expected to form a tighter cluster with other life history-related traits including motivation, personality, self-regulation, and so forth. It follows that maturation timing and rate should be stronger predictors of psychopathology in females than in males. This prediction is well supported by empirical research; the bulk of evidence indicates that individual differences in sexual maturation are more robustly associated with psychopathology in girls than in boys (see Ge & Natsuaki, 2010; Mendle, Turkheimer, & Emery, 2007).

Predictions about sex differences based on life history theory (Del Giudice, 2014a) can be integrated with those from a recent evolutionary model advanced by Martel (2013). Martel employed sexual selection theory to explain the male-biased prevalence of childhood-onset externalizing disorders and the symmetrical, female-based prevalence of adolescent-onset internalizing disorders. Because of differential sexual selection for social dominance versus interpersonal competence in males and females, she also predicted that males should be more sensitive to early environmental stressors related to the broader ecological conditions (including those occurring prenatally), whereas females should be more sensitive to interpersonal stressors occurring around puberty. These predictions are supported by considerable empirical evidence, and can be extended to the neurobiological level to yield insight in the role of prenatal testosterone, dopamine, and serotonin in the etiology of common mental disorders in the two sexes (reviewed in Martel, 2013).

Toward a Life History Taxonomy of Mental Disorders

The general framework outlined in this section can be applied to individual disorders and categories of disorders, yielding an initial life history taxonomy based on the fast-slow continuum. In what follows, we briefly discuss how six common categories of mental disorders relate to the fast–slow distinction. For an extended analysis and review of the relevant empirical literature, see Del Giudice (2014a, 2014b).

Externalizing disorders

The externalizing spectrum comprises various disorders marked by aggressive, antisocial, and/or disruptive behavior, including oppositional defiant disorder (ODD), conduct disorder (CD), and antisocial personality disorder (APD). Externalizing disorders are also associated with

high risk for substance abuse. Disorders in the externalizing spectrum are strongly male-biased and show high phenotypic and genetic correlations with one another, indicating the existence of a coherent, heritable dimension of externalizing behavior. At the same time, the development of externalizing behaviors is strongly conditioned by environmental factors, such as harsh-rejecting parenting, aggregation of high-risk youth in after-school programs, and exposure to neighborhood violence and criminality (reviewed in Beauchaine, Hinshaw, & Pang, 2010).

In a life history perspective, externalizing spectrum disorders are prototypical instances of fast spectrum psychopathology. Externalizing symptoms are associated with impulsivity and undercontrol, early puberty timing and fast sexual maturation in both sexes, earlier onset of sexual activity, and larger numbers of partners in adolescence and young adulthood. Low socioeconomic status, harsh or unpredictable parental discipline, parental conflict, family disruption, and child abuse—all cues of danger and unpredictability—are consistent predictors of externalizing behavior, consistent with predictions derived from life history theory.

Evolutionary models of externalizing spectrum disorders tend to stress the potential biological adaptiveness of aggressive, exploitative, and risky behavior—especially when coupled with promiscuous short-term sexuality (e.g., Barr & Quinsey, 2004; Figueredo & Jacobs, 2010; Jonason et al., 2009; Mealey, 1995). Accordingly, many evolutionary scholars see externalizing disorders as adaptive but undesirable constellations of traits. In some instances, externalizing disorders may represent maladaptive extremes of potentially adaptive traits (see MacDonald, 2012). It should be stressed that externalizing disorders can be adaptive even if their social outcomes are negative *on average*. This can happen if successful outcomes yield disproportionate fitness returns, even in a minority of cases. Finally, high-risk behavioral strategies are likely to involve downregulation of defensive mechanisms; indeed, externalizing disorders in adolescents and adults are often associated with reduced anxiety, fearlessness, and dampened responsivity of the SRS.

Schizophrenia Spectrum Disorders

Schizophrenia is a family of mental disorders characterized by delusions, hallucinations, and cognitive disorganization. Given the severe reduction in reproductive success associated with a schizophrenia diagnosis, most evolutionary scholars regard this disorder as a maladaptive outcome of dysregulated sociocognitive processes (e.g., Burns, 2004; Keller & Miller, 2006). While schizophrenia spectrum disorders (SSDs) are highly heritable, schizophrenia risk is also increased by adverse environmental factors such as nutritional deficiencies, infections, and birth complications. This suggests that accumulated deleterious mutations and environmental insults may converge on common neurobiological pathways, increasing the risk of cognitive breakdown.

Even if SSDs are biologically maladaptive conditions, there may be evolutionary advantages associated with *schizotypal traits*—a constellation of personality traits associated with increased risk of psychosis. Most individuals who have psychotic experiences at some point in their life recover completely, and never transition to a diagnosable SSD. Various authors have proposed that schizotypal traits may be maintained by sexual selection processes based on mate choice. According to the sexual selection model of schizotypy (Nettle, 2001, 2006; Shaner, Miller, & Mintz, 2004), schizotypy-increasing alleles affect brain processes so as to increase traits such as verbal and artistic creativity, thus conferring mating advantages on those individuals who do not develop a psychiatric condition. However, the outcomes of schizotypy may be either beneficial (mating success) or harmful (schizophrenia), depending in part on the individual's genetic quality (i.e., lack of deleterious mutations) and developmental condition (e.g., good nutrition and low exposure to pathogens).

Consistent with the sexual selection model, positive schizotypal traits—unusual cognitive and perceptual experiences, tendency to magical ideation, reference and paranoid thoughts—are associated with verbal and artistic creativity, larger numbers of sexual partners, unrestricted sociosexuality, and reduced investment in long-term couple relationships. Large-scale studies of patients and their relatives show a robust familial association between schizophrenia and creativity. Schizotypal traits peak in adolescence/young adulthood and show a marked decline with age, mirroring typical changes in mating effort. In addition, positive schizotypy is associated with lower agreeableness and higher levels of aggression, suggesting a degree of overlap between the schizophrenia spectrum and the externalizing spectrum.

In light of this convergent evidence, SSDs can be provisionally classified as belonging to the fast spectrum of psychopathology, although there are reasons to expect a degree of functional heterogeneity (see Del Giudice, 2014a). According to sexual selection models, schizotypy can be understood as a high-risk strategy oriented toward short-term mating, whose negative outcomes become manifest as schizophrenia and other SSDs. Alternatively,

the milder disorders of the schizophrenia spectrum (e.g., schizotypal personality disorder, brief psychotic disorder) may result from maladaptive levels of expression of potentially adaptive traits associated with fast life history strategies.

Autism spectrum disorders

The autism spectrum comprises disorders of variable severity characterized by impairments in social interaction, communication problems, and restricted and repetitive behaviors/interests. Severe autism is almost certainly maladaptive, and some theorists have focused specifically on the negative aspects of autism spectrum disorders (ASDs). For example, Shaner and colleagues (Shaner, Miller, & Mintz, 2008) hypothesized that autism—like schizophrenia—may represent the negative extreme of a fitness indicator, a hypothesis consistent with the large number of deleterious mutations found in ASD patients.

This negative emphasis should be balanced by accumulating evidence that autistic-like traits in the normative range—also known as the *broader autistic phenotype*—have a number of desirable and potentially adaptive correlates. Specifically, autistic-like traits predict higher systemizing abilities and attention to detail, better visuospatial skills, and enhanced low-level sensory processing in the visual and auditory domains. The autistic facets of repetitive behaviors, restricted interests, and detail-oriented cognitive style are associated with the development of outstanding talents in children. More generally, autistic-like traits are higher in people with technical-scientific interests and careers. Accordingly, several theorists have argued that ASDs can be seen as extreme and usually maladaptive manifestations of otherwise adaptive traits (e.g., Baron-Cohen, 2003; Crespi & Badcock, 2008).

In this perspective, Del Giudice and colleagues (2010) hypothesized that sexual selection may contribute to maintain autistic-like traits in the population despite the fitness costs of severe ASDs. Specifically, they argued that autistic-like traits in their non-pathological form contribute to a male-typical strategy geared toward high parental investment, low mating effort, and long-term allocation of resources—in other words, a male-typical manifestation of slow life history strategy. This hypothesis offers a parsimonious explanation of the male-biased distribution of both autistic-like traits and ASDs. In support of this hypothesis, autistic-like traits predict lower interest in short-term mating, increased investment of time and resources in one's partner, and stronger commitment to long-term romantic relations. People high in autistic-like traits report shorter duration of friendships but longer duration of romantic relationships, and their partners are on average just as satisfied as those of people low in autistic-like traits.

In a life history perspective, ASDs are thus likely candidates for inclusion in the slow spectrum of psychopathology. Further evidence comes from the finding that sexual maturation is delayed in women high in autistic-like traits as well as in women with ASD. Autistic-like traits may function adaptively as part of a slow life history strategy—especially in males—and become maladaptive only when they cross a certain threshold. Given the remarkable heterogeneity of ASDs, this functional explanation is likely to apply only to a subset of people diagnosed with autistic disorders. Different ASD subtypes may well require different explanations. The existence of functionally distinct subtypes of ASDs may explain the inconsistent correlation of autism risk with socioeconomic status in epidemiological studies.

Obsessive-Compulsive Spectrum Disorders

Disorders in the obsessive-compulsive spectrum are primarily characterized by patterns of compulsive, repetitive thoughts and/or behaviors, usually associated with worry and anxiety. In addition to obsessive-compulsive disorder (OCD), the OC spectrum includes body dysmorphic disorder, hoarding disorder, grooming disorders (skin picking and hair pulling), and obsessive-compulsive personality disorder (OCPD)—a pervasive profile of orderliness, rigid perfectionism, and need to control one's self and environment.

In the evolutionary literature, OCD is usually treated as a maladaptive exaggeration of an adaptive trait or the result of a dysfunction in precautionary cognitive systems. However, the milder forms of the disorder are not necessarily maladaptive in the biological sense. Current models converge on the idea that the main functional substrate of OCD is an adaptive mechanism—the *hazard-precaution system* or *security motivation sy*stem—specialized for dealing with potential low frequency threats such as food poisoning (e.g., Boyer & Lienard, 2006; Szechtman & Woody, 2004; Woody & Szechtman, 2011). The peculiar logic of potential threats explains many features of compulsions (see Woody & Szechtman, 2011); obsessions can be explained as the involuntary generation of potential risk scenarios, a mechanism designed to increase future harm avoidance. Consistent with a threat prevention account and with the prediction that females should be more likely to develop symptoms reflecting upregulated defenses, adult OCD patients are overwhelmingly women.

A life history analysis indicates that the OC spectrum is best understood as a functionally heterogeneous category comprising two clusters of disorders—a slow spectrum one and a fast spectrum one. Slow-spectrum OCD is marked by *reactive* obsessions (Lee & Kwon, 2003); reactive obsessions concern realistic fears of contamination, mistakes, accidents, or disarray. They are triggered by cues of potential threats and are typically followed by preventive behaviors such as ordering or cleaning; anxiety is directed at the possible consequences of one's actions rather than at the obsession itself. Reactive obsessions are associated with high conscientiousness, perfectionism, heightened responsibility and personal standards, normal levels of motor and cognitive inhibition, and a prevalence of contamination/cleaning symptoms. Reactive OCD fits straightforwardly in the slow spectrum of psychopathology, as a combination of exaggerated trait expression, upregulation of adaptive defenses, and dysfunctional protective responses. Obsessive-compulsive personality disorder (OCPD) also fits this classification, given its many overcontrol features and strong association with conscientiousness.

Fast-spectrum OCD is characterized by *autogenous* obsessions—obsessions with sexual, aggressive, or blasphemous content. Autogenous obsessions tend to be bizarre, ego-dystonic, and threatening. They often have no apparent trigger, or are triggered by remote/bizarre thought associations (Lee & Kwon, 2003). Autogenous obsessions are associated with positive schizotypy, indices of psychotic thought disorganization, low conscientiousness, and reduced inhibitory control. The heterogeneous nature of the OC spectrum explains why OCD shows high comorbidity with both ASDs and SSDs. The two OC clusters can be expected to show markedly different epidemiological profiles; for example, traumatic events and low SES should be more strongly associated with fast-spectrum OCD, whereas slow-spectrum OCD should often arise in safe and predictable environments. Consistent with placement in the slow-spectrum cluster, OCPD is uniformly associated with high education levels, and OCDP patients have the highest socioeconomic status of all personality disorders (for extended discussion see Del Giudice, 2014b).

Eating Disorders

Eating disorders (EDs) are defined by heightened concern with body shape and weight and associated behaviors such as dieting, binge eating, purging, and exercising. Eating disorders occur almost exclusively in females, and their age of onset peaks in adolescence. Most evolutionary models of eating disorders focus on the connection between dieting behavior and female reproduction. Two main alternative hypotheses have been proposed so far. First, dieting may work as a means to suppress fertility and delay or forego reproduction when the social environment is not optimal—for example, when social support by relatives and partners is low, or when social competition is too harsh (e.g., Mealey, 2000; Surbey, 1987). Second, dieting may work primarily as a female strategy in mating and status competition (e.g., Abed, 1998; Ferguson, Winegard, & Winegard, 2011; Salmon et al., 2009). Thinness is a reliable signal of youth, and dieting can increase one's attractiveness because of men's strong preference for younger partners; in addition, dieting can enhance status in female groups (thus indirectly influencing mating success), especially when cultural emphasis on thinness is strong. This hypothesis is supported by the robust pattern of associations among perceived sexual competition, dieting behavior, and eating symptoms. Under both hypotheses, the psychological processes that underlie dieting behavior are fundamentally adaptive, and lead to maladaptive outcomes (such as severe EDs) only when they become dysregulated or get trapped in vicious cycles.

The mating competition hypothesis of eating disorders can be easily reframed in a life history perspective. Both fast and slow strategists can face intense competition for mates; the main difference is that fast strategists compete primarily to become desirable sexual partners, whereas slow strategists compete primarily to be chosen as long-term partners in committed relationships. Thus, eating disorders can arise at both ends of the fast-slow continuum.

A life history analysis confirms that EDs are indeed a functionally heterogeneous category. Slow spectrum EDs are associated with *high-functioning/perfectionist* personality profiles, low comorbidity rates (mostly with OCD and OCPD), and the most favorable clinical outcomes (see e.g., Thompson-Brenner et al., 2008; Westen & Harnden-Fischer, 2001). This cluster of eating disorders is associated with high self-esteem, relatively intact family and couple relationships, and a history of *fewer* stressful life events. Another profile that can be included in the slow spectrum is that of *overcontrolled* patients. This profile is associated with high rates of depression, low self-esteem and passivity, restricted emotionality, and comorbidity with OCPD. Overcontrolled ED patients might be engaging in reproductive suppression—an intrinsically future-oriented strategy—following loss of status or social support, as suggested by their depressed mood, low self-esteem, and acute sense of social exclusion.

In contrast, fast spectrum EDs are associated with *dysregulated* personality profiles (see Thompson-Brenner et al., 2008). Dysregulated ED patients show high levels of impulsivity and antisocial/externalizing behavior, high comorbidity (especially with borderline personality disorder), and many stressful life events including high rates of sexual abuse. While patients in the high-functioning/perfectionist and overcontrolled groups can be diagnosed with either anorexia nervosa (AN) or bulimia nervosa (BN), the dysregulated subtype is strongly associated with BN (Westen & Harnden-Fischer, 2001). As a result, patients with BN—considered as a whole—show higher average levels of impulsivity, earlier sexual maturation, and earlier sexual debut than AN patients.

Depression

Depression is characterized by protracted episodes of distress and low, dejected mood. The clinical presentation of depression is quite heterogeneous; attempts to subtype depressive disorders based on empirical patterns of symptom co-occurrence consistently identify (1) a subtype characterized exclusively by depressed mood and feelings of worthlessness; (2) one or more subtypes characterized by somatic symptoms in absence of depressed mood; and (3) one or more subtypes in which depressed mood and somatic symptoms coexist. Somatic symptoms of depression include sleep disturbances (insomnia or hypersomnia), appetite disturbances (increased or decreased appetite), psychomotor disturbances (agitation or retardation), fatigue, and pain. All these symptoms are functionally related to the SRS, and in particular the HPA axis.

Most evolutionary theories of depression focus on low mood and its motivational and behavioral correlates. In the prevailing view, depressed mood is an adaptive defensive mechanism, whereas clinical depression is usually maladaptive and reflects a dysfunction of the same mechanism (e.g., Allen & Badcock, 2003; Nesse, 2006; Nettle, 2004, 2012). Some theorists have argued that clinical depression may be an adaptation itself (e.g., Price, Sloman, Gardner, Gilbert, & Rohde, 1994; Watson & Andrews, 2002). Although this hypothesis appears reasonable in the specific case of postpartum depression (Hagen, 1999), there are many reasons to doubt its general applicability. The function of low mood as a protective mechanism is twofold. First, low mood helps people disengage from the pursuit of central life goals that have become unproductive. Second and more specifically, it promotes a risk-averse approach in unfavorable social circumstances—especially following losses in social support (typically in females), close relationships, and social status or dominance (typically in males). While affective reactivity determines one's susceptibility to episodes of low mood, stress reactivity is the crucial factor in the development of somatic symptoms. Thus, a complete evolutionary account of depression cannot be separated from evolutionary models of SRS functioning.

By synthesizing the ACM with evolutionary models of depressed mood, it is possible to predict a complex relation between depression and life history strategy. Both fast and slow strategists can fail to obtain or maintain crucial social resources—status, dominance, and support—resulting in episodes of depressed mood and risk for clinical depression. At the slow end of the continuum, males and females are both expected to develop relatively high levels of stress responsivity (Del Giudice et al., 2011), even if the actual intensity of stress responses is buffered by the availability of social support and lack of chronic stressors. As a result, symptom profiles at the slow end of the spectrum should not differ greatly between the sexes. Intriguingly, some subtypes of depression—in particular those characterized by pure depressed mood or pure somatic symptoms—are associated with very low rates of trauma, neglect, and abuse.

Moving toward the fast end of the continuum, both sexes face increasing threats to their ability to gain and maintain social resources. The availability of social support and stable, intimate relationships declines rapidly as environments become dangerous and unpredictable, exposing females to increased risk for depressed mood. At the same time, sex differences in stress responsivity can be expected to become proportionally larger, as more males develop unemotional responsivity patterns. Vigilant SRS profiles can be adaptive in dangerous and unpredictable contexts, especially in females; however, they also increase the risk of SRS dysregulation and dysfunction. In total, fast life history strategies should lead to increased risk for depression in both sexes, with females showing the highest rates of depressed mood and somatic symptoms. Consistent with these predictions, early and/or fast sexual maturation is a risk factor for depression in both sexes, with stronger effects in females. In addition, depression subtypes involving a combination of low mood and somatic symptoms are overwhelmingly more common in females, and are also associated with the highest rates of early trauma, neglect, and abuse. In conclusion, depression may occur at both ends of the fast–slow continuum, suggesting the existence of functionally distinct clusters of depressive disorders. Unfortunately, the current literature defines depression subtypes exclusively in terms of symptom co-occurrence; further research in a life history framework should attempt

to identify functional subtypes of depression based on motivation, personality, self-regulation, and comorbidity with other fast and slow spectrum disorders.

Summary and Integration

A life history analysis of mental disorders reveals a coherent picture of associations between individual differences in life history strategy and specific patterns of risk for psychopathology. The constellation of fast spectrum conditions includes externalizing disorders, schizophrenia spectrum disorders, OCD with autogenous obsessions, the dysregulated subtype of eating disorders (typically expressed as BN), and depressive disorders characterized by a combination of mood and somatic symptoms. These disorders tend to co-occur, both within families and within individuals; many of them share elements of impulsivity, disinhibition, and/or bizarre ideation. Slow spectrum psychopathology includes OCPD, OCD with reactive obsessions, autism spectrum disorders, the perfectionist and overcontrolled subtypes of eating disorders, and a cluster of depressive disorders of lesser severity. These comorbid disorders tend to share elements of inhibition, overcontrol, and cognitive rigidity. They are also characterized by lack of association with standard risk factors for psychopathology such as stressful life events, low SES, and early abuse; in some cases, they are actually associated with more favorable ecological and socio-economic conditions. The same approach can be easily extended to other disorders. For example, borderline personality disorder (BPD) bears the hallmarks of fast life history strategies—impulsivity, unstable attachments, risk taking, promiscuous sexuality, antisocial and paranoid personality features, and high comorbidity with externalizing disorders (Brüne et al., 2010; see also Crowell et al., 2013). Similarly, disorders in the bipolar spectrum show substantial genotypic and phenotypic overlap with schizotypy and schizophrenia, including a familial association with enhanced creativity (see Del Giudice, 2014a, 2014b). A provisional classification of slow and fast spectrum disorders is shown in Figure 1.7.

This classification is still tentative and incomplete, and many gaps and questions remain—for example about the possible functional heterogeneity of autism and schizophrenia, the role of reproductive suppression in disordered eating, or the identification of fast and slow spectrum subtypes of depression (see Del Giudice, 2014b). However, even this initial analysis illustrate how a life history framework can bring an integrative perspective to psychopathology, highlight connections between previously separate models, and suggest novel empirical questions. Even more importantly, this approach has the potential to overcome the limitations of current taxonomic systems and offer a more solid foundation for the classification of mental disorders. In particular, the fast-slow distinction is both more *inclusive* and more *accurate* than the interalizing–externalizing distinction. It is more inclusive because it integrates mood and anxiety disorders with personality disorders, schizophrenia spectrum disorders, and autism spectrum disorders—all within the same conceptual framework. It is more accurate because it resolves many inconsistencies inherent in the basic interalizing–externalizing distinction. For example, the ambiguous placement of OCD in the internalizing spectrum is explained by the heterogeneity of OCD; specifically, the autogenous subtype of OCD is a fast spectrum disorder with strong functional connections with externalizing symptoms. More generally, the interalizing–externalizing distinction may be problematic because it is in large part

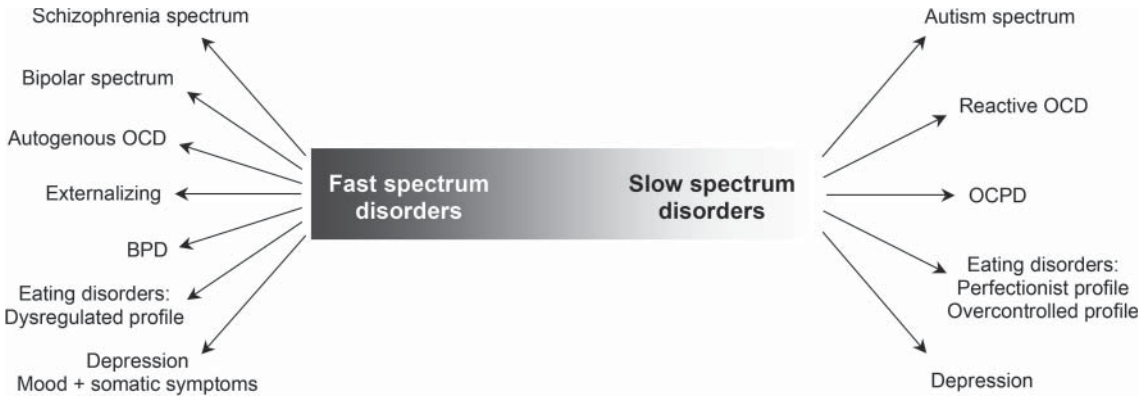


Figure 1.7 Provisional life history taxonomy of common mental disorders. BPD = borderline personality disorder, OCD = obsessive-compulsive disorder, OCPD = obsessive-compulsive personality disorder. *Source:* Reprinted from M. Del Giudice, An evolutionary life history framework for psychopatholgy, Psychological inquiry, 25, 285, 2014a.

illusory. The obvious genotypic and phenotypic coherence of the externalizing spectrum may have led researchers to assume that internalizing disorders must form a symmetrical category with similar properties of coherence. A life history perspective suggests that this assumption is probably mistaken, and that the internalizing spectrum may turn out to be a largely artificial collection of disorders with divergent functional properties.

Implications for the Core Points of Developmental Psychopathology

The life history framework discussed in this section has important implications for developmental psychopathology. Most crucially, it shows how *equifinality* and *multifinality* in the development of mental disorders can be explained in a functional perspective. On one hand, the same kind of symptom—for example eating symptoms and obsessions—can arise in relation to different life history strategies. As a result, phenotypically similar disorders can be associated with opposite profiles of personality, sexual maturation, ecological factors, and so forth. On the other hand, the same basic dimensions of life history strategy can play a role in the etiology of functionally related but superficially different disorders. While these manifestations of equifinality and multifinality may be problematic in the context of the standard externalizing–internalizing distinction, they can be easily understood in terms of the fast–slow distinction advanced by Del Giudice (2014a).

A closely related point is that, in this perspective, not all disorders are expected to arise in association with typical *risk factors* such as early stress, negative family relationships, and low SES. This helps make sense of the puzzling fact that some disorders seem to develop more frequently in safe, predictable ecologies and families with high socioeconomic status. The model presented here may also explain why insecure attachment—a robust psychological correlate of fast life history strategy—is consistently associated with externalizing symptoms but only weakly predictive of internalizing symptoms (Groh, Roisman, van IJzendoorn, Bakermans-Kranenburg, & Fearon, 2012). Finally, the coexistence of fast and slow spectrum subtypes within the same diagnostic category may go a long way toward explaining inconsistent or contradictory patterns of epidemiological findings.

CONCLUSION

We started this chapter with a promise—to show how an evolutionary approach can help developmental psychopathology realize its full potential, and to demonstrate how EDP provides an integrative, powerful metatheory for the field. We hope we fulfilled our promise and succeeded in arousing the reader's interest in the EDP approach. Throughout the chapter, we sought to illustrate how an evolutionary-developmental perspective supports and extends the core points of developmental psychopathology. Consider for example the concept of *multifinality*. In the standard view, multifinality is a ubiquitous, general property of complex developmental systems. However, the mechanisms that generate of multifinality are usually left unspecified; as a result, the concept is often used to redescribe empirical findings rather than explain them. The EDP approach demystifies multifinality by grounding the concept in adaptive function, and provides the tools for predicting *when* multifinality should apply (or not) to a given developmental process, stage, or outcome. Thus, multifinality can be understood as a necessary consequence of differential susceptibility; the logic of the ACM predicts when similar physiological profiles may predict widely divergent behavioral outcomes; and life history theory (together with sexual selection theory) explains why similar developmental experiences may set the stage for phenotypically different but functionally related disorders. Even more importantly, these apparently disparate aspects of development can be understood in relation to one another and unified within an integrative theoretical framework.

Even if we covered a lot of ground, we barely scratched the surface of our topic. The evolutionary approach to development and psychopathology is a growing multidisciplinary enterprise, and new theories, models, and findings are published at an ever increasing pace. We therefore conclude by suggesting a reading list for further explorations of the field. Ellis and Bjorklund (2005) and Burgess and MacDonald (2005) offer a more complete overview of EDP, including discussion of cognitive processes such as memory and language. Special sections of *Development and Psychopathology* on differential susceptibility (Ellis & Boyce, 2011) and *Developmental Psychology* on conditional adaptation (Ellis & Bjorklund, 2012) provide useful collections of relevant work. An introduction to theories and models in evolutionary psychopathology can be found in Brüne (2008) and McGuire and Troisi (1998). Finally, Ellison and Gray (2009) show how evolutionary thinking can be applied to neurobiological and endocrinological processes. Explaining the development of psychopathology is a formidable task, calling for convergence and integration across myriad disciplines and levels of analysis. We believe that evolutionary theory offers invaluable tools for

this task, and hope that developmental psychopathology will join forces with EDP toward a common understanding of human development in all its living complexity.

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CHAPTER 2

Differential Susceptibility to Environmental Influences

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DIFFERENTIAL SUSCEPTIBILITY TO ENVIRONMENTAL INFLUENCES

Central to much thinking about human development is the presumption that experiences in the early years of life—and even thereafter—influence individual differences in later development. Indeed, such developmental plasticity is a central tenant of most theories of human development, including attachment theory, social-learning theory and life-course sociology. Moreover, it guides a diverse array of research, including, for example, work chronicling links between prenatal maternal stress and temperament in infancy (Huizink, de Medina, Mulder, Visser, & Buitelaar, 2002), between maternal sensitivity in the first year and attachment security thereafter (Bakermans-Kranenburg, van IJzendoorn, & Juffer, 2003), between quality of child care in the preschool years and vocabulary scores at age 10 (Belsky, Vandell, et al., 2007), between parental divorce/separation in early adolescence and school grades in the later teenage years (Lansford et al., 2006), and

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between early family environment and depression symptomatology in early adulthood (Taylor et al., 2006).

In this chapter we provide a detailed introduction to theory and evidence pertaining to differential susceptibility (DS) (Belsky, 1997b, 2005; Belsky & Pluess, 2009a, 2013a), a relatively new conceptual framework stipulating that individuals differ substantially in their degree of developmental plasticity, with some being generally more and some generally less plastic. Importantly, this differential susceptibility hypothesis is based on evolutionary reasoning about developmental plasticity. What many developmentalists have failed to appreciate regarding developmental plasticity is that such plasticity carries costs (DeWitt, Sih, & Wilson, 1998; Frankenhuis & Del Giudice, 2012; Schlichting & Pigliucci, 1998; Sih, 2011). First there is the cost associated with increased phenotypic complexity that may be required for an organism to be able to develop in diverse ways, depending on contextual conditions. Some of these costs derive from the fact that as complexity increases, so does the risk of something going wrong, in the same way that a machine with more moving parts has more ways of breaking down than one with fewer. Consider as well the following and related costs of plasticity enumerated by DeWitt and associates (1998): energetic costs of the sensory and regulatory mechanisms of plasticity; the production cost of environmentally inducible structures and processes; the cost of acquiring information about the environment, including the energy expended and potential risks incurred; and the imprecision in manufacturing a phenotype based on environmental experience. Collectively, these would seem to imply a trade-off between the benefits of being able to adjust development in accord with prevailing or anticipated contextual conditions—and thus being able to thrive in more than a single ecological niche—and the costs of a breakdown in the developmental machinery and processes needed to do so.

Also important to appreciate with respect to the costs of plasticity is that modifying development early in life in response to developmental experiences and environmental exposures may result in a "mismatch" between the developed organism and the environment in which it finds itself later in life (Nederhof & Schmidt, 2012; Sih, 2011). In this way, seemingly adaptive developmental plasticity, selected to allow the organism to be programmed on the basis of early experience to fit the later environment, may, in some cases, actually undermine developmental opportunity and eventual fitness rather than enhance it.

The potentially high costs associated with developmental plasticity as well as the potential risk of mismatch between programmed phenotype and future environment would seem to provide grounds to expect individual differences in the degree of developmental plasticity within a species, the fundamental focus of this chapter. After all, individuals whose development is more canalized and less programmable by environmental exposures would be less likely to experience a mismatch resulting from developmental plasticity. Of course, such highly canalized specialists with more or less fixed characteristics could still end up mismatched to their environment, but for reasons different from that of the more plastic, programmable generalist who may develop in a manner guided by experiences had earlier in life.

In sum, what these observations imply is that being developmentally malleable should not be regarded, as it typically is by developmental scholars, as an unmitigated good for the developing organism and thus as something that should be pronounced in all individuals. In some cases it would appear wiser not to be plastic or to be less malleable—manifesting a more canalized pattern of development—than others and thus less susceptible to environmental regulation. What this suggests, as now noted repeatedly, is that we should expect individual differences in developmental plasticity. In other word, developmental plasticity should be conceptualized as a phenotype in its own right, something that will vary across individuals—for a variety of reasons (Belsky & Pluess, 2009b).

As it turns out, this notion of individual differences in developmental plasticity has long been appreciated by students of both normal development and psychopathology, even if not always expressed in such terms. Indeed, the notion of individual differences in plasticity is central to the model of human development and environmental action that dominates so much thinking and research. For example, the diathesis–stress framework presumes that not all individuals are equally vulnerable to the negative effects of adverse environmental influences (Gottesman & Shields, 1967; Monroe & Simons, 1991; Zuckerman, 1999). In recent years, an alternative framework has been advanced, that of differential susceptibility to environmental influence (Belsky, 1997b, 2005; Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Belsky & Pluess, 2009a; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011), which is the primary subject of this chapter. We thus begin by considering the diathesis–stress framework before outlining that of differential susceptibility. We then discuss some methodological issues pertinent to the investigation of differential susceptibility before proceeding to review evidence consistent with the latter, highlighting organismic factors (i.e., temperament, physiology, genotype) that moderate responsiveness to environmental influences. Because

all the work reviewed through this point is observational in character, a subsequent section focuses on experimental manipulations of the environment that illuminate whether intervention effects are moderated by plasticity factors. Thereafter, we call attention to studies that actually consider repeated-measurement involving how the very same individuals behave when exposed to both negative and positive contextual conditions. Finally, we raise a host of issues under the guise of unknowns in the differential susceptibility equation to guide future research before drawing some general conclusions.

DIATHESIS–STRESS

Developmental Psychopathology Foundations

As already noted, behavioral scientists and developmental psychopathologists have long appreciated that individuals vary in their susceptibility to the influence of environmental factors and forces. It is this presumption, after all, that has long motivated interest among many in treatment–aptitude interactions, including personalized medicine today (Shoham & Insel, 2011). But in the realm of both normal and psychopathological functioning and development, it is the diathesis–stress model of environmental action (Gottesman & Shields, 1967; Monroe & Simons, 1991; Zuckerman, 1999) that most clearly highlights the issue at hand—*individual differences in responsiveness to the environment*. Of especial importance is that the diathesis–stress framework is principally, even exclusively, concerned with variation in response to contextual *adversity*. More specifically, diathesis–stress thinking stipulates that some individuals are disproportionately, if not exclusively, likely to succumb to the negative effects of some contextual stressor (e.g., poverty, negative life events). This heightened vulnerability to adversity may be due to organismic characteristics of the individual, such as genetic makeup, personality or temperament, which will be of principal concern here, as well as family factors and processes or extrafamilial conditions.

Not unrelatedly, developmental psychopathologists have embraced the concept of resilience, which is really the inverse of vulnerability (Garmezy, Masten, & Tellegen, 1984; Masten, Best, & Garmezy, 1990; Rutter, 1987; Werner & Smith, 1982). Empirical research on risk and resilience first emerged in the 1970s (e.g., Garmezy, 1974; Rutter, 1979; Werner & Smith, 1977) and has come to exert a major influence on the study of development and psychopathology (for reviews, see Luthar, Cicchetti, & Becker, 2000; Masten, 2007; Rutter, 2012). Indeed, one of the most important and valuable insights that emerged over the past decades has been that individuals differ in the degree to which they are affected by contextual adversity. Whereas some vulnerable children and adults are likely to develop problematically in response to negative contextual conditions—by becoming emotionally and behaviorally dysregulated or disordered—others are not and thus regarded as resilient. Like vulnerability, resilience may be a function of a variety of factors, including organismic (e.g., intelligence, humor, genes) and contextual ones (e.g., supportive friend or teacher (Garmezy, 1974)) (Figure 2.1). To be appreciated, however, is that resilience from this perspective is understood as a dynamic process rather than an inherent characteristic of an individual (Cicchetti & Rogosch, 2012; Rutter, 2012).

Prior to the emergence of theorizing about adaptive functioning in the face of significant adversity (i.e., resilience), investigations of risk and psychopathology generally portrayed the developmental process as somewhat deterministic, resulting in negative or maladaptive outcomes (Cicchetti & Rogosch, 2012). Ultimately, the concept of resilience had its origins in the observation that "there is huge heterogeneity in response to all manner of environmental hazards: physical and psychosocial"

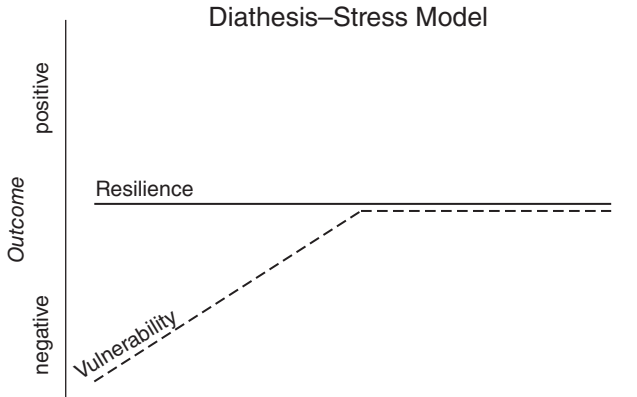


Figure 2.1 Graphical illustration of diathesis–stress. Vulnerability (i.e., diathesis) describes the propensity to respond negatively to adverse experiences, as a function of individual characteristics, whereas resilience reflects protective resistance from the same negative influences. No differences are predicted in response to positive influences. *Source:* Adapted from M. J. Bakermans-Kranenburg & M. H. van IJzendoorn, Gene–environment interaction of the dopamine D4 receptor (DRD4) and observed maternal insensitivity predicting externalizing behavior in preschoolers. *Developmental Psychobiology, 48*(5), 2006, Figure 1.

(Rutter, 2012, p. 336). But it needs to be appreciated given what is to follow in the discussion of differential susceptibility that "resilience is defined in terms of a better outcome than that seen in other individuals from a similarly adverse background . . . there is no requirement of superior functioning in relation to the non-deprived population as a whole" (Rutter, 2012, p. 342). As we will see, this feature of the resilient individual distinguishes diathesis–stress thinking from that of differential susceptibility.

Intriguingly, similar views were advanced by ecological scientists and biologists (Hanson & Gottesman, 2012), starting with Holling's (1973) work on ecological systems, with resilience defined as the capacity of a system to absorb disturbance and reorganize while undergoing change to retain essentially the same function, structure, identity, and feedbacks (Walker, Hollin, Carpenter, & Kinzig, 2004). Developmental geneticists captured a similar notion using the term *canalization* (Gottesman, 1974; Waddington, 1942).

A Psychological Challenge

It is not surprising that those who think predominately in diathesis–stress and resilience terms when considering human development—given their specific research interest in disordered, troubled and problematic functioning or the absence thereof—have rarely wondered about what might be regarded as the other half of the person–context interaction equation: How do individual differences, including with regard to organismic vulnerability factors, play out when circumstances are not adverse but benign, supportive or even enriching (Pluess & Belsky, 2013)? This critical question is central to this chapter because the differential susceptibility paradigm posits that those putatively vulnerable to adversity are also likely to be more responsive to positive and growth-facilitating developmental experiences and environmental exposures (Belsky, 1997b, 2005; Belsky, Bakermans-Kranenburg, et al., 2007; Belsky & Pluess, 2009a; Ellis, Boyce, et al., 2011). From this perspective, questions can be raised as to whether one should even speak of vulnerability factors (alone). By the same token, from the differential susceptibility perspective, those resilient and thus protected or buffered from the negative effects of adversity are also less likely—or entirely unlikely—to reap the rewards of a benign, supportive or enriching environment. This alternative analysis raises the prospect that so-called vulnerable individuals are not as unlucky or unfortunate as they might appear, nor are the so-called resilient as fortunate as they would seem to be according to traditional developmental psychopathological thinking.

An Evolutionary Challenge

An evolutionary perspective also raises issues about the prevailing developmental-psychopathological analysis of dysfunctional or maladaptive outcomes within settings of adversity. In particular, it contends that both stressful and supportive environments have been part of human experience throughout our evolutionary history, and that developmental systems shaped by natural selection respond adaptively to both kinds of contexts. Thus, when people encounter stressful environments, this does not so much *disturb* their development—as widely assumed—as *direct or regulate* it toward strategies that are *adaptive* under stressful conditions—even if those strategies are currently harmful vis-à-vis the long-term welfare of the individual or society as a whole (Ellis, Boyce, et al., 2011; Hinde & Stevenson-Hinde, 1990; Main & Solomon, 1990).

Consider the extensive experimental work conducted by Michael Meaney and colleagues showing that putatively low-quality maternal care in the rat (i.e., low levels of maternal licking and grooming) alters pups' stress physiology and brain morphology. Although such changes seem disadvantageous (i.e., higher corticosterone levels, shorter dendritic branch lengths, and lower spine density in hippocampal neurons), they actually *enhance* learning and memory processes under stressful conditions (Champagne et al., 2008). Moreover, such physiological and morphological changes mediate the effects of maternal behavior on central features of defensive and reproductive strategies—behavior under threat, open-field exploration, pubertal development, sexual behavior, and parenting (Cameron, Fish, & Meaney, 2008; Cameron et al., 2005)—in ways consistent with evolutionary models of adaptive reproductive strategies (Belsky, Steinberg, & Draper, 1991; Chisholm, 1993).

In the rodent model, then, enhanced learning under stressful conditions, increased fearful and defensive behaviors, accelerated sexual maturation, increased sexual behavior, and reduced parental investment in offspring apparently represent strategic—that is, functional—ways of developing when suffering parental neglect. In this context, neglect itself can be regarded as a mechanism through which rat mothers guide or program their offspring's development toward optimal survival and reproductive strategies *under conditions of adversity*. It would seem mistaken, therefore, to view diminished licking and grooming as inherently negative or the development induced by such care as disturbed. From an evolutionary perspective, the care provided by the putatively neglectful parents may be appropriate preparation of their offspring for the

ecological conditions into which they are likely to mature (Ellis, Boyce, et al., 2011).

It is important to note that optimal adaptation (in the evolutionary sense) to challenging environments is not without real consequences and costs. Harsh environments often harm or kill children, and the fact that children developmentally adapt to such rearing conditions (reviewed in Ellis, Figueredo, Brumbach, & Schlomer, 2009; Pollak, 2008) does not imply that such conditions either promote child well-being or should be accepted as unmodifiable facts of life (i.e., David Hume's naturalistic fallacy). There can be no doubt that high-stress environments that are dangerous and lack essential resources, compared with low-stress environments that are safe and well-resourced, cause substantial distress and eventually undermine fitness. In other words, developmental adaptations to high-stress environments simply enable individuals to make the best of a bad situation (i.e., to mitigate the inevitable fitness costs), even though the best may still constitute a high-risk strategy that jeopardizes the person's health, well-being and survival (e.g., Mulvihill, 2005; Shonkoff, Boyce, & McEwen, 2009). It is also important to mention here the possibility of genuinely novel environments that are beyond the normative range of conditions encountered over human evolution. Exposures to such challenging yet (evolutionarily) unprecedented conditions can be expected to induce pathological development that does not reflect evolutionarily adaptive strategies (Ellis, Boyce, et al., 2011).

In sum, an evolutionary-developmental perspective emphasizes *conditional adaptation*: "evolved mechanisms that detect and respond to specific features of childhood environments, features that have proven reliable over evolutionary time in predicting the nature of the social and physical world into which children will mature, and entrain developmental pathways that reliably matched those features during a species' natural selective history" (Boyce & Ellis, 2005, p. 290; for a comprehensive treatment of conditional adaptation, see West-Eberhard, 2003; for applications to human development, see Belsky et al., 1991, 2000; Chisholm, 1996; Ellis, 2004). From within such a perspective, the highly susceptible child who responds to a dangerous environment by developing insecure attachments, adopting an opportunistic interpersonal orientation, and sustaining an early sexual debut is no less functional than the context-sensitive child who responds to a well-resourced and supportive social environment by developing the opposing characteristics and orientations. Children have evolved to function competently—to survive and ultimately reproduce—in a variety of contexts, and the default assumption should be that alternative patterns of development in response to both stressful and supportive environmental conditions (within the range encountered over human evolution) constitute adaptive variation (Ellis, Boyce, et al., 2011).

BEYOND DIATHESIS–STRESS

Evolutionary-Developmental Theories of Differential Susceptibility

In addition to shaping species-typical developmental responses to diverse environmental conditions, natural selection has also maintained variation—adaptive individual differences—in neurobiological susceptibility to the environment. Two different evolutionary accounts of such variation in human development have emerged in recent years (Ellis, Boyce, et al., 2011): DS (Belsky, 1997b, 2005; Belsky, Bakermans-Kranenburg, et al., 2007); and biological sensitivity to context (BSC; Boyce & Ellis, 2005; Boyce et al., 1995; Ellis, Essex, & Boyce, 2005). With a central focus on person–environment interactions, both models highlight the role of organismic characteristics of individuals in moderating the effects of both stressful and supportive environmental conditions on human development (Figure 2.2). Thus, both presume that there

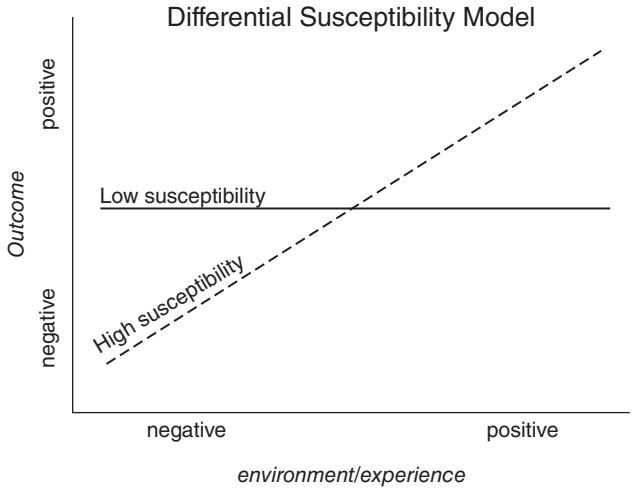


Figure 2.2 Graphical illustration of differential susceptibility. High susceptibility is characterized by increased responsivity to both negative and positive experiences, as a function of individual characteristics, in contrast to low susceptibility, which reflects a general psychological inertia to environmental influences independent of quality. *Source:* Adapted from M. J. Bakermans-Kranenburg & M. H. van IJzendoorn, Gene–environment interaction of the dopamine D4 receptor (DRD4) and observed maternal insensitivity predicting externalizing behavior in preschoolers. *Developmental Psychobiology, 48*(5), 2006, Figure 1.

are individual differences in sensitivity and responsiveness to environmental influence but, importantly, not in the manner of diathesis–stress. Both theories incorporate the traditional diathesis–stress view while extending it, by making the critical observation that those individuals most likely to be adversely affected (according to conventional mental health standards) by negative environmental conditions are also most likely to benefit from supportive ones.

Focusing on the role of the person in moderating environmental effects on development, DS and BSC theories follow in the tradition of Bronfenbrenner's (1993) person–process–context model, which posits that parenting and other environmental factors may vary in their developmental influence as a function of the characteristics of the child. The theories also converge with Wachs and Gandour's (1983) organismic-specificity hypothesis, which posits differential reactivity of children to similar rearing experiences as a function of differences in children's cognitive, behavioral, or emotional characteristics.

Before proceeding with a review and comparison of DS and BSC theories, it is important to note that these perspectives share much in common with Aron and Aron's (1997; Aron, Aron, & Davies, 2005) theory of sensory-processing sensitivity (SPS). The main difference is that DS and BSC began with a focus on child-developmental processes, whereas SPS started with a focus on cognitive processes in adults (in terms of variation in depth of processing of sensory information, with more sensitive individuals processing information more thoroughly before acting). Although some SPS studies have included retrospective assessments of childhood experiences, SPS did not originate from a developmental perspective. Given that longitudinal work on the role of SPS in regulating child (or adult) development has yet to be conducted, we consider it premature to endeavor to integrating SPS theory with BSC and DS at this time.

Differential Susceptibility Theory

The question of why childhood experiences should influence later development—one rarely posed by developmentalists concerned principally with how experience influences development—was the origin of DS theory, along with challenges posed by behavior-genetic critiques by Rowe (2000) of Belsky et al.'s (1991) evolutionary theory of socialization (Belsky, 2000). From an evolutionary perspective, developmental mechanisms that use earlier experiences to guide later development should only evolve in recurring contexts in which the future is tolerably related to the past (Pigliucci, 2001), at least within generations. Only then could there be reliable fitness payoffs in using experiences in childhood to regulate adolescent and adult development (i.e., conditional adaptation). The fact that the future is inherently uncertain, however, meant that conditional adaptation was theoretically problematic (i.e., risk for potential mismatch). This realization led Belsky (1997a, 1997b, 2000, 2005) to propose that, as a form of bet-hedging against an uncertain future, natural selection has maintained genes for both conditional and alternative developmental strategies. Whereas conditional strategies are shaped by environmental factors to better fit the organism to the future environment, alternative strategies, in a manner consistent with much behavior-genetic thinking, are largely fixed and less subject to environmental regulation (Rowe, Vazsonyi, & Figueredo, 1997).

Because the future is and always has been uncertain, no parent could ever know for certain what rearing strategies, whether consciously or unconsciously implemented, would prove most successful in terms of promoting the child's reproductive fitness and thus the parent's inclusive fitness. This suggested to Belsky (1997a, 1997b, 2000, 2005) that—especially within families—children should vary in their susceptibility to the rearing environment, broadly construed. Indeed, while it would make sense for parents to produce some children who pursued *alternative* strategies, perhaps entirely impervious to socialization efforts, and who would thrive in particular contexts that fit their proclivities, it would also make sense for them to bear some *conditional* strategists capable of fitting and thriving in a variety of niches depending upon the rearing conditions encountered while growing up.

Belsky (2005) subsequently observed not only that parents would be (unconsciously) hedging their bets by diversifying their progeny's susceptibility to rearing influence but also that the same would be true of children themselves. This was due to the fact that, just like parents and children, siblings share 50% of the same genetic alleles. Thus, if one child benefited from parental influence, so would the other, less susceptible sibling—but indirectly, via shared genes. By the same token, if one child's development was undermined, inadvertently, by parental influence, the less susceptible child would be protected, thereby providing an indirect, inclusive-fitness benefit to the child whose susceptibility proved counterproductive in individual terms. From the perspective of both parent and child, then, differential susceptibility to rearing and perhaps other environmental factors and processes was considered to be evolutionarily advantageous.

Although Belsky's theorizing stipulated that children should vary in their susceptibility to environmental

influence, it did not specify what might distinguish those children who were more susceptible from those who were less. Indeed, the theory lacked any explanatory mechanism, something we will see distinguished it substantially from BSC theorizing which was stimulated by mechanistic thinking. Early attempts to identify potential susceptibility factors or markers called attention, somewhat surprisingly, to negative emotionality or difficult temperament early in life (Belsky, 1997a, 2005; Belsky, Hsieh, & Crnic, 1998), whereas gene × environment interaction work, as well as theory and research on physiological reactivity by Boyce and Ellis (Boyce et al., 1995, 2005), called attention to physiological and genetic markers of variation in susceptibility (e.g., Bakermans-Kranenburg & van IJzendoorn, 2007; Belsky & Pluess, 2009a).

The differential susceptibility hypothesis, while not directly influenced by Plomin and Daniel's (1987) important insights about nonshared environmental effects, was eminently consistent with it. Indeed, in some respects the differential susceptibility perspective offered an explanation as to why nonshared, within-family effects should be the rule, as they have proven to be in behavior-genetic research, rather than the exception, with shared environmental effects proving so modest (Plomin & Daniels, 1987; Reiss, Neiderhiser, Hetherington, & Plomin, 2000; Turkheimer & Waldron, 2000). Because children within families vary in their susceptibility to rearing influences, they should be differentially affected by exposure to the very same developmental experience. Differential susceptibility thinking could also account for why environmental effects have proven both variable and generally modest across studies—perhaps because samples have varied, inadvertently, in the proportion of more and less susceptible individuals which they include, and because such individuals have not been distinguished in estimations of average rearing effects (Belsky, Hsieh & Crnic, 1998).

Biological Sensitivity to Context Theory

Whereas DS thinking emerged initially as a totally theoretical account of human development, not stimulated by any empirical findings, just the reverse proved true of BSC thinking. Indeed, the concept of BSC has its early roots in Boyce and colleagues' (1995) two studies of naturally occurring environmental adversities and stress reactivity as predictors of respiratory illnesses in 3–5-year-old children. Results revealed, first, that children showing low cardiovascular or immune reactivity to stressors had approximately equal rates of respiratory illnesses in both low and high adversity settings. Second, and consistent with the prevailing diathesis–stress model, highly biologically reactive children exposed to high adversity child care settings or home environments had substantially higher illness incidences than all other groups of children. The third—and unexpected—finding was that highly reactive children living in lower adversity conditions (i.e., more supportive child care or family settings) had the *lowest* illness rates, significantly lower than even low reactivity children in comparable settings. Such unanticipated results—in need of an explanation—led Boyce et al. (1995, p. 419) to suggest that "reactive children . . . with a heightened sensitivity to . . . the environment might . . . be expected to experience unusually poor outcomes in high-stress, unsupportive social conditions. The same children might flourish, on the other hand, under low-stress, nurturing, and predictable conditions. . . ." Such a conclusion would subsequently lead to the differential susceptibility view that some children are more responsive to the environment for better and for worse (Belsky, Bakermans-Kranenburg, et al., 2007).

Of critical and distinguishing importance is that the initial Boyce et al. (1995) research, together with subsequent work (Boyce & Ellis, 2005), identified a *physiological mechanism* of environmental susceptibility—autonomic, adrenocortical, or immune reactivity to psychosocial stressors—and proposed that psychobiologic reactivity moderated the effects of early environmental exposures on physical and mental health outcomes in a bivalent manner. More reactive children displayed heightened sensitivity to both positive and negative environmental influences and thus were given the shorthand designation of orchid children, signifying their special susceptibility to both highly stressful and highly nurturing environments. Children low in reactivity were designated as dandelion children, reflecting their relative ability to function adequately in species-typical circumstances of all varieties (Boyce & Ellis, 2005).

Mechanistic analysis of BSC led Boyce and Ellis (2005) to highlight the significance of the stress response system, but not just as a long-appreciated means of regulating behavior in the face of adversity, but also in response to resources and support in the ambient environment (e.g., positive social opportunities, cooperative information). This dual function signified the need to re-conceptualize stress reactivity more broadly as biological sensitivity to context, which Boyce and Ellis (2005) defined as neurobiological susceptibility to both cost-inflicting and benefit-conferring features of the environment and operationalized as a physiological property indexed by heightened reactivity in one or more of the stress response systems. Depending on levels of nurturance and support versus harshness and unpredictability in their

developmental environments, highly reactive children experience either the best or the worst of psychiatric and biomedical outcomes within the populations from which they are drawn (Boyce, 1996; Boyce et al., 1995, 2006; Bubier, Drabick, & Breiner, 2009; Ellis, Shirtcliff, Boyce, Deardorff, & Essex, 2011; Essex, Armstrong, Burk, Goldsmith, & Boyce, 2011; Obradovic, Bush, & Boyce, 2011; Obradovic, Bush, Stamperdahl, Adler, & Boyce, 2010; Quas, Bauer, & Boyce, 2004). BSC theory therefore posits that individual differences in the magnitude of biological stress responses function to regulate openness or susceptibility to environmental influences, ranging from harmful to protective.

Given past evidence that early trauma can increase stress reactivity and newer evidence that high reactivity can enhance developmental functioning in highly supportive settings, Boyce and Ellis (2005) postulated a curvilinear, U-shaped relation between levels of early support-adversity and the magnitude of biological response dispositions. Specifically, Boyce and Ellis hypothesized that: (1) exposure to acutely stressful childhood environments up-regulates BSC, increasing the capacity and tendency of individuals to detect and respond to environmental dangers and threats; (2) exposure to especially supportive childhood environments also up-regulates BSC, increasing susceptibility to social resources and support; and (3) by contrast, and typical of the majority of children, exposure to childhood environments that are not extreme in either direction down-regulates BSC, buffering individuals against the chronic stressors encountered in a world that is neither highly threatening nor consistently safe.

Toward an Integrated Differential Susceptibility Paradigm

Even though DS and BSC theories emerged independently and differ in important respects, they share much in common (Ellis, Boyce, et al., 2011). First, both theories, based as they are on an evolutionary analysis of human development, advance the claim that individuals differ systematically in their susceptibility to environmental influences (i.e., developmental plasticity) and seek to explain the nature of such individual differences. As will become apparent in the next major section of this chapter, this begins with the recognition that susceptibility to the environment is instantiated in the multiple genetic polymorphisms, physiological mechanisms, and behavioral phenotypes that operate as susceptibility factors, moderating the influence of environmental exposures on developmental and life outcomes. Several of the physiological mechanisms may be considered endophenotypes (Gottesman & Gould, 2003) constituting links between genes and behavior, whereby (single or multiple) genetic markers of differential susceptibility operate through the same neurobiological processes in which behavioral indicators of differential susceptibility are grounded.

Second, both DS and BSC theories presume that individuals *should* differ in their neurobiological susceptibility to environmental influence, and that such differential susceptibility underlies many reliable person–environment interactions regulating human development and functioning. Indeed, both theories embrace, implicitly if not explicitly, Bronfenbrenner's (1979) dictum that when it comes to human development, *the main effects are in the interactions*, be those gene–environment, temperament–parenting, stress reactivity–family stress, or other person–environment processes. More specifically, central to both DS and BSC theories is the assumption that environmental influences on developmental and life outcomes are moderated by neurobiological susceptibility to the environment. Both theories thus conceptualize variation in neurobiological susceptibility as a central mechanism in the regulation of alternative patterns of human development.

Third, neither theory presumes that differential susceptibility is restricted to any one developmental period or even just to childhood; both appreciate that at all developmental stages during the life span, individuals may differ in the extent to which they are affected by both supportive and challenging environments. Along these lines, research documenting differential susceptibility in children, adolescents, and adults is considered later in this chapter. Nonetheless, both DS and BSC theories were originally developed to explain neurobiological susceptibility in childhood, as clearly reflected in the preceding summaries of these perspectives.

Finally, a core assertion of both DS and BSC theories is that individuals differ in neurobiological susceptibility to environmental contexts that are both positive in character (i.e., afford resources and support that potentially enhance fitness) and negative in character (i.e., embody stressors and adversities that potentially undermine fitness). In other words, and in contrast to widely embraced diathesis–stress models, it is not simply that some individuals are more susceptible to the negative effects of adversity, making them vulnerable. Rather, DS and BSC theories regard those disproportionately vulnerable to adversity as also disproportionately likely to benefit from supportive and enriching environments. Such individuals are thus affected by the environment in a manner that can be characterized as for better and for worse (Belsky, Bakermans-Kranenburg, et al., 2007). Another way of

describing or even conceptualizing the individual differences in question is in terms of reaction norms (Manuck, 2010). Whereas some individuals have a wide range of reaction in terms of their developmental functioning, depending on the environments they encounter, others have a much narrower range of reaction, responding less markedly—if at all—to positive and negative life experiences.

It is critical to appreciate that differential susceptibility to positive and negative environments has different implications when viewed from developmental-psychopathology and evolutionary perspectives (Ellis, Boyce, et al., 2011). In the developmental-psychopathology framework, heightened neurobiological susceptibility increases the ability and tendency of individuals to experience good outcomes in positive environments (i.e., for better, as defined by dominant Western values like secure attachment, happiness, high self-esteem, emotion regulation, educational and professional success, stable marriage) and bad outcomes in negative environments (i.e., for worse, as defined by that same value system such as insecure attachment, substance abuse, conduct problems, depression, school failure, teenage pregnancy). By contrast, according to the evolutionary perspectives central to both DS and BSC theories, heightened neurobiological susceptibility to the environment functions to direct or regulate development in ways that, over human evolution, recurrently matched individuals to both positive and negative environments, thereby promoting reproductive fitness. In positive environments, this translates into adjusting development to optimize reproductively relevant processes and behaviors such as growth, status, fertility, and offspring quality. This form of conditional adaptation would typically be considered for better in a developmental psychopathology framework. In negative environments, however, this translates into making the best of a bad situation, often resulting in developmental outcomes that are typically regarded as nonoptimal in Western culture. A key difference, then, between the evolutionary and developmental-psychopathology perspectives is that evolutionary models conceptualize conditional adaptation to negative environments as a functional and strategic output of evolved developmental systems shaped by natural selection in the service of fitness goals. Consequently, even though susceptible individuals in negative environments may be especially vulnerable to poor mental health (as defined by dominant Western values), for example, they may still be acting in ways that promote—or once promoted—status and reproductive success in dangerous environments (e.g., gang membership in bad neighborhoods (see Palmer & Tilley, 1995), advantage taking, sexual promiscuity, limited parental investment).

Beyond these points of agreement, it is worth highlighting that both DS and BSC theories derive from evolutionary analyses of human development which, even if not identical, are grounded in the view that natural selection maintains alternative patterns of development (phenotypic variation) in the context of multiniche environments (e.g., Hinde & Stevenson-Hinde, 1990; Penke, Denissen, & Miller, 2007). Both theories posit that variation in neurobiological susceptibility to the environment has been adaptively structured and functions as a central mechanism in regulating alternative developmental pathways to match—as best possible—different environmental niches (Ellis, Boyce, et al., 2011). Fundamental to this view is the assumption that optimal developmental strategies vary as a function of the physical, economic, and social parameters of an individual's specific environment. Levels of neurobiological susceptibility that promote success in some environments may therefore lead to failure in others. It is this kind of environmental heterogeneity—multiniche environments in which a trait's effect on fitness varies across time or space—that provides the ecological basis for the maintenance of adaptive phenotypic variation (whether through balancing selection, conditional adaptation, bet hedging, or a combination thereof; see Ellis, Jackson, & Boyce, 2006; Ellis, Shirtcliff, Boyce, & Essex, 2009; Penke et al., 2007).

In sum, the DS and BSC models largely converge on an integrated theory of neurobiological susceptibility to the environment. Taken together, these perspectives shed new light on the potency—and impotency—of a broad range of environmental contexts, from highly positive and enriching to dangerous and corrosive, to shape the gamut of developmental outcomes.

Having delineated the theoretical framework of differential susceptibility while contrasting it to that of diathesis–stress, attention now turns to empirical evidence, seemingly consistent with differential susceptibility. Before reviewing relevant research, however, some methodological comments are regarding the empirical evaluation of differential susceptibility.

METHODOLOGICAL CONSIDERATIONS IN EVALUATING DIFFERENTIAL SUSCEPTIBILITY

Three distinct methodological issues relating to differential susceptibility are of concern here: measurement of the environment; cultural and racial variation; statistical evaluation.

The Importance of Securing Adequate Environmental Variance

Because the essence of the differential susceptibility model is that individuals who display high neurobiological susceptibility to the environment are not only disproportionately affected by negative contexts but also respond more favorably to positive environmental influences (Figure 2.2), it is imperative that tests of this hypothesis secure adequate variance in environmental conditions (Belsky, Bakermans-Kranenburg, et al., 2007; Ellis et al., 2005). This is because targeting risky environments may obscure the potential benefits of exposure to positive contexts for susceptible individuals, while a narrow focus on only positive environments or outcomes (though less often seen in practice) may have the opposite effect. Thus, a broad range of environmental qualities is a minimum condition to reveal differential susceptibility—a condition that is often not met in studies of developmental psychopathology and much of the research to be cited below.

The importance of careful measurement of the environment (and the outcome) cannot be overestimated (Ellis, Boyce, et al., 2011). Some two decades ago Wachs and Plomin (1991) identified what they called Plomin's paradox: if interaction effects—which are central to the evaluation of differential susceptibility—are ubiquitous in nature, why are they so difficult to detect in behavioral studies (see, McClelland & Judd, 1993)? One of the explanations could have to do with unstable or unreliable measures of the environment. When the error components of the genetic and environmental parts of the GxE equation strongly diverge, testing for moderation is at risk for both type 1 and type 2 errors. Therefore, in studies on differential susceptibility, more than usual care should be taken to assess the environment (and behavioral outcome) reliably and validly by extended behavioral observations in various situations, the use of multiple informants, and aggregation of data across settings and measures. Many of these conditions are not met in the research to be reviewed.

Tests of differential susceptibility involve variation in organismic characteristics, environmental factors, and developmental outcomes (Figure 2.2). These variance components may be highly interdependent and context-dependent. Indeed, child effects and by extension person–environment-interaction effects are highly dependent on variance in the environment (Ellis, Boyce, et al., 2011). Quite importantly, person–environment interactions are much more likely to emerge in the range of average expectable environments than at environmental extremes (Cicchetti & Valentino, 2006; Hartmann, 1958), where the power of context to shape human development may restrict the range of phenotypic variation. In twin studies, for example, physical growth (e.g., height) and IQ have been shown to be highly heritable, but the majority of children growing up in institutions show delays in growth and diminished IQ that become exponentially greater with longer institutionalization (e.g., Rutter & English Romanian Adoptees, 1998; van IJzendoorn, Luijk, & Juffer, 2008). Drastically improved care through adoption, foster care, or interventions within institutions results in massive catch up for virtually all children (Marian J. Bakermans-Kranenburg, van IJzendoorn, & Juffer, 2008; Nelson et al., 2007), leaving little room for interaction effects between environment and child characteristics.

Ecological, Cultural, and Racial-Ethnic Dimensions of Differential Susceptibility

Further, cross-cultural research raises the issue of the cultural specificity of the environment, the susceptibility/plasticity factor, and the developmental outcome that together constitute the differential susceptibility equation (Ellis, Boyce, et al., 2011). Cross-cultural studies of differential susceptibility have documented that the meaning and context of specific parental behaviors, as well as the value placed on specific developmental outcomes, may vary between different cultural groups and across different ecological niches (Deater-Deckard, Pinkerton, & Scarr, 1996; Hinde & Stevenson-Hinde, 1990; Scheper-Hughes, 1992). Moreover, and with regard to race/ethnicity, it is not just familial factors and developmental outcomes that may be different, but neurobiological susceptibility as well. Attempting to replicate and extend Caspi and associates' (2002) GxE findings (on child maltreatment, the MAOA genotype, and antisocial behavior), Widom and Brzustowicz (2006) replicated the original GxE result and detected evidence of differential susceptibility (Belsky & Pluess, 2009a). However, they also discovered that the GxE finding only applied to Caucasians, not to African Americans. (For examples pertaining to dopamine-related genes, see Bakermans-Kranenburg & van IJzendoorn, 2011).

The explanation for this racial difference may be that the genetic effects in question are dependent on race: Short alleles of 5-HTTLPR are associated with the production of *higher* levels of serotonergic function in the central nervous system of African American participants but *lower* levels of serotonergic function among European American participants (Williams et al., 2003). Moreover, the distributions of genotypes differs substantially among the various parts of the world, showing for instance lower prevalence of

the DRD4–7-repeat allele on the African continent and more carriers of the 5HTT short allele in Asia compared with Europe and North America (Chen, Burton, Greenberger, & Dmitrieva, 1999; Gelernter, Cubells, Kidd, Pakstis, & Kidd, 1999). Ethnically homogeneous samples are thus preferred in GxE investigations but not restricted to Caucasian samples in Western countries. The generalizability of GxE interaction effects reflecting differential susceptibility to populations of different cultures and races is not self-evident but should each time be empirically established.

Statistical Criteria for Evaluating Differential Susceptibility

The statistical test of differential susceptibility first proposed by Belsky et al. (2007) consists of a series of five consecutive steps. In short, the first always concerns the application of conventional statistical criteria for evaluating moderation (Dearing & Hamilton, 2006). The second step refers to various shapes moderator effects can take, not all of which are indicative of differential susceptibility (see Belsky, Bakermans-Kranenburg, et al., 2007, for a figure delineating various interaction effects). Interactions with regression lines that do not cross (sometimes referred to as removable interactions) do not document differential susceptibility, although they are not necessarily incompatible with aspects of differential susceptibility (depending on the range of environments covered). Differential susceptibility is more conclusively shown when the moderation reflects a crossover interaction that covers both the positive and the negative aspects of the environment. The slope for individuals high in neurobiological susceptibility should be significantly different from zero and at the same time significantly steeper than the slope for the individuals low in neurobiological susceptibility. If both slopes are significantly different from zero but in opposite directions (i.e., look like an X), contrastive effects rather than differential susceptibility effects are indicated.

The next step requires that there be no association between the moderator (i.e., the susceptibility factor) and the environment (see Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001). In other words, differential susceptibility should be distinguished from GxE or temperament–environment correlations (which may reflect rearing experiences evoked by child characteristics) and from dual-risk models (Figure 2.1). Belsky et al. (1998), for example, tested the independence of negative emotionality and parenting as a critical step in their investigation of differential susceptibility. Had these factors been correlated, then the evidence would not have shown that the predictive power of parenting was greater for highly negative infants. Instead, it would have indicated either that highly negative infants evoke negative parenting or that negative parenting fosters infant negativity. Similarly, Caspi and Moffitt (2006) determined that boys' MAOA genotype did not elicit maltreatment. Correlations between the environment and the moderator may be dealt with by partialling out the variance in the moderator explained by the environmental factor prior to testing for differential susceptibility as described already. Pluess and Belsky (2010) used this approach to overcome the problem in their investigation of differential susceptibility to parenting. A further step concerns the association between moderator (i.e., susceptibility factor) and outcome, which has to be zero to reflect differential susceptibility. If the susceptibility factor and the outcome are related, dual risk (or gain, when positive factors are involved) may be a more plausible model. Along these lines, if an intervention proves successful in counter acting the negative effects of a risk gene (or other risk factor) that is correlated with the outcome (e.g., 5-HTTLPR and youth risk behavior initiation, as in Brody, Beach, Philibert, Chen, & Murry, 2009), the experiment tests a protective factor model more than a differential susceptibility model in which the polymorphism should be a risk as well as a susceptibility gene. As a final step, Belsky et al. (2007) suggested testing the specificity of the effect by replacing the susceptibility factor (i.e., moderator) and outcomes (see Caspi, Harrington, et al., 2003, for an example of such replacement establishing discriminant validity in the GxE tradition).

Because we are still in the early stages of testing differential susceptibility, not all of the empirical work to be considered below actually meets all the statistical criteria just enumerated. Moreover, as we will highlight in the last major section of the chapter on unknowns in the differential susceptibility equation, new statistical approaches have been proposed recently which afford competitive evaluation of differential susceptibility and other models of environmental action, including diathesis–stress. Now, however, attention turns to research chronicling differential susceptibility, organized in terms of first psychological, then physiological and finally genetic susceptibility factors.

BEHAVIORAL MARKERS OF DIFFERENTIAL SUSCEPTIBILITY

The first evidence of differential susceptibility to be considered comes from research showing that temperamental and

emotional characteristics of (mostly very young) children moderate the effect of developmental experience on behavioral development. Some of this work highlights the role of early negative emotionality/difficult temperament vis-à-vis parenting effects, some of it the moderated influence of child-care experience, and some of it individual differences in plasticity beyond the early childhood years. Each set of evidence is considered in turn. Of note is that unless otherwise indicated the work to be cited was conducted without regard to the differential susceptibility hypothesis and, if anything, informed by diathesis–stress thinking. It is highlighted, nevertheless, due to evidence generated of differential susceptibility, whether appreciated by the investigators or not.

Negative Emotionality and Difficult Temperament as Plasticity Markers

Some of the earliest and most suggestive evidence of differential susceptibility to environmental influences emerged in research on temperament–parenting interaction, a long-standing focus of inquiry, typically conducted from a dual-risk/diathesis–stress perspective (Rothbart & Bates, 2006). In fact, after advancing the differential susceptibility hypothesis that, it will be recalled, included no claims regarding proximate factors or mechanisms that would make some children more susceptible than others, Belsky sought to identify some in existing and continually emerging developmental research. Indeed, well before any GxE research on humans was reported, he called attention to infant and toddler negative emotionality and difficult temperament as potential differential susceptibility factors (for review, see Belsky, 2005). Whether operationalized in terms of difficult temperament, irritability, fearfulness, or inhibition, cross sectional and longitudinal studies by Kochanska (1993); Belsky, Hsieh, and Crnic (1998); and Feldman, Greenbaum, and Yirmiya (1999) showed, for example, that diverse measures of rearing of infants and toddlers (e.g., discipline, interactional synchrony, positive and negative parenting) accounted for substantially more variance in self-control, externalizing problems and inhibition in the case of more negatively emotional infants/toddlers than other children. (All but the Kochanska, 1993, study were explicitly designed to test differential susceptibility.) But it was not just in research on very young children that such shorter and longer term rearing effects emerged. Morris and associates (2002) found, for example, that harsh and hostile mothering also proved to be a stronger predictor of teacher-reported externalizing problems in first and second grade when children scored high rather than low on irritable distress.

Most of the research on children reviewed by Belsky (2005) showed, following documentation of significant temperament–parenting interactions, that *greater variance* in a variety of developmental outcomes could be explained by rearing experiences in the case of more negatively emotional children, statistical analyses in the studies reviewed often did not afford determination of whether this result was itself a function of a for-better-and-for-worse parenting effect. In consequence, it remained undetermined whether individual differences in plasticity—or just vulnerability—were responsible for the repeatedly detected finding that more variance was explained in one group's functioning than in another's by the environmental factor investigated.

Fortunately, a growing number of studies provide substantial empirical evidence that rearing and other environmental effects do not just account for more variance in the functioning of more negatively emotional children—or even that such individuals are simply more vulnerable to negative experiences as the dual-risk/diathesis–stress model would suggest—but that they are indeed differentially susceptible to environmental experiences in a for-better-and-for-worse manner. Van Aken, Junger, Verhoeven and Dekovic (2007) found, for example, that 16–19-month-old boys (N = 115) with difficult temperament showed the smallest increase six months later in externalizing problems scores when reared by highly sensitive mothers who only infrequently used negative control, but the largest increase when highly insensitive mothers relied heavily on negative control. These striking parenting effects simply did not obtain in the case of other children.

In a series of investigations Kochanska, Aksan, and Joy (2007) evaluated whether child temperament moderated parenting effects on positive developmental outcomes. In one study children's fearfulness, maternal power assertion, and mother–child positive relations were assessed behaviorally when children were 22 and 33 months old and children's moral self was measured using a puppet interview at 56 months ($N = 74$). Although no parenting effects emerged in the case of children who, as toddlers, scored low in fear, those who were highly fearful evinced a greater moral sense if their mothers (at 22 months only) relied little on power assertion to regulate their behavior, but a limited one if their mothers relied heavily on power to control earlier child behavior. The fact that child fearfulness was itself significantly and negatively related to maternal power assertion raises some questions about how much confidence to place in this study when it comes

to inferring individual differences in plasticity. Recall that in circumstances such as these in which the putative susceptibility factor is itself related to the environmental factor, thereby raising the prospect of evocative person effects, a better approach would be to partial the effect of the susceptibility factor from the environmental one before testing interactions between the two. This would statistically eliminate the potential evocative effect that confounds interpretation of differential susceptibility.

In a second study ($N = 100$ families), this time focused on father's reliance on power assertion (15 months), children's fearfulness (7 and 15 months) and their rule compatible conduct (38 months), Kochanska et al. (2007) once again documented evidence of for-better-and-for-worse parenting effects: Whereas high versus low power assertiveness made no apparent difference for children scoring low in fearfulness (at 7 and 15 months), children who had been highly fearful infants proved less obedient than all others when fathers' power assertion was high, yet more obedient than all others when fathers' power assertion was low. And this time child fearfulness was not associated with paternal power assertion or rule-compatible conduct, hence fulfilling important criteria for inferring differential susceptibility.

Drawing on data of the large-scale longitudinal National Institute of Child Health and Human Development (NICHD) study of Early Child Care and Youth Development (NICHD Early Child Care Research Network, 2005) and focusing on maternally reported difficult temperament at one and six months (composited), Bradley and Corwyn (2008) specifically tested and discerned (repeated) evidence of differential susceptibility. More specifically, these investigators evaluated effects of three measures of parenting quality (sensitivity, harshness, productive activity), each composited and averaged across multiple measurement occasions from infancy through first grade, on teacher-reported behavior problems in first grade ($N = 929$). Results showed that children with more difficult temperaments had more behavior problems in first grade than all other children if they experienced low-quality parenting, but fewer problems than all other children if they experienced high-quality parenting; the anticipated effect of parenting quality was weaker in the case for children with intermediate levels of difficult temperament and weaker still in the case of children scoring very low on difficult temperament (i.e., easy temperament). Such findings suggest that rather than conceptualizing some children, categorically, as malleable and others as not, it might be more appropriate to conceptualize and measure individual differences in plasticity dimensionally, in terms of a plasticity gradient (Belsky, 2000; see also Warren & Simmens, 2005, for similar results using the same data).

Stright, Gallagher, and Kelley (2008) were able to extend work explicitly testing differential susceptibility to positive developmental outcomes by also drawing on data from the NICHD study of Early Child Care (NICHD Early Child Care Research Network, 2005). Once again a temperament–parenting interaction emerged, this time between difficult temperament (at 6 months) and parenting style (composited across 6, 15, 24, 36, and 54 months) in predicting teacher-rated academic competence, social skills, teacher–child relationships, and peer-status at first grade. Predictive power proved greater for infants with more difficult temperaments than for infants with less difficult temperaments. Although all interactions were of a cross-over nature and in line with a for-better-and-for-worse parenting effect for only some children, not all criteria for differential susceptibility were met; of special significance, as already noted, is that the temperament susceptibility factor itself predicted the parenting predictor (as well as at least one outcome measured).

Pluess and Belsky (2010) overcame this problem in their analysis of differential susceptibility while drawing on the same NICHD study. After finding that parenting quality prior to school entry predicted reading, math, picture vocabulary, social competence and academic work habits in the fifth grade more strongly for children with difficult temperament than for those with easy temperaments—and in a for-better-and-for-for worse manner—they reran their analysis using the method proposed earlier for discounting discerned evocative effects of a putative susceptibility factor (i.e., temperament) on the environmental predictor (i.e., parenting quality). When the composite measure of parenting quality was statistically adjusted to control for the effect of 6-month, mother-reported difficult temperament, differential susceptibility findings remained virtually unchanged.

Since reviewing the just-cited evidence some years ago (Belsky & Pluess, 2009a), even more evidence of this differential susceptibility related, negative emotionality/difficult temperament moderational effect has emerged in the case of children. This has been revealed in research linking maternal empathy (Pitzer, Jennen-Steinmetz, Esser, Schmidt, & Laucht, 2011) and anger (Poehlmann et al., 2012) with externalizing problems, mutual responsiveness observed in the mother–child dyad with effortful control (Kim & Kochanska, 2012), intrusive maternal behavior (Conway & Stifter, 2012), and poverty (Raver, Blair, & Willoughby, 2013) with executive functioning; and sensitive

parenting with social, emotional and cognitive-academic development (Roisman et al., 2012).

Moreover, other new research suggests that "emotion regulation in part explains why negative reactivity can be associated with poor outcomes in supportive contexts and beneficial outcomes in supportive contexts" (Ursache, Blair, Stifter, & Voegtline, 2013, p. 129). More specifically, after discovering that executive functioning at 4 years of age was highest among children who were highly negatively reactive (to fear-evoking stimuli) and high in regulating such reactivity at 15 months of age, but lowest among 4-year-olds who were similarly high in negativity but low in regulation as toddlers, Ursache and associates (2013) tested—and found support for—the proposition that the former children had experience especially positive parenting. Considered together, such data suggest that by promoting emotional regulation, supportive rearing sets the stage for highly negatively reactive children to become especially competent.

Although discussion through this point has focused upon the influential role of parenting, it is important to note that it is not just susceptibility to the effects of parenting that negativity seems to moderate in a for-better-*and*-for-worse manner, as documented in recent work examining the influence of teacher-child conflict on change in symptomology during the primary-school years (Essex et al., 2011). We would be remiss, however, if we failed to call attention to studies showing it was less rather than more negatively emotional or reactive children who proved highly responsive to environmental experiences in a manner consistent with differential susceptibility (Essex et al., 2011, Figure 2, bottom; Schudlich, White, Fleischhauer, & Fitzgerald, 2011) and to other evidence showing that sometimes difficult temperament operates only in a manner consistent with the diathesis–stress rather than differential susceptibility framework (Kochanska & Kim, 2013; Roisman et al., 2012; Yaman, Mesman, van IJzendoorn, & Bakermans-Kranenburg, 2010).

The fact that the research cited reveals that diverse indices of negative emotionality function as plasticity factors (e.g., fear, inhibition, distress, difficult temperament, negative affect) raises several issues that future research should address. First, is there a particular component or feature of negativity that is principally responsible for the moderational effects detected (Buss, 2011)? Or might more progress be made with regard to this issue by embracing the integrated, evolutionary, hawk-dove model of temperament (Korte, Koolhaas, Wingfield, & McEwen, 2005) that Sturge-Apple, Davies, Martin, Cicchetti, and Hentges (2012) recently found to be empirically useful. Whereas hawk-like strategies are characterized by approach, dominant-negative affect (e.g., anger), and activity, dove-like ones involving avoidance, inhibition, and vulnerable affect (e.g., fear) seem more consistent with heightened plasticity according to existing research.

We can also wonder about the extent to which the moderational effect of negative emotionality depends on the origins of this plasticity factor, given evidence that negativity is heritable (e.g., Buss & Plomin, 1984; Rhee et al., 2012), but also shaped by prenatal and postnatal experience (Belsky & Pluess, 2009b; Davis, Glynn, Waffarn, & Sandman, 2011; Glynn & Sandman, 2011; for review, see Pluess & Belsky, 2011)—though sometimes more so in the case of some genotypes than others (Ivorra et al., 2010; Pluess et al., 2011). Thus, what may be particularly important is distinguishing negative emotionality, which reflects an experience-induced failure to self-regulate and a general hypersensitivity to the environment.

Beyond Parenting: Child-Care Quality

All of the rearing data considered through this point pertains to parenting. But as children, especially in the contemporary Western world, are routinely cared for by alternative caregivers in child-care settings, the question arises as to whether quality of child care differentially affects children's development as a function of their phenotype. In perhaps the earliest pertinent study, Volling and Feagans (1995) detected a relevant and thus noteworthy interaction between children's social fear (i.e., negative emotionality?), as rated by mothers, and the observed quality of center-based child care in the prediction of observed nonsocial activity (i.e., solitary play, onlooker behavior) a year later when children were 14–48 months of age ($N = 36$). The highly fearful children manifested both the most and least nonsocial activity, depending on the quality of child care, whereas no such environmental effect emerged in the case of the low-fear children.

Given Volling and Feagan's (1995) small sample size, perhaps more convincing evidence that differential susceptibility characterizes some effects of child care comes from a recent analysis of data from the aforementioned NICHD Study of Early Child which investigated both negative and positive developmental outcomes (Pluess & Belsky, 2009). In this work on samples ranging from 761 to 915 children that explicitly tested differential susceptibility, the observed quality of care (averaged across measurements at 6, 15, 24, 36, and 54 months) differentially predicted behavior problems and social competence rated by caregivers in the year before school entry and by kindergarten teachers. Not

only did children with difficult temperament (6 months) have more behavior problems when reared in low-quality environments and fewer problems when quality was high compared with children with easy temperaments, but also the regression lines (i.e., slopes) proved significant only for the children who scored high on difficult temperament as infants. Similar results emerged when Pluess and Belsky (2010) extended their research to determine if, after imputing missing data and thereby increasing their sample size to 1,364, differential susceptibility to the effects of good and poor quality child care in the first 4.5 years of life extended to teacher-reported behavior problems and teacher–child conflicts when children were 10–11 years of age.

Beyond the Early Years: Middle Childhood

Although the Pluess and Belsky (2009, 2010) work indicates that differential susceptibility effects pertaining to early parenting and child-care experience and involving phenotypic susceptibility factors extend beyond the early childhood years, the question arises as to whether rearing and related experiences *in later childhood* operate in a similar manner. Evidence that they might emerges in research on conflict in families with 7–10-year-olds. Using structural equation modeling with nested-group comparisons, Ramos, Wright Guerin, Gottfried, Bathurst, and Oliver (2005) found that greater conflict predicted more behavior problems ($N = 108$), but principally in the case of children evaluated as having difficult temperaments when 3–5 years of age and not in the case of those scoring low in difficulty. Unfortunately, the manner in which data are presented precludes determination of whether a true for-better-and-for-worse rather than just dual-risk pattern of results was responsible for the findings reported.

Perhaps somewhat more compelling differential susceptibility evidence comes from Lengua's (2008) temperament–parenting interaction study that sought to explain change in internalizing and externalizing problems using a community sample ($N = 188$) of 8–12-year-old boys and girls. Children's reports of their mothers' parenting style (i.e., rejection–acceptance, inconsistent discipline) predicted change over a 1-year period in mother-reported internalizing and externalizing problems, but differentially as a function of temperament. No doubt in line with expectations developed through this point, results revealed that children highly prone to negative emotion in the form of frustration increased in externalizing problems over time when mothers were rejecting, but decreased when mothers manifested little rejection, with no such apparent effects of rejection evident in the case of children scoring low on frustration. It needs to be noted, however, that other findings from this inquiry, even when consistent with the differential susceptibility hypothesis, clearly seem to be at odds with what other cited investigations have found. For example, Lengua (2008) also reported that it was children who scored high on frustration who were *not* affected by inconsistent discipline with respect to the development of internalizing problems and children who scored low on frustration who were. Although another interaction indicated that inconsistent discipline did not affect the development of internalizing problems in low-anxious boys but did so in the case of high-anxious ones, thus being in line with previously cited evidence, other reported results proved inconsistent with expectations. Most notable was the fact that low levels of inconsistent parenting predicted increases in internalizing problems among high-anxious boys, with high levels of such putatively problematic parenting predicting decreases.

Other perhaps surprising middle-childhood findings emerge in Leve, Kim, and Pears (2005) work on behavior-problem trajectories from ages 5–17 years ($N = 373$). After controlling for marital adjustment, parental depression and income (all at age 5), evidence indicated, consistent with expectations, that highly impulsive 5-year-old girls manifest both the most and least externalizing problems across the developmental period under study (parental report) and that this depended on whether they experienced, respectively, high or low levels of harsh punishment at age 5 (parental interview). No such rearing effect emerged in the case of those rated low on impulsivity. At the same time, however, girls rated high on fear/shyness proved less susceptible than those rated low in terms of the influence of harsh punishment on externalizing problems. In summary, even though evidence in line with the differential susceptibility hypothesis emerged in all cases just considered, it should be clear that the substantive nature of differential effects, including who proves most susceptible, are by no means always nor entirely consistent across—or even within—studies.

Given claims by Harris (1998) that when it comes to influences on development, peers are actually more important than parents, recent research in middle childhood chronicling differential susceptibility-like effects takes on special importance. In a noteworthy inquiry focused on peer effects, Mezulis, Hyde, and Abramson (2006) observed that 11-year-olds ($N = 289$) reporting more negative life events involving age mates showed greater cognitive vulnerability to depression when 9 and 11 but somewhat less negative cognitive style when experiencing fewer life events compared with children low in the temperamental trait of withdrawal negativity.

Also of special interest is work that treats physiological traits, rather than just behavioral functioning, as developmental outcomes shaped by developmental experience. Gilissen, Bakermans-Kranenburg, van IJzendoorn, and van der Veer (2008) detected a significant interaction between child fearfulness (parent report) and parent–child relationship quality (observed during interaction or based on a story-completion task administered to children) in the prediction of skin conductance level (SCL) reactivity in response to a fear-inducing film clip. This cross sectional investigation involving 78 4-year-olds and 92 7-year-olds specifically testing differential susceptibility found that more fearful children manifest lower and higher SCL reactivity than all low-fear children, depending on whether their parent–child relationships were, respectively, secure or insecure. Of indisputable interest is that SCL reactivity—a marker for the activity of the sympathetic nervous system—has been found to moderate effects of the environment in a differential susceptibility manner, as will be reported in the next major subsection dealing with physiological susceptibility factors. Important to mention, the just summarized Dutch findings are consistent with the Boyce and Ellis (2005) claim that plasticity may itself be a function of environmental influence (Belsky & Pluess, 2009b).

Beyond Middle Childhood: Adulthood

Intriguingly, there is also suggestive evidence of the legacy or even operation of differential susceptibility in early adulthood. Of importance in this regard are a series of cross sectional studies testing hypothesized interactions between sensory-processing sensitivity, a personality characteristic measureable by means of the Highly Sensitive Person scale (see Aron & Aron, 1997) and various environmental factors in predicting adult shyness and negative affectivity (Aron et al., 2005). According to Aron and Aron (1997), about 20% of the population are characterized by a high-sensitive personality which encompasses a sensitive nervous system, awareness of subtleties in surroundings, and a tendency to be more easily overwhelmed when in a highly stimulating environment. One study of especial relevance showed that a problematic (and retrospectively reported) childrearing history predicted high levels of (self-reported) shyness and negative affectivity in a sample of 213 undergraduate students, whereas its absence predicted low levels of these same dependent constructs; but this relation obtained principally in the case of students scoring high on sensory-processing sensitivity, resulting in significant differences between regression lines (i.e., slopes) for high- and low-sensitivity groups. Also of note is research showing that marital quality proves more strongly related to sensitive mothering—and in a for-better-and-for-worse manner—in the case of mothers who score high on negative affect (Jessee et al., 2010). Considered together, the findings just summarized make it clear that it is not just children who prove differentially susceptible to environmental effects.

Comment

The repeatedly discerned moderational effect of negative emotionality/difficult temperament in the case of parenting, child care quality, and other environmental experiences raises the question of why this should be the case. This would seem especially important to address in view of the fact that even though Belsky (1997a, 2005) theorized that children should vary in their susceptibility to environmental influences (i.e., developmental plasticity) for evolutionary-biological reasons, his differential susceptibility hypothesis did not stipulate that more negatively emotional children or those with difficult temperament would prove especially malleable; this was an empirical observation (Belsky, 2005). One possible reason why those high in negative emotionality, operationalized as it has been in a variety of ways, may prove most susceptible to environmental influence is because a negatively emotional/difficult temperament reflects a highly sensitive nervous system on which experience registers especially strongly, irrespective of whether the experience is positive and growth-promoting or negative and undermining of well-being, broadly conceived (see also Aron & Aron, 1997).

Whatever the mechanisms involved in making more negatively emotional children seemingly more malleable—in an often for-better-and-for-worse manner, consistent with differential susceptibility thinking—it would be mistaken to conclude that this is the most important psychological marker of plasticity. Even though this could turn out to be the case, it may well be an artifact of the disproportionate attention that investigators guided by diathesis–stress/dual-risk perspective pay to individual risk factors that interact with contextual adversity in producing problematic functioning (Belsky & Pluess, 2009b). If this is so, then it certainly behooves the field to consider other potential behavioral markers of plasticity/malleability rather than reify one. Nevertheless, the evidence considered through this point indisputably suggests that differential susceptibility is operative in not just the opening years of life and, most critically, that regarding negatively emotional or difficult infants and children as

at risk and vulnerable may represent a fundamental mischaracterization of their more general highly malleable/plastic nature.

PHYSIOLOGICAL MARKERS OF DIFFERENTIAL SUSCEPTIBILITY

Recall that central to Boyce and Ellis' (2005) biological-sensitivity-to-context theorizing is the claim that children who are highly physiologically reactive to stress manifest the most developmental plasticity. Given that many such children probably begin life as highly negative infants or ones with difficult temperaments, it seems likely that many of the very same children Belsky (1997a, 2005) first called attention to in this regard are being identified by different means. In any event, what Boyce and Ellis (2005) viewpoint highlights is the fact that physiological characteristics, not just the psychological ones considered in the preceding section, might moderate environmental influences, functioning thereby as plasticity markers. In this section evidence consistent with the claim is considered after first providing a brief summary of the two separate physiological systems with specific functions—the autonomous nervous system and the neuroendocrine system.

The so-called fight-or-flight response to stress is primarily controlled by the autonomous nervous system (ANS), which is further divided into the sympathetic (SNS) and the parasympathetic nervous system (PNS). The SNS controls those activities that are mobilizing during stress and anxiety (e.g., acceleration of heart rate, increased blood pressure, enhanced blood flow to the skeletal muscles, decreased blood flow to the internal organs and extremities, sweating). Physiologically opposing activities under PNS control serve the basic functions of rest, repair, and relaxation of the body and restoration of energy stores (e.g., decreases in heart rate and blood pressure, stimulation of the digestive system, sexual arousal, sleep). The neuroendocrine response to stress is primarily controlled by the hypothalamus-pituitary-adrenal axis (HPA). Corticotropin releasing hormone (CRH)—which is released from the hypothalamus in response to stress—activates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland, which then causes the adrenal cortex to release cortisol into the general bloodstream. Finally, cortisol leads to a large number of diverse physiological and metabolic changes to prepare the organism for optimal functioning under stressful conditions (e.g., increase of blood pressure and blood sugar, breakdown of lipids and proteins, mobilization of amino acids, reduction of immune responses).

In the earliest pertinent investigation of physiological reactivity of which we are aware that detects differential susceptibility-like effects, Gannon, Banks, Shelton and Luchetta (1989) studied 50 undergraduates on whom a range of SNS markers of physiological reactivity were obtained (before and after a math-problems' stress test; plasticity factor). These students also reported on daily hassles (environmental factor), as well as common physical symptoms and depression. Compared to individuals showing low reactivity of blood volume pulse amplitude, high-reactive students reported both few physical symptoms when experiencing few daily hassles and many when experiencing many hassles. Also consistent with differential susceptibility thinking, those students showing slow heart rate recovery after the stress test reported fewer depressive symptoms when experiencing fewer daily hassles and more symptoms when experiencing more daily hassles compared with individuals with a fast recovery.

Findings in line with those just presented, but evident at much younger ages, emerged in Boyce and associates (1995) aforementioned test of the hypothesis that mean arterial blood pressure reactivity to a stress test at ages 3–5 would interact with a composite measure of child-care quality (measured across a 2-year period) in predicting frequency of respiratory illness during the six months following the physiological-reactivity assessment. Specifically, children with higher blood pressure reactivity exhibited higher rates of respiratory illness than other children when growing up in stressful rearing contexts, yet under low-stress conditions such high-reactive children had a significantly lower incidence of respiratory illnesses than other children.

Reactivity-moderated effects of environmental experiences are also evident when skin conductance level (SCL) reactivity serves as the index of physiological functioning. This is perhaps noteworthy in view of the fact that SCL is controlled solely by the SNS, in contrast to the other cardiovascular-reactivity measures that are generally innervated and controlled by both SNS and PNS. Thus, El-Sheikh, Keller, and Erath (2007b) investigated associations between SCL reactivity (assessed during a star-tracing problem solving task), marital conflict (parent report), and change (from age 9–11.5 years) in adjustment problems (parent report). Compared with girls with low SCL reactivity, highly reactive girls showed the largest increase in internalizing problems if from highly conflicted homes, but the smallest increase when marital conflict was low in their families. A significant cross-over interaction consistent with differential susceptibility also emerged for boys with respect to change in externalizing problems but, rather surprisingly, it was those scoring low in physiological

reactivity who appeared (exclusively) susceptible to the adverse effect of marital conflict.

The same research team has also used vagal tone (indexed by respiratory sinus arrhythmia [RSA]) and vagal suppression (during exposure to an audio recording of a male-female verbal conflict) to investigate whether and how PNS measures moderate effects of marital conflict on child adjustment in middle childhood (El-Sheikh, Harger, & Whitson, 2001). Compared to children with high vagal tone (who were not seemingly affected by marital conflict), those scoring low in vagal tone proved less anxious when growing up in families with little marital conflict, but more anxious when residing in high-conflict homes. Similar cross-over-interaction results emerged with respect to vagal suppression, but for boys only.

In a cross sectional study of more than 300 5-years-olds, Obradovic, Bush, Stamperdahl, Adler, and Boyce (2010) reported yet more data chronicling the role of RSA in moderating environmental effects, along with some pertaining to cortisol reactivity (both assessed during a stress test). In this research, a composite index of childhood adversity (based on parental reports of financial stress, parenting overload, marital conflict, negative/anger expressiveness, maternal depression, and harsh and restrictive parenting) proved predictive of composite well-being measures (based on parent, teacher, and child reports); but this proved true more so in the case of children with a more reactive parasympathetic nervous system (in contrast to El-Sheikh, Erath, & Keller, 2007; El-Sheikh et al., 2001). More specifically, children with high RSA reactivity were rated as more prosocial under low-adversity conditions and less prosocial under high-adversity conditions compared with children with low-RSA reactivity. High RSA reactivity children also scored higher on school engagement under low-adversity conditions and lower under high-adversity conditions compared with children with low-RSA reactivity.

Despite the fact that multiple PNS investigations provide evidence in line with the differential susceptibility hypothesis, seeming to highlight individual differences in plasticity, not just vulnerability, work involving the *neuroendocrine system* appears to provide comparable evidence. In the just summarized work by Obradovic et al. (2010), children with high-cortisol reactivity were rated as more prosocial under low adversity and less prosocial under high adversity relative to children with low-cortisol reactivity. It is difficult to be sure that this apparent imbalance in evidence across the autonomous nervous system and the neuroendocrine system is due to the two stress reactivity systems playing fundamentally different roles vis-à-vis environmental influences; the alternative possibility is that one has just received more empirical attention as a moderator of environmental effects. This would seem likely given that most developmentalists measuring cortisol reactivity in studies of environmental effects treat it as an outcome to be explained rather than as a moderator of environmental influences on development (Fernald, Burke, & Gunnar, 2008; Gunnar & Quevedo, 2007).

Beyond the work just cited and summarized by Belsky and Pluess (2009a), ever more research highlights the potential role of physiological reactivity as a plasticity factor. Consider in this regard recent evidence indicating that more physiologically reactive children are more susceptible, in a for-better-and-for-worse fashion, to the effect of actual marital conflict (Obradovic et al., 2011) and simulated interparental aggression (Davies, Sturge-Apple, & Cicchetti, 2011), on externalizing problems; of family adversity on school achievement (Obradovic et al., 2010); of chronic family aggression on adolescent anti-social behavior and symptoms of posttraumatic stress disorder (Saxbe, Margolin, Shapiro, & Baucom, 2012); of peer victimization on self-reported depressive symptoms (Rudolph, Troop-Gordon, & Granger, 2011); and of teacher–child conflict on change in symptom severity (Essex et al., 2011). Work showing similar moderational effects of physiological reactivity with respect to family influences on female pubertal development by Ellis and associates (2011) is especially noteworthy, given the roots of this work in psychosocial acceleration theory (Belsky et al., 1991) and the way its findings proved consistent with the differential susceptibility-related revision of the theory (Belsky, 2000). After all, Belsky (2000) postulated that some females would be alternative strategists whose pubertal development proved unrelated to their rearing experiences, just as Ellis and associates (2011) found for girls low in physiological reactivity, whereas others would be conditional strategists susceptible to the accelerating and delaying effects of unsupportive and supportive rearing, respectively, just as Ellis et al. (2011) observed in the case of highly reactive girls. Once again, though, we would be remiss if we did not highlight some evidence inconsistent with the BSC thinking, such as that from the aforementioned Obradovic et al. (2011) investigation showing that it was young children with low—rather than high—RSA reactivity who seemed, in some analyses, to benefit from growing up under supportive family conditions characterized by little marital strife.

As it turns out, it may not just be high levels of physiological *reactivity* that demarcates more malleable individuals. In studying the effects of change over time

in parent depressive symptoms on change in children's internalizing problems, Laurent and associates (2013) recently observed plasticity-like processes when evaluating the moderating effect of children's evening cortisol levels. Thus, children with higher evening levels of cortisol increased in internalizing problems over time if fathers' depressive symptoms increased, but decreased if they had declined; no father depression effect of any kind was discernible in the case of children scoring low in evening cortisol. The fact that the study was focused on adoptive parents and their adopted children means, of course, that the physiologically moderated environmental effects discerned in this inquiry could not be the result of genes shared between parent and child.

One of the key questions that still remains to be answered regarding BSC concerns its life span implications. More specifically, do those individuals who are induced to be highly physiologically reactive early in life—and thus developmentally plastic—remain that way over time? It seems hard to imagine that a child induced by supportive rearing to be highly physiologically reactive, in accordance with the theory (Boyce & Ellis, 2005), would remain highly reactive as the years go by. But, of course, this is an empirical question—one that has implications for our understanding of the role physiological reactivity does or does not play as a plasticity factor as the individual develops.

GENETIC MARKERS OF DIFFERENTIAL SUSCEPTIBILITY

Whereas almost all the evidence cited through this point derives from studies of children, gene–environment (GxE) interaction findings consistent with the differential susceptibility hypothesis often derive from research with adults. This is especially true of psychiatric research focused upon pathological outcomes (e.g., depression, antisocial behavior). The fact that most of this work has been guided by traditional diathesis–stress thinking—at least until recently—means that on many occasions evidence that those carrying a putative risk allele actually function better than others when not exposed to the risk condition being studied (e.g., negative life events) frequently goes unnoticed or at least is not discussed in primary reports. Uher and McGuffin (2008) called attention to such differential susceptibility-like findings, even if not in such terms, in their review of GxE research on life events, the serotonin-transporter gene and depression. Here we discuss findings seemingly reflective of differential susceptibility across a diverse array of candidate genes.

Dopamine Receptor D4 Gene (DRD4)

A number of genes are known to play a role in regulating the dopaminergic system, which is engaged in attentional, motivational, and reward mechanisms have figured importantly in GxE research. One of these—which probably has revealed more evidence of genetic plasticity than any other polymorphism—is the dopamine receptor D4 (DRD4) gene. Variants of the DRD4 differ by the number of 48-base pair tandem repeats in exon III, ranging from 2 to 11. The 7-repeat variant has been identified in psychiatric-genetic studies as a vulnerability factor due to its links to ADHD (Faraone, Doyle, Mick, & Biederman, 2001), high novelty seeking behavior (Kluger, Siegfried, & Ebstein, 2002), and low dopamine reception efficiency (Robbins & Everitt, 1999), among other correlates.

A number of observational studies indicate that children carrying this putative risk allele are not only more adversely affected by poorer quality parenting than other children; they also benefit more than others from good-quality rearing. The first two investigations to be considered may be regarded as particularly important because a good environment was not just operationalized as the absence of adversity—as is all too often the case in GxE investigations—but in terms of high-quality parenting. In a longitudinal investigation of 47 infants, maternal sensitivity observed when children were 10 months predicted externalizing problems reported by mother more than two years later, but only for children carrying the 7-repeat DRD4 allele (Bakermans-Kranenburg & van IJzendoorn, 2006). Moreover, although children with the 7-repeat DRD4 allele displayed the most externalizing behavior of all children when mothers were judged insensitive, they also manifested the least externalizing behavior when mothers were highly sensitive (but see, for contradictory results, Propper, Willoughby, Halpern, Carbone, & Cox, 2007).

A cross sectional study of sensation seeking in 45 18–21-month-old children generated results in line with those just summarized. Toddlers carrying the 7-repeat allele were rated by parents as showing, compared with children without the 7-repeat allele, less sensation seeking behavior when parenting quality was high but more when it was low (Sheese, Voelker, Rothbart, & Posner, 2007). Whereas parenting proved significantly associated with sensation seeking in the 7-repeat individuals, it did not in other children.

The same team of Dutch of investigators whose work examining effects of maternal sensitivity on toddler's externalizing problems also found evidence that the DRD4 7-repeat allele moderated the effect of a maternal

psychological condition, unresolved loss or trauma (as measured by means of the Adult Attachment Interview), on a known early developmental marker of psychological disturbance later in life, infant attachment disorganization (Carlson, 1998). But, importantly, this proved true only in the case of infants carrying the 7-repeat allele (van IJzendoorn & Bakermans-Kranenburg, 2006). Such infants manifest both the most and least disorganized attachment behavior when stressed depending on whether their mothers had or had not experienced unresolved loss or trauma in their own lives.

In a study with a focus rather different from all those previously considered, Seeger, Schloss, Schmidt, Ruter-Jungfleisch, and Henn (2004) evaluated whether the *season of the year* in which a child was born interacted with the dopamine DRD4 polymorphism in predicting hyperkinetic conduct disorder (ADHD). Employing a cross sectional design involving 64 children with the disorder and 163 healthy controls (mean age 11–12, +/–3 years), they found that it did—and in ways consistent with what is known about photoperiod exposure during pregnancy. When comparing patients with controls, children with one copy of the DRD4 7-repeat allele born in autumn and winter (i.e., long photoperiod during pregnancy) had a 5.4-fold decreased relative risk for hyperkinetic conduct disorder, whereas children with the same genotype born in spring and summer (i.e., short photoperiod) had a 2.8-fold increased relative risk for hyperkinetic conduct disorder. Neither season of birth nor the presence of DRD4 7-repeat allele increased the risk of hyperkinetic conduct disorder on their own.

Beyond these DRD4-related studies first reviewed by Belsky and Pluess (2009a), even more recent work has emerged indicating the 7R allele functions as a plasticity factor. Consider in this regard work showing heightened—or exclusive—susceptibility of individuals carrying the 7-repeat allele when the environmental predictor and developmental outcome were, respectively, maternal positivity and prosocial behavior (Knafo, Israel, & Ebstein, 2011); early nonfamilial childcare and social competence (Belsky & Pluess, 2013b); contextual stress and support and adolescent negative arousal (Beach et al., 2012); childhood adversity and young adult persistent alcohol dependence (Park, Sher, Todorov, & Heath, 2011); and newborn risk status (i.e., , gestational age, birth weight for gestational age, length of stay in NICU) and observed maternal sensitivity (Fortuna et al., 2011). To be noted, however, is that at least one investigatory team finds that it is those without the 7-repeat allele who prove most responsive to childhood adversities—in a diathesis–stress manner (Das, Cherbuin, Tan, Anstey, & Easteal, 2011). Nevertheless, a recent meta-analysis of GxE research involving dopamine-related genes revealed that children eight and younger respond to positive and negative developmental experiences and environmental exposures in a manner consistent with differential susceptibility (Bakermans-Kranenburg & van IJzendoorn, 2011).

Serotonin Transporter Gene (5-HTT)

The serotonin-transporter-linked polymorphic region (5-HTTLPR) is another genetic polymorphism that has figured importantly in psychiatric-genetic research. The 5-HTTLPR is a degenerate repeat polymorphic region in SLC6A4, the gene that codes for the serotonin transporter. Most research focuses on two variants—those carrying at least one short allele (s/s, s/l) and those homozygous for the long allele (l/l)—though more variants than these have been identified (Nakamura, Ueno, Sano, & Tanabe, 2000). The short allele has generally been associated with reduced expression of the serotonin transporter molecule—which is involved in the reuptake of serotonin from the synaptic cleft—and thus considered to be related to depression, either directly or in the face of adversity.

Caspi and associates (2003a) were the first to show that the 5-HTTLPR moderates effects of stressful life events during early adulthood on depressive symptoms and on probability of suicide ideation/attempts and of major depression episode at age 26 years. Individuals with two s alleles proved most adversely affected whereas effects on l/l genotypes were weaker or entirely absent. Of special significance, however, is that carriers of the s/s allele scored best on the outcomes just mentioned when stressful life events were absent—though just as was true among low-MAOA activity individuals in Caspi et al. (2002)—not by very much.

Multiple research groups have attempted to replicate Caspi et al.'s findings (2003) of increased vulnerability to depression in response to stressful life events for individuals with one or more copies of the s allele, with many succeeding (see below), even if not all (Surtees et al., 2006). Of note is that the data presented in quite a number of these studies indicates that individuals carrying short alleles (s/s, s/l) did not just function most poorly when exposed to many stressors, but best—showing least problems—when encountering few or none. While calling explicit attention to such a pattern of results, Taylor and associates' (2006) reported that young adults homozygous for short alleles (s/s) manifested greater depressive symptomatology than individuals with other allelic variants when exposed to

early adversity (i.e., problematic childrearing history), as well as many recent negative life events, yet the fewest symptoms when they experienced a supportive early environment or recent positive experiences, that is, not just the absence of adversity.

A similar pattern of environmental effects emerged in still other investigations of stressful life events and depression, including one targeting depressed patients, healthy controls and experiences during the six-month prior to study enrollment (Zalsman et al., 2006), and another of a sizeable community sample ($N = 567$) and life events up to two years prior to the assessment of depression (Lazary et al., 2008). The same for-better-and-for-worse pattern of results are evident—and noted—in Brummett et al.'s (2008) investigation of more than 200 adults (mean age 58 years) who differed in whether or not they served as caregiver of a relative with Alzheimer's disease and in Eley et al.'s (2004) research on adolescent girls who were and were not exposed to risky family environments. In fact, secondary analysis of the latter findings revealed that the for-better environmental effect size exceeded the routinely evaluated for-worse size (Belsky et al., 2009). Although all the work just cited, with the exception of Caspi et al. (2003), was cross sectional in design, Wilhelm and associates' (2006) longitudinal data also shows that individuals with the s/s genotype had the lowest probability of lifetime major depression if exposed to no adverse life events in a five-year study period, but the highest probability when reporting two, three, or more adverse life events compared with other genotypes.

The effect of 5-HTTLPR in moderating environmental influences in a manner consistent with differential susceptibility is not restricted to depression and its symptoms. It also emerges, perhaps unsurprisingly, in studies of anxiety and ADHD. Gunthert et al. (2007) documented the former result in longitudinal research on 350 college students. At study entry and a year later, participants reported anxiety and negative events daily for 30 days. Genotyping distinguished three alleles, but the L_G allele was grouped with s alleles due to its functional equivalence vis-à-vis promoter activity. Individuals homozygous for short alleles (including s/L_G and L_G/L_G) reported more anxiety in the evening when daily-event stress was high compared with individuals with different genotypes, but also less anxiety than other genotypes when experiencing little daily-event stress; this pattern of results proved consistent across measurement occasions.

In a second study focused on undergraduate students ($N = 247$) and anxiety (Stein, Schork, & Gelernter, 2008), but this time concerned with (retrospectively reported) emotional abuse in childhood, a GxE interaction once again emerged. The significantly steeper abuse–anxiety slope in the case of students homozygous for short alleles relative to those with one or more long alleles indicated that s/s individuals scored highest in anxiety sensitivity when exposed to abuse and lowest when not exposed.

Moving on to consider ADHD (in childhood and adulthood), Retz and associates (2008) focused on the moderated effects of an adverse childhood environment in their study of 184 male delinquents who averaged 34 years of age. Using a retrospective assessment of childhood ADHD, as well as of early adversity, but a clinical interview to assess functioning in adulthood, these investigators detected a crossover interaction with respect to the persistence of ADHD over time. Compared with l/l genotypes, individuals with s alleles had more and less persistent ADHD, depending on whether or not, respectively, they experienced an adverse early environment.

Yet another differential susceptibility-relevant finding involving 5-HTTLPR comes from Manuck, Flory, Ferrell, and Muldoon (2004) test of a GxE interaction involving socioeconomic status in the prediction of central nervous serotonergic responsivity; the sample included 139 adults ranging in age from 26 to 60. Central serotonergic responsivity was measured indirectly by means of the fenfluramine challenge test. Fenfluramine increases serotonergic neurotransmission by release of serotonin stores and reuptake inhibition. Such stimulation of hypothalamic serotonin receptors promotes as well the pituitary release of the hormone prolactin. This relative release in circulating prolactin concentration provides an index of the serotonergic responsivity in the HPA axis. Consistent with all the findings summarized above pertaining to depression, anxiety and persistent ADHD, s/s individuals manifest the most and least serotonergic responsivity, depending on whether they were, respectively, low or high SES.

In the short time since the aforementioned studies involving 5-HTTLPR were reviewed by Belsky and Pluess (2009a), yet more evidence that short alleles operate as plasticity factors has emerged. Consider in this regard, evidence showing for-better-and-for-worse results in the case of those carrying one or more 5-HTTLPR short alleles when the rearing predictor and child outcome were, respectively, maternal responsiveness and moral internalization (Kochanska, Kim, Barry, & Philibert, 2011), child maltreatment and antisocial behavior (Cicchetti, Rogosch, & Thibodeau, 2012), and supportive parenting and positive affect (Hankin et al., 2011). Differential susceptibility-related findings also emerged (among male African American adolescents) when perceived racial

discrimination was used to predict conduct problems (Brody et al., 2011); when life events were used to predict neuroticism (Pluess, Belsky, Way, & Taylor, 2010) and life satisfaction of young adults (Kuepper et al., 2012); and when retrospectively reported childhood adversity was used to explain aspects of impulsivity among college students (e.g., pervasive influence of feelings, feelings trigger action; Carver, Johnson, Joormann, Kim, & Nam, 2011).

Just to be clear, other 5-HTTLPR-related findings prove more consistent with the diathesis–stress than differential susceptibility framework (e.g., Bakermans-Kranenburg, Dobrova-Krol, & van IJzendoorn, 2012; Brody et al., 2013; Pluess et al., 2011), sometimes even in GxE studies which also provide evidence of differential susceptibility (e.g., Kochanska et al., 2011). Moreover, in apparently rare instances it is—surprisingly—those with long rather than short alleles who prove most susceptible to environmental influences, even when differential susceptibility-related findings emerge (e.g., Cicchetti, Rogosch, & Oshri, 2011; Sulik et al., 2012). Especially noteworthy, therefore, are the results of a recent meta-analysis of GxE findings pertaining to children under 18 years of age showing that short-allele carriers are more susceptible to the effects of both positive and negative developmental experiences and environmental exposures, at least in the case of Caucasians (van IJzendoorn, Belsky, & Bakermans-Kranenburg, 2012).

Monoamine Oxidase A Gene (MAOA)

The neurotransmitter-metabolizing enzyme monoamino oxidase A or MAOA gene is located on the X chromosome. It encodes the MAOA enzyme, which metabolizes neurotransmitters such as norepinephrine, serotonin, and dopamine, rendering them inactive. Two sets of evidence—one linking the low-activity MAOA allele to antisocial behavior and another linking abuse and neglect in childhood to the same developmental outcome—led Caspi and associates (2002) to hypothesize that inconsistency in findings in both literatures could be a result of the fact that maltreatment effects are moderated by genotype. This is exactly what they discovered in their groundbreaking and widely cited GxE research carried out on a New Zealand birth cohort followed into young adulthood. More specifically, it was principally young men—females were not studied—with one form of the gene (i.e., that associated with low MAOA activity) who proved more violence prone when subject to child maltreatment. For those children with the high-MAOA-activity allele, a substantially smaller effect of child maltreatment emerged.

Although most interpret these findings, not unreasonably, in diathesis–stress terms, few seem to have noticed that those most vulnerable to the adverse effects of maltreatment actually scored lowest in antisocial behavior when not exposed to maltreatment, suggesting perhaps greater plasticity rather than just greater vulnerability to adversity in the case of those with the low-activity MAOA allele. This interpretation would seem substantiated by results of a significant number of efforts to replicate the Caspi et al. (2002) findings. For example, Kim-Cohen et al. (2006) studied 975 boys to determine whether the MAOA polymorphism moderated effects of mother-reported physical abuse in early childhood on later mental health problems. At age 7 years boys with the low-MAOA-activity variant were rated by mothers and teachers as having more mental health problems—and specifically ADHD symptoms—if they had been victims of abuse, but fewer problems if they had not, compared with boys with the high-MAOA-activity genotype. In a longitudinal study of 514 adolescent twin boys aged 8 to 17 years, Foley et al (2004) found that childhood adversity—based on parent and child report—predicted three-month history of conduct disorder (DSM-III) differently for children with the low- and high-activity MAOA allele. Once again, boys with the low-MAOA-activity allele were more likely to be diagnosed with conduct disorder if exposed to higher levels of childhood adversity and less likely if exposed to lower levels of adversity, compared with boys with the high-MAOA-activity allele. Similar results emerged in Nilsson and associates' (2006) cross sectional investigation of 81 adolescent boys when the predictor was psychosocial risk, operationalized in terms of maltreatment experience and living arrangement. Only boys with the low-MAOA-activity allele were affected by such risk, such that those with a history of adversity engaged in more criminal behavior (composite of vandalism, violence, stealing) and those lacking this history engaged in less.

Three additional studies extend the Caspi et al. (2002) findings: One was a prospective investigation of 631 male and female and white and black victims of (court-substantiated) child abuse and neglect, along with a comparison group matched on age, sex, race/ethnicity, and social class background (Widom & Brzustowicz, 2006); the second a retrospective study of 235 adult psychiatric outpatients and healthy controls who reported on trauma experienced in childhood and physical aggression in adulthood (Frazzetto et al., 2007); and the third a cross sectional retrospective study with an American Indian sample of 291 adult women, 50% of whom had a history of childhood sexual abuse (Ducci et al., 2008). White (but not black)

males and females with the low-MAOA-activity allele in the longitudinal study manifest the most violent and antisocial behavior during adolescence and across their lifetimes when measured around 40 years of age, if they had been maltreated. But those with the same alleles engaged in the least such behavior (at both times of measurement) if they had not been victims of abuse. In the second study, men (only) with the low-MAOA-activity variant reported more physical aggression if they experienced one or more (retrospectively reported) objective traumatic events while growing up (e.g., death of mother, severe physical handicap of sibling) and less physical aggression if there was no history of trauma, compared with high-MAOA-activity men (for whom trauma proved unrelated to aggression). In the third study, women homozygous for the low MAOA activity variant had the highest count of antisocial personality disorder symptoms when reporting childhood sexual abuse and the lowest count when having no history of sexual abuse, compared with women homozygous for the high-MAOA-activity genotype.

The fact of the matter is that since the just-cited studies were reviewed by Belsky and Pluess (2009a), no additional GxE evidence has emerged suggesting that MAOA should be regarded as a plasticity rather than vulnerability factor. The same is true for the remaining genes to be considered in this section, raising questions about the confidence that can be placed in genes other than perhaps DRD4 and 5-HTTLPR as plasticity genes. To be appreciated, of course, is that none of these other genes have received the empirical attention in the GxE literature that DRD4 and 5-HTTLPR have, which could account, at least in part, as to why no new differential susceptibility-related findings have emerged for these other genes that Belsky and Pluess (2009a) highlighted in their review of relevant research.

Serotonin Receptor 2A Gene (HTR2A)

Irrespective of these necessary and cautionary comments, evidence consistent with differential susceptibility thinking emerges from GxE studies of another serotonergic system related genetic polymorphism: the single nucleotide polymorphism (SNP) rs6313, located on the serotonin receptor gene (HTR2A), which comes in two forms—the C and the T allele. Whereas some research reveals an association between the C allele and depression (e.g., see Du, Bakish, Lapierre, Ravindran, & Hrdina, 2000), others find the T allele to confer depression risk (Eley et al., 2004). Recent work by Jokela and associates (Jokela, Keltikangas-Jarvinen, et al., 2007a; Jokela, Lehtimaki, & Keltikangas-Jarvinen, 2007b, c)—drawing from data of a longitudinal population-based study in Finland, the Cardiovascular Risk in Young Finns Study, that will be cited frequently in coming paragraphs—suggests that individuals carrying the T allele are generally more affected by environmental factors than others in a for-better-and-for-worse manner. When nurturance reported by mother was averaged across baseline—when 820–1212 study participants were 3–18 years old—and again 3 years later, offspring with at least one T allele scored highest and lowest on self-reported depression some 2 decades after baseline, depending on whether they experienced, respectively, more or less supportive care (Jokela, Keltikangas-Jarvinen, et al., 2007a). Similar results emerged when the predictor was family SES and the outcome to be explained was self-reported harm avoidance; those carrying one or more T alleles scored highest on harm avoidance if they grew up in low-SES households but lowest if they grew up in high-SES ones (Jokela, Lehtimaki, et al., 2007b). This result led the investigators to suggest that this allele might function as an opportunity allele, not just a risk gene.

Yet more support for this differential susceptibility interpretation comes from a third Finnish report focused on whether adults resided in remote rural, rural, suburban, or urban areas. T/T individuals showed the most and least depressive symptoms of all study participants depending on whether they resided, respectively, in remote rural or urban areas (Jokela et al., 2007b). In sum, these Finnish findings are consistent with a differential susceptibility interpretation.

Tryptophan Hydroxylase 1 Gene (TPH1)

As it turns out, the same research group identified similar interaction effects involving yet another SNP on a serotonergic system related gene: rs1800532 located in the tryptophan hydroxylase 1 gene (Jokela, Räikkönen, Lehtimäki, Rontu, & Keltikangas-Järvinen, 2007); this gene codes for a rate-limiting enzyme in the biosynthesis of serotonin. Of the two variants A and C, the A allele has been associated with low serotonin levels (Jönsson et al., 1997) and suicidal behavior/depression, though findings are not consistent (e.g., see Bellivier, Chaste, & Malafosse, 2004; Lalovic & Turecki, 2002).

Jokela, Räikkönen, et al. (2007) detected a moderating effect of TPH1 on the association between social support and depressive symptoms, again using data from the Cardiovascular Risk in Young Finns Study. Depressive symptoms and social support were assessed when participants were between 20 and 35 years old, with the

former measurements taken again four year later. A GxE interaction emerged irrespective of when the depression outcome was assessed. A/A individuals experienced the most and least depression compared with all other individuals, depending on whether they experienced, respectively, low or high social support. This proved to be even more so the case when change in depressive symptoms was the outcome to be explained.

When the Finnish researchers turned their attention to the effect of a hostile childhood environment (based on maternal report) on harm avoidance in adulthood, yet more differential susceptibility like findings emerged involving TPH. Keltikangas-Jarvinen and associates (2007b) found that female participants carrying the A/A genotype reported more adulthood harm avoidance if raised in a hostile environment but less if raised in a non-hostile one relative to those with one or two A alleles. In fact, no apparent effect of childhood environment was detected in the case of women carrying C alleles (or in men).

Dopamine Receptor D2 Gene (DRD2)

Another polymorphism in the dopaminergic system that has been a focus of GXE research is located on the DRD2 gene that encodes the D2 subtype of the dopamine receptor. The Taq1A (A1) SNP (rs1800497)—a C to T substitution located in a noncoding region of the DRD2 locus—is thought to affect dopamine receptor D2 availability in postmortem striatal samples (Thompson et al., 1997). The A1 allele has been associated with low dopamine density and lower mean relative glucose metabolic rate in dopaminergic regions in the human brain (Noble, Gottschalk, Fallon, Ritchie, & Wu, 1997), high novelty seeking (Suhara et al., 2001), and a number of substance use disorders, particularly alcoholism (Bowirrat & Oscar-Berman, 2005).

Some study findings suggest that the DRD2 polymorphism moderates environmental influences in differential susceptibility terms. For example, Mills-Koonce and associates (2007) detected an interaction between DRD2 and sensitive mothering observed when children were 6 and 12 months of age in the prediction of children's psychological well-being. Infants with the A1 allele reared by more and less sensitive mothers had, respectively, fewer and more affective problems at 3 years of age than agemates with other genotypes. Indeed, rearing experience proved unrelated to well-being among these latter children.

A differential susceptibility like effect also emerged in what appears to be the first ever report of GxE in humans, one involving an interaction between the DRD2 gene and family stress in the prediction of visuospatial ability (i.e., line orientation test) and 2 years later, P300 amplitude in ERP research (Berman & Noble, 1997). In this cross sectional study of 10–13-year-old boys, those carrying the A1 allele scored lower than those lacking this allele under high stress conditions, but higher under low stress conditions (even if the differential was more substantial under higher stress conditions).

Focusing as well on a physiological outcome, Propper et al. (2008) found DRD2 to moderate effects of 6-month maternal sensitivity on, 6 months later, respiratory sinus arrhythmia (RSA) reactivity. Children carrying the A1 allele had lower RSA change at 12 months when experiencing low maternal sensitivity and higher RSA change when experiencing high maternal sensitivity compared with children without the A1 allele.

Turning to cognitive outcomes, Keltikangas-Järvinen et al (2007b) found DRD2 to moderate the association between birth weight, presumed to reflect quality of the uterine environment to which the fetus has been exposed, and educational achievement in the Cardiovascular Risk in Young Finns Study, though only in the case of males in this large-sample study of 1,512 adults (27 to 34 years old). Whereas men with the A1 allele achieved less academically if born of low birth weight but more if born of high birth weight, no such birth-condition-achievement association emerged in the case of other men. (Individuals with birth weight > 5000g were excluded from the analysis.)

Somewhat surprisingly given the DRD2 work already reviewed, other findings from the Cardiovascular Risk in Young Finn's study suggest that it is not always individuals carrying the A1 genotype who appear disproportionately susceptible to environmental conditions. When it came to predicting depressive symptoms in 1,636 24–39-year-olds, Elovainio et al. (2007) found that it was young adults lacking the A1 allele who had more depressive symptoms if they experienced many negative life events and fewer depressive symptoms if they reported no such events across the preceding 9-year period compared with their counterparts carrying this allele.

Additional Plasticity Genes?

Emerging evidence has also begun to suggest that a polymorphism in the brain-derived-neurotrophic factor gene (BDNF) may function a plasticity gene (e.g., Chen, Li, & McGue, 2012; Gunnar et al., 2012; Juhasz et al., 2011; Mata, Thompson, & Gotlib, 2010; Suzuki et al., 2011) and a polymorphisms in the oxytocin receptor gene (OXTR; Johansson et al., 2012; Poulin, Holman, & Buffone, 2012; Sturge-Apple, Cicchetti, Davies, & Suor, 2012),

and the FKBP5 gene (Bevilacqua et al., 2012; Xie et al., 2010; Zimmermann et al., 2011). There are perhaps less frequent indications of this in the case of a SNP in the catechol-o-methyl transferase gene (COMT; Laucht et al., 2012; Nijmeijer et al., 2010). It will be worth monitoring these polymorphism—and others—as more work emerges to see whether additional evidence proves consistent with differential susceptibility.

In fact, given that virtually all the polymorphisms just considered have been studied in GxE perspective as a result of the original interests of psychiatric geneticists in simple genotype-phenotype linkages, we cannot but wonder whether an entirely different set of polymorphisms reflecting sensitivity to the environment would have emerged had the phenotype of interest been not some psychiatric disorder but developmental plasticity itself. It therefore behooves investigators to expand the list of genetic suspects beyond those thought to be related to disturbances in functioning by thinking biologically about genes that might be related to physiological processes instantiating plasticity. An excellent recent example of this approach is to be found in Grazioplene and associates (2013) work showing that a polymorphisms located on CHRNA4 interacts with childhood maltreatment to predict features of personality in a differential susceptibility-related manner. Of especial significance is that this polymorphism was selected for investigation because it is involved in the production of the neurotransmitter acetylcholine, a component of the cholinergic system that is strongly involved in neural plasticity and learning. A similarly noteworthy GxE study focused on a GABRA2 polymorphism on the presumption that it enhances responsiveness to the environment due to the role it plays in regulating neuronal excitability. Simons and associates (2013) observed that it functioned just as one would expect of a plasticity gene when investigating the influence of parenting experienced at age 10–12 on hostility toward romantic partners in early adulthood.

Polygenetic Plasticity

Most GxE research, like that just considered, has focused on one or another polymorphism. In recent years, however, work has emerged which we believe should be encouraged, focusing on multiple polymorphisms and thus reflecting the operation of epistatic (i.e., GxG) interactions (e.g., Beaver, Sak, Vaske, & Nilsson, 2010; Conner, Hellemann, Ritchie, & Noble, 2010), as well as GxGxE ones. One can distinguish polygenetic GxE research in terms of the basis used for creating multigene composites. One strategy that seems fundamentally problematic to us involves identifying genes that show main effects and then compositing only these to then test an interaction with some environmental parameter (e.g., Docherty, Kovas, & Plomin, 2011). What leads us to question the wisdom of this approach is that genes—or any other factors for that matter—that do not exert main effects could still be involved in interactions with the environment, just as some recent GxE research reveals (e.g., Cicchetti & Rogosch, 2012; Cicchetti, Rogosch, & Oshri, 2011; Pluess et al., 2011).

Another approach is to composite genes for a secondary, follow-up analysis that have been found in a first round of inquiry to generate significant GxE interactions (e.g., Brody, Chen, & Beach, 2013; Simons et al., 2013; Sonuga-Barke et al., 2009). When Cicchetti and Rogosch (2012, Figure 2) applied this approach using four different polymorphisms, they found that as the number of sensitivity-to-the-environment genotypes increased (i.e., S/S of 5-HTTLPR, zero copies of CRH1 TAT haplotype, the T/T genotype of DRD4–521C/T, and A carrier of OXTR), so did the degree to which maltreated and nonmaltreated low-income children differed on a composite measure of resilient functioning—in a for-better-and-for-worse manner.

A third approach which has now been used successfully a number of times to chronicle differential susceptibility involves compositing a set of genes selected on an a-priori basis before evaluating GxE (e.g., Brody et al., 2013). Consider in this regard evidence indicating that two-gene composites moderate links between sexual abuse and adolescent depression/anxiety and somatic symptoms (Cicchetti, Rogosch, & Sturge-Apple, 2007), between perceived racial discrimination and risk-related cognitions reflecting a fast versus slow life-history strategy (Gibbons et al., 2012, Figure 2), between contextual stress/support and aggression in young adulthood (Simons et al., 2011) and between social class and postpartum depression (Mitchell et al., 2011); that a three-gene composite moderates the relation between a hostile-demoralizing community and family environment and aggression in early adulthood (Simons et al., 2011); and that a five-gene composite moderates the relation between parenting and adolescent self-control (Belsky & Beaver, 2011), as well as between marital stability experienced across the first 15 years of life and income earned in young adulthood (Wickrama & O'Neal, 2013).

No matter how informative the approach to compositing polymorphisms on a-priori grounds has proven to be when it comes to detecting differential susceptibility, we suspect that the wave of the future will be the system-level genetic approach. This involves combining

genes considered to collectively influence a particular biological process or pathway, such as the dopaminergic or serotonergic system (e.g., Brody et al., 2013; Conner et al., 2010; Nikolova, Ferrell, Manuck, & Hariri, 2011) or neurological endophenotypes for increased susceptibility, such as amygdala volume (Yap et al., 2008), hippocampus volume (Whittle et al., 2011) and ventral striatum reactivity (Nikolova, Bogdan, Brigidi, & Hariri, 2012), to list just a few possibilities. Further insight could be gained, conceivably, by even more refined analysis of such subsystems, including those reflecting synthesis, degradation/transport, receptor and modulation (Chen et al., 2011).

GxE Mechanisms

There are likely multiple explanations as to why—in terms of mechanisms—the GxE findings we have highlighted and the ones we have not prove consistent with differential susceptibility and thus Belsky and Pluess's (2013a) claim that developmental plasticity should be regarded as a phenotype in its own right. When considering mechanisms, however, we must be sensitive to the fact that this term means very different things to different scholars. For a brain scientist, mechanism may refer to brain structure or function, whereas for an endocrinologically oriented investigator it may refer to a hormonal phenomenon, for a geneticist to an epigenetic cascade, and for a cognitive neuroscientist an attentional process, to name just some of the possibilities. Thus, what for a cognitive scientist may qualify as a proximate mechanism (e.g., attentional bias) may well be regarded by a geneticist focused on the epigenome as a distal predictor. Developmental and behavioral scientists should not be arrogant, then, when it comes to stipulating what does and does not qualify as a mechanism. It ultimately depends on the level—or levels—of analysis one is working at.

In what follows we call attention, based on recent empirical evidence, to some possible differential susceptibility-related mechanisms—at different levels of analysis. But rather than emphasizing—as most genotype–phenotype and even GxE reports do—findings linking particular genes directly to particular psychological or biological processes, we highlight instead research showing that such processes are themselves responsive to environmental exposures in a differential susceptibility-related manner.

When it comes to *cognitive processes*, the following have been found to be moderated by 5-HTTLPR and an environmental factor in a for-better-and-for-worse manner: positive and negative attentional biases (Fox, Zougkou, Ridgewell, & Garner, 2011; see also Pergamin-Hight, Bakermans-Kranenburg, van IJzendoorn, & Bar-Haim, 2012); reward sensitivity (Roiser, Rogers, Cook, & Sahakian, 2006); and accurate processing of emotional faces (Jacobs et al., 2011). The same is true of inattention in the case of DRD4 (Berry, Deater-Deckard, McCartney, Wang, & Petrill, 2013); working-memory accuracy and reaction time in the case of BDNF (Gatt et al., 2009); and rumination in the case of a two-gene composite (5-HTTLPR, BDNF: Clasen, Wells, Knopik, McGeary, & Beevers, 2011) and street code reflecting high value placed on being tough and aggressive, standing up for one's rights and being ready to fight in the case of a three-gene one (5-HTTLPR, DRD4, MAOA: Simons et al., 2012).

When it comes to *physiological processes*, 5-HTTLPR and an environmental factor have been found to interact in a differential susceptibility related manner in predicting cortisol reactivity (Way & Taylor, 2010), with the same being true of BDNF when the dependent variable is heart rate (Gatt et al., 2009) or evening salivary cortisol (Vinberg et al., 2009). Turning to *brain measurements*, Alexander and colleagues (2012) present evidence that 5-HTTLPR interacts with stressful life events in a for-better-and-for-worse manner to predict left amygdala reactivity to fearful faces, while Gatt et al. (2009) document much the same when using BDNF to forecast grey matter volume in both the hippocampus and the amygdala. Additionally, Klucken and associates (2013) report that BDNF interacts with positive and negative feedback in a for-better-and-for-worse manner during appetitive conditioning when predicting hemodynamic response in the amygdala. Also worth considering is evidence that individuals homozygous for the Iso allele of the rs5522 SNP located on the mineralocorticoid receptor gene (MR) manifest the most and least right amygdala reactivity, relative to Val carriers, when they (retrospectively) reported experiencing, respectively, high and low levels of emotional neglect in childhood (Bogdan, Williamson, & Hariri, 2012).

But it may not be just adversity to which the amygdala of certain individuals proves especially sensitive to. After all, an extensive meta-analysis showed that the amygdala responds to both negative and—even more strongly—to positive stimuli (Sergerie, Chochol, & Armony, 2008). This suggests to us, as does the work cited in the preceding paragraph, that amygdala reactivity might be one of several central nervous mechanism by which differential susceptibility operates. This would certainly be consistent with the hypothesis, proposed by the differential susceptibility framework (Belsky & Pluess, 2009a) as well as the concept of sensory-processing sensitivity (Aron & Aron, 1997; Aron, Aron, & Jagiellowicz, 2012), that heightened

susceptibility is the function of a more sensitive central nervous system on which experiences register more easily and deeply. According to this neurosensitivity hypothesis (Pluess & Belsky, 2013), specific gene variants (e.g., 5-HTTLPR short allele, DRD4 7-repeat) contribute to the increased sensitivity and responsivity of specific brain regions that then manifests itself in increased negative emotionality and physiological reactivity (Pluess, Stevens, & Belsky, 2013), in part because highly sensitive individuals are more easily aroused.

What this brief summary of diverse findings related to putative plasticity genes should make clear is that a variety of plausible mechanisms—at multiple levels of analysis—may help to account for the GxE findings noted or referred to earlier. Not only is more such research required, but the big challenge going forward will surely be to put Humpty Dumpty together, even if not again, so that a multilevel *system of causation* can be illuminated (Hyde, Bogdan, & Hariri, 2011). Needless to say, this represents a huge agenda, if not the holy grail of inquiry.

EXPERIMENTAL EVALUATION OF VARIATION IN DEVELOPMENTAL PLASTICITY

All the research cited through this point has been observational and correlational, even if often longitudinal, in character. One of the fundamental risks of interpreting evidence of such work, as noted earlier when considering methodological issues, is that what appears to be a function of person–environment interaction could actually reflect person–environment correlation. In other words, rather than such interaction effects reflecting the moderation of environmental influence by some person characteristic, they could reflect the fact that person characteristics and environments are correlated, perhaps due to the shared heritability of each, the fact that certain people tend to be exposed to certain experiences or that individuals with certain attributes evoke or provoke particular developmental experiences. The common strategy employed in observational work for discounting the possibility that organism-environment correlation is masquerading as organism–environment interaction is to insure that the temperamental, physiological, or genetic moderator under study is not correlated with the contextual predictor under consideration. However laudable such efforts are, they are not without limits. For example, just because the moderating polymorphism under investigation (e.g., DRD4) proves unrelated to the contextual predictor of interest (e.g., sensitive parenting) does not mean that this is true of all other unmeasured or unexamined organismic factors (e.g., BDNF). Ultimately, the fact that environments have not been systematically manipulated in most plasticity-related research means that one cannot be certain, even in the case of the putatively malleable, that truly causal environmental effects are being detected (van IJzendoorn & Bakermans-Kranenburg, 2012).

One way around this problem, pioneered by Dutch investigators in the case of genetic plasticity factors (Bakermans-Kranenburg, van IJzendoorn, Mesman, Alink, & Juffer, 2008b; Bakermans-Kranenburg, van IJzendoorn, Pijlman, Mesman, & Juffer, 2008c), involves conducting intervention experiments in which individuals are randomly assigned to a treatment condition. Because it is unethical to assign individuals, especially children, to conditions of adversity, this approach has only been used to evaluate differential response—as a function of some hypothesized plasticity factor—to an experience presumed to promote positive functioning. Such a design is of course limited, as it can only evaluate the for-better side of developmental plasticity (Pluess & Belsky, 2013). Nevertheless, it represents an ideal way to determine whether those considered to be resilient to adversity on the basis of observational research also prove relatively unresponsive to supportive conditions and whether those considered vulnerable to adversity disproportionately benefit from environmental enrichment. As it turns out, there is ever growing experimental evidence that this is indeed the case.

Negative Emotionality and Physiological Reactivity

With regard to the plasticity factor of negative emotionality, consider the re-analysis of data from the Infant Health and Development Program (1990), a well-known, early intervention which involved the random assignment of poor, low-birth infants and their families to treatment or control condition, putatively generating positive, across-the-board program effects. Blair (2002) tested Belsky's (1997a, 1997b) proposition that an enriched rearing experience (involving educational day care in the second and third year of life, combined with home visiting and parent support over the child's first three years) would differentially impact children with varying temperaments. As predicted, infants who were highly negatively emotional and assigned to the early-intervention group scored substantially lower on externalizing problems at 3 years of age than did similarly tempered infants randomly assigned to the control group; no such treatment effect occurred in the case of other infants. Especially intriguing given the fact that virtually all research considered through this

point has focused on differential susceptibility vis-à-vis social and emotional functioning, is that exactly the same results emerged when the outcome in question was severely impaired cognitive functioning. More specifically, highly negative infants assigned to the experimental intervention were five times less likely to score at or below 75 on an IQ test at age three than their negatively emotional counterparts assigned to the control condition; no such experimental effect occurred in the case of infants scoring low on negative emotionality.

Not inconsistent with these findings are those showing that (1) it was infants who scored relatively low on irritability as newborns who failed to benefit from an otherwise security-promoting intervention (Cassidy, Woodhouse, Sherman, Stupica, & Lejuez, 2011) and (2) infants who showed few, if any, mild perinatal adversities—known to be related to limited negative emotionality—who failed to benefit from computer-based instruction otherwise found to promote preschoolers' phonemic awareness and early literacy (van der Kooy-Hofland, van der Kooy, Bus, van IJzendoorn, & Bonsel, 2012). In other words, only the putatively vulnerable—those manifesting or likely to manifest high levels of negativity—experienced developmental enhancement as a function of the interventions cited. Similar results emerge among older children. Consider in this regard the results of Scott and O'Connor's (2012) parenting intervention that generated the most positive change in conduct among emotionally dysregulated children (i.e., loses temper, angry, touchy). Van de Wiel and associates (2004) presented related results when the plasticity factor was physiological reactivity, finding that an intervention for children with disruptive behavior disorder proved effective, but only for those displaying high cortisol-related, stress reactivity.

Genetics

Recent genetically informed evaluations of intervention programs also indicate that alleles presumed to place individuals at risk in the face of adversity (e.g., 5-HTTLPR short allele, DRD4 7-repeat) or to promote resilience (i.e., no 5-HTTLPR short allele/no DRD4 7-repeat) are associated with them being, respectfully, susceptible or not to the benefits of intervention (but see Cicchetti, Rogosch, & Toth, 2011, for counter evidence). Consider first experimental intervention research designed to enhance parenting which chronicles a moderating effect of the 7-repeat allele on parenting. When Bakermans-Kranenburg, van IJzendorn, Pijlman, Mesman, and Juffer (2008) looked at change over time in parenting—from before to well after a video-feedback parenting intervention was provided on a random basis to 157 mothers of 1–3-year-olds who scored high on externalizing problems—they found that the intervention succeeded in promoting more sensitive parenting and positive discipline. Moreover, this intervention effect translated into improvements in child behavior, but only for those children carrying the DRD4 7-repeat allele. The same was true when, at post-treatment follow up, stress reactivity was measured by means of change in salivary cortisol before and after the administration of an experimental stressor (i.e., area under the curve) (Bakermans-Kranenburg, van IJzendoorn, Mesman, et al., 2008). Indeed, DRD4 7-repeat children in the experimental group not only showed the least physiological stress reactivity of all children, but the most if their mothers had been assigned to the control group.

Of note, too, is that the most pronounced reduction in children's problem behavior occurred when two conditions obtained: (1) the parenting intervention *substantially* improved mother's use of positive discipline techniques; and (2) the child carried the DRD4 7-repeat allele. When only the first condition was met, children's behavior did not change. One cannot help but wonder why some mothers benefited more from the experimental treatment than others in terms of improved parenting and thus whether an untested GxGxE interaction was responsible for the problem-behavior findings discerned. Could it be that mothers with certain susceptibility genes—including perhaps the 5-HTTLPR short allele—proved most responsive to the intervention and it was this, in combination with their child's genetic susceptibility to rearing, that generated the results described? This question raises a more general one: when parenting interventions prove effective in changing child behavior, does a small subset of parent–child dyads carry the overall treatment effect—and, specifically, ones comprised of a parent and a child who are both highly malleable for genetic reasons? As no intervention investigation has considered parent as well as child genotype, this possibility remains to be evaluated.

Further evidence of DRD4 in moderating intervention effects can be found in Kegel, Bus, and van IJzendoorn's (2011) work showing that it was DRD4 7-repeat carriers who benefited from specially designed computer games promoting phonemic awareness and, thereby, early literacy in their RCT. Other RCT results point in the same direction with regard to DRD4 7-repeat, including research on African-American teens in which substance use was the outcome examined (Beach, Brody, Lei, & Philibert, 2010; Brody et al., 2013, 2014)

Also of importance is intervention evidence highlighting the moderating role of 5-HTTLPR. Consider in this regard Drury and associates' (2012) data showing that it was only children growing up in Romanian orphanages who carried short alleles who benefited from being randomly assigned to high-quality foster care—in terms of reductions in the display of indiscriminant friendliness. Eley and associates (2012) also documented intervention benefits restricted to short-allele carriers, but their design included only treated children (i.e., not RCT).

Attention must be called, however, to another non-RCT intervention study which found that it was individuals suffering from Posttraumatic Stress Disorder who carried short alleles who benefited the least from cognitive behavior therapy (Bryant et al., 2010).

Last to be considered is research examining genetically moderated intervention effects using multigene composites rather than single candidate genes. Consider in this regard the Drury et al. (2012) findings showing that even though BDNF—all by itself—did not operate as a plasticity factor when it came to distinguishing those who did and did not benefit from the foster-care intervention, the already-noted moderating effect of 5-HTTLPR was amplified if a child carried BDNF Met alleles *along with* short 5-HTTLPR alleles. In other words, the more putative plasticity alleles children carried, the more their indiscriminant friendliness declined over time when assigned to foster care and the more it increased if they remained institutionalized. In light of these results and other research from nonintervention studies focused on BDNF suggesting that BDNF Met alleles are associated with susceptibility to environmental effects in a positive and negative manner (e.g., Chen et al., 2012; Gunnar et al., 2012; Juhasz et al., 2011; Mata et al., 2010; Suzuki et al., 2011), it is somewhat surprising to discover that in a non-RCT treatment study it was individuals carrying BDNF Val rather than Met alleles who benefitted the most from exposure therapy when it came to reducing the symptoms of posttraumatic stress disorder (Felmingham, Dobson-Stone, Schofield, Quirk, & Bryant, 2013).

In an intervention study that involved a RCT, Brody, Beach and Chen (2013) confirmed their prediction that the more GABAergic and dopaminergic plasticity-related gene variants African American teens carried, the more protected they were from increasing their alcohol use over time when enrolled in a whole-family prevention program. These findings along with those of Drury et al. (2012) once again call attention to the benefits of moving beyond single polymorphisms when it comes to operationalizing the plasticity phenotype. Moreover, the Drury et al. (2012) results indicate that even if a single gene may not by itself moderate an intervention (or other environmental) effect, in could still play a role in determining the degree to which an individual benefits. These are insights future investigators—and interventionists—should keep in mind when seeking to discover what works for whom.

REPEATED MEASUREMENTS

All the differential susceptibility-related work cited herein, as well as in our earlier reviews (Belsky, 2005; Belsky & Pluess, 2009a; Ellis, Boyce, et al., 2011), essentially presumes that children and adults who share the same characteristics, be they temperamental, physiological or genetic plasticity factors, would function in a manner opposite to what was observed were they exposed to contrasting conditions. For example, we have presumed that children carrying the DRD4 7-repeat and showing high levels of externalizing problems in the face of insensitive parenting would score low on such problems if they were raised by skilled caregivers, and this is certainly what some of the just summarized research on genetically moderated intervention effects suggests. But the truth is that there is almost no research validating this assumption, in part because it is unethical to provide a child growing up under for-better, supportive conditions with for-worse, adverse ones just to test for differential susceptibility. One of the few studies that systematically addressed the repeated-measurement issue under consideration, even if not in such differential susceptibility-related terms or with children, examined the probability of taking a risk in a gambling-decision-making game when the chances of winning were high (i.e., for-better condition) and when they were low (i.e., for-worse condition) (Roiser et al., 2006). Results revealed the more 5-HTTLPR short alleles an individual carried, the more likely the person would make a bet (i.e., take a risk) when the chance of winning was high (i.e., for-better condition) and the less likely such a decision would be made when the probability of winning was low (i.e., for-worse condition).

In addition to constructing repeated-measurement experiments of the kind just described—though not necessarily having to do with gambling decision making—future researchers would be well advised to take advantage of experiments in nature that could serve this purpose. Consider in this regard the imaginative work of Verschoor and Markus (2011) who took advantage of days in which undergraduates did and did not have examinations to see how those homozygous for long and short 5-HTTLPR

alleles functioned, finding that that the latter experienced the most tension, negative mood and perceived stress on exam days (i.e., for-worse condition), yet the least on nonexam days (i.e., for-better condition). Consider as well Schoebi and associates' (2012) marital research indicating that spouses homozygous for 5-HTTLPR short alleles proved more sensitive to their partner's positive and negative emotion during marital interactions, seeming to reflect exposure to for-better and for-worse conditions.

UNKNOWNS IN THE DIFFERENTIAL SUSCEPTIBILITY EQUATION

As much as anything else, the central thesis of this chapter, namely, that individuals differ in their developmental plasticity and thus susceptibility to environmental influence, raises many issues in need of further investigation, many of which have already been highlighted. Here we call attention to additional ones.

Same Individuals, Different Plasticity Markers?

Is the research conducted by investigators often working in different fields—psychology, physiology, genetics—actually identifying the same more-and-less-susceptible individuals by different means? Consider in this regard that the very children who score high in negative emotionality, physiological stress reactivity and who have 5-HTPLR short alleles could often be one and the same (5-HTTLPR and cortisol reactivity: Gotlib, Joormann, Minor, & Hallmayer, 2008; 5-HTTLPR and infant negative emotionality: Holmboe, Nemoda, Fearon, Sasvari-Szekely, & Johnson, 2011). Some recent evidence raises the possibility, however, that empirically related plasticity factors may not be interchangeable. Even though recent work indicates that DRD4 and negative emotionality early in life are related (Holmboe et al., 2011; Ivorra et al., 2010), Belsky and Pluess (2013b) observed that the moderating effect of DRD4 does not account for a parallel moderating effect of negative emotionality, at least in a study of effects of child care on children's social functioning.

Categorical or Dimensional Scaling of Plasticity?

Another issue that merits consideration in future work is whether individual differences in plasticity are best conceptualized in typological or dimensional terms. Adopting evolutionary terminology pertaining to reproductive strategy, we can ask whether there exist plastic and fixed strategists who are and are not, respectively, susceptible to environmental experiences, thereby following conditional and alternative pathways of development (Belsky, 2000). Or does it make more sense to think in terms of a plasticity gradient, as mentioned earlier, with individuals varying in *degree* of susceptibility to environmental influences? But perhaps in the same way that light is best conceived as both a wave and a particle, depending upon the circumstance, the choice between a typological and dimensional conceptualization and parameterization of plasticity is a false one, as the approach which proves best will vary across conceptual purposes and empirical inquiries.

Domain Specific or Domain General?

Also unknown is whether it makes the most sense to regard more and less plasticity as a global, macro, trait-like characteristic of individuals or consider it in more domain-specific terms? Are some people simply more malleable than others across the board, almost irrespective of the environmental factor and aspect of functioning under consideration, or are people a complex mosaic of components that are more and less susceptible to environmental influence, thus making them both more and less malleable relative to others? Whereas the latter conceptualization might make more intuitive sense, two new sets of evidence underscore the domain generality of plasticity. The first involves the nature and effects of two dramatically different and already cited Dutch interventions which used different approaches to influence children, one indirectly and the other directly, and focused on different developmental outcomes, yet revealed that children sharing the same plasticity factor were the primary beneficiaries of each. More specifically, even though one intervention promoted sensitive parenting via video feedback to reduce toddler's externalizing behavior (Bakermans-Kranenburg, van IJzendoorn, Pijlman, et al., 2008) and cortisol-related stress reactivity (Bakermans-Kranenburg, van IJzendoorn, Mesman, et al., 2008) and the other relied on a computerized instructional program to promote preschooler's phonemic awareness and, thereby, early literacy (Kegel et al., 2011), it was children carrying the DRD4–7-repeat allele who disproportionately or exclusively benefited in both cases.

Then there is the longitudinal data evaluated by Roisman and associates (2012) showing that infants with difficult temperaments measured in the first six months of life proved more susceptible to the positive and negative effects, respectively, of sensitive and insensitive mothering experienced during their first three years of life when

it came to predicting teacher-reported social competence, behavior problems, and academic skills across the primary-school years. Also, this was so even with different teachers rating the children each and every academic year. Moreover, even though a diathesis–stress rather than differential susceptibility model fit the data best when it came to predicting performance on objective tests of academic performance through 15 years of age, it once again proved to be children who as infants had difficult temperaments who were disproportionately susceptible to the shorter and longer term effects of early mothering.

Despite such evidence, it still seems premature to embrace the broad domain-general interpretation of developmental plasticity. Nevertheless, the results just summarized caution against its premature dismissal. Ultimately, further work is called for before any firm conclusions can be drawn. Our own suspicion is that there will be variation across individuals in that some will prove highly susceptible to many developmental experiences and environmental exposures (i.e., extremely plastic) and that some will prove susceptible to virtually none (i.e., extremely fixed), but that most will prove to be intermediate between these extremes. One might even envision a bell curve with regard to the degree of plasticity that individuals manifest.

Origins of Plasticity: Nature or Nurture (or Both)?

A fundamental issue that should be raised for future research pertains to whether, or at least the extent to which, plasticity should be regarded as principally a function of nature or nurture. Certainly the GxE evidence calls attention to heritable individual differences in plasticity, as well as to the fact that so-called vulnerability genes or risk alleles might in many cases be better conceptualized as plasticity genes (Belsky et al., 2009). After all and with regard to the latter point, why would natural selection, for example, maintain much less select genes that only functioned to foster depression in the face of negative life events or antisocial behavior in the face of child maltreatment? Were these perhaps down-side costs of selecting and preserving genes that engendered benefit in the face of supportive contextual conditions, or even operated as adaptations when also functioning in a diathesis–stress manner, it would seem to make more sense for them to be selected.

But just because GxE studies are replete with evidence, often unnoticed, of differential susceptibility should not lead to the presumption that plasticity is only function of genetics. Central to Boyce and Ellis's (2005) thinking, it will be recalled, is the role of extremely supportive and unsupportive environments in fostering physiological reactivity and, thereby, developmental plasticity. Especially notable, in fact, is recent research on the putatively adverse effects on the developing child of maternal stress during pregnancy. This is because so-called fetal programming appears to influence several of the very susceptibility factors already considered that seem to be markers of differential susceptibility (Belsky & Pluess, 2009b; Pluess & Belsky, 2011). Consider in this regard research showing (1) that maternal stress during pregnancy predicts difficult temperament at 3 months of age (Huizink et al., 2002) and emotional reactivity to novelty in 4-month-olds (Möhler, Parzer, Brunner, Wiebel, & Resch, 2006); (2) that prenatal maternal depression and elevated cortisol levels in late pregnancy predict negative reactivity at age 2 (Davis et al., 2007); and (3) that maternal prenatal anxiety predicts awakening cortisol in 10-year-olds (O'Connor et al., 2005).

On one hand, such data suggest that very early experience—in the womb—may shape plasticity, not just genetics, as the outcomes just mentioned are among the very child characteristics found in work cited herein to demarcate heightened susceptibility to environmental influences. Just as importantly, this re-interpretation of putatively negative effects of prenatal stress raises fundamental questions about the disturbance-focused perspective that pervades virtually all research and theory on prenatal programming: Is it the case that prenatal stressors compromise later development, as prevailing thinking presumes, or do these prenatal experiences promote plasticity—and thus the organism's openness to future experiential input, be it positive or negative in character? That is, is there prenatal programming of postnatal programming (Pluess & Belsky, 2011)? Oberlander et al.'s (2008) epigenetic findings showing that maternal depressed mood in pregnancy predicts increased methylation of the human glucocorticoid receptor gene (NR3C1, measured in neonatal cord blood), which itself forecasts elevated cortisol stress reactivity at age three months, illuminates at least one biological mechanism that may be central to such fetal programming of postnatal plasticity. Recall in this regard that cortisol reactivity may well demarcate heightened susceptibility to rearing influences (Boyce & Ellis, 2005).

Before concluding on the basis of fetal programming research that plasticity may be a function of experience as much as a function of genetics, we should not lose sight of the fact that GxE may characterize the fetal programming process (Gluckman & Hanson, 2005). This raises the possibility that some fetuses may be more susceptible to fetal programming than others, for genetic reasons.

If they are, it would suggest that plasticity is a function not just of nature or nurture, but of their interaction (Belsky & Pluess, 2009b). That is, some individuals may be more likely than others to be affected by experience, most notably perhaps fetal experience, in ways that subsequently affect whether or to what degree they will be influenced by the postnatal world they encounter. Initial evidence to this effect was found in recent GxE work based on data from a large Dutch cohort study in which maternal anxiety during pregnancy significantly predicted negative emotionality—a putative susceptibility factor—in infants carrying one or more copies of the 5-HTTLPR short allele, but not in those homozygous for the long allele (Pluess et al., 2011). These results provide the first empirical evidence consistent with the aforementioned hypothesis that individuals with certain genotypes who are also exposed to specific prenatal environments may be more likely than those not carrying such alleles or not so exposed to prove susceptible to postnatal environmental influences (Pluess et al., 2011). However, it has to be noted that whether infants characterized by high negative emotionality where also more affected by subsequent postnatal contextual factors, consistent with a differential susceptibility pattern, has not yet been determined within this sample. This would be necessary to conclusively test whether genetic factors moderate the effects of prenatal programming on postnatal plasticity (Pluess & Belsky, 2011).

Not to be ignored in this discussion of the determinants of developmental plasticity is evidence that physiological and behavioral susceptibility factors are also shaped by postnatal experiences (e.g., Heim et al., 2000; Kaplan, Evans, & Monk, 2008). Figure 2.3 represents a schematic model outlining the multiple means and pathways by which developmental plasticity is likely regulated: (1) genetic contributions to susceptibility; (2) genetic contributions mediated by behavioral and physiological susceptibility factors; (3) prenatal and (4) postnatal environmental effects on behavioral and physiological susceptibility factors; (5) GxE interactions involving the prenatal and (6) postnatal environment; and (7) interactions between the prenatal and postnatal environment in shaping susceptibility factors.

Population Variation in Plasticity?

Do populations differ in the degree to which children are malleable? If we consider for a moment the fact that selection for plasticity perhaps only pays off in fitness terms, especially given its potential costs, if what happens at one point in time is systematically related to what happens at a later point in time, the possibility emerges that human populations may vary in the degree to which children are malleable. After all, in some ecological niches past and future could have been more systematically related than in others. Future research can thus address whether in ecological niches in which the present and future are (or have been) more related, the payoff for plasticity could well be greater, with greater selection for plasticity in human populations.

Three observations seem noteworthy in this context. First, the DRD4 7-repeat allele not only recently

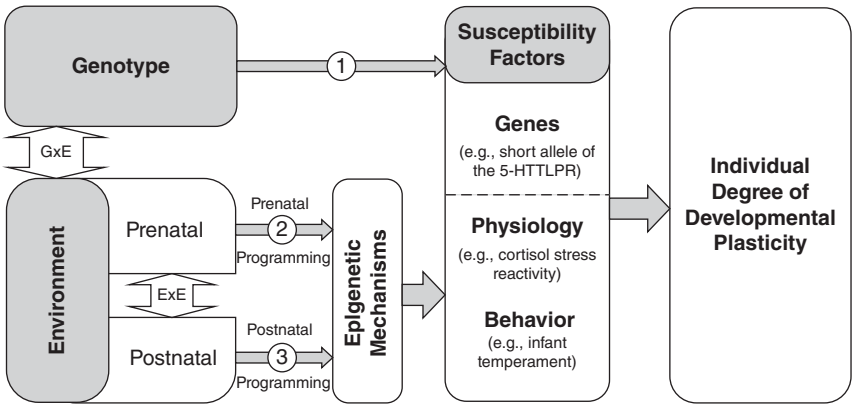


Figure 2.3 Nature, nurture, and differential susceptibility: a process model. 1 = genetic contribution to general susceptibility partially mediated by susceptibility factors (nature); 2 = prenatal environment shapes susceptibility factors (nurture); 3 = postnatal environment shapes susceptibility factors (nurture). In addition, genotype interacts with both prenatal and postnatal environment and prenatal and postnatal environments interact with each other to shape susceptibility factors. GxE = Gene–environment interaction; ExE = environment–environment interaction. *Source:* Pluess, M., Stevens, S., & Belsky, J. (2013). Differential Susceptibility: Developmental and Evolutionary Mechanisms of Gene-Environment Interactions. In M. Legerstee, D. W. Haley & M. H. Bornstein (Eds.), *The Infant Mind: Origins of the Social Brain* (pp. 77–96). New York: Guilford.

emerged in human populations (~40k years ago), but varies substantially across them, having an extremely low incidence in Asia yet a high frequency in the Americas (Ding et al., 2002); intriguingly, the reverse is true of another possible plasticity gene, the s/s genotype of 5-HTTLPR (Kim et al., 2007). Second, one wild bird population shows evidence that selection favoring individuals who are highly plastic with regard to the timing of reproduction has intensified over the past three decades, perhaps in response to climate change causing a mismatch between the breeding times of the birds and their caterpillar prey (Nussey, Postma, Gienapp, & Visser, 2005). Finally, Suomi (2006) observed that only two species of primates fill diverse ecological niches around the world, humans and rhesus macaques, and that what distinguishes these two weed species from all other primates is the presence of a polymorphism in the serotonin transporter gene (5-HTTLPR). In the same way, then, that not all primates seem to share the 5-HTTLPR, populations may differ generally in the presence of plasticity alleles, as already noted, due to variation in historical continuity of contextual conditions over time.

Gender Differences in Plasticity?

Originally, the differential susceptibility hypothesis did not have anything to say about the prospect of gender differences in developmental plasticity (Belsky, 1997b, 2005; Belsky & Pluess, 2009b). Therefore, it is not surprising that most research pertaining to differential susceptibility do not consider gender other than as a covariate to control for gender differences in the dependent variables under investigation. Nevertheless, it seems potentially—even if not certainly—noteworthy that some research on differential susceptibility has revealed gender differences in developmental plasticity. Consider in this regard one study involving a behavioral susceptibility factor, infant negativity, which detected differential susceptibility related effects of father involvement on prosocial behavior, but only in the case of girls (Ramchandani, van IJzendoorn, & Bakermans-Kranenburg, 2010). Consider next research focused on physiological reactivity as a susceptibility factor, with El-Sheikh, Keller, et al. (2007) reporting that skin conductance reactivity of children moderated the effects of marital conflict on externalizing problems, again in a differential susceptibility related manner, but this time only in the case of boys.

Several GxE studies involving the 5-HTTLPR have also detected the for-better-and-for-worse pattern of environmental influence, but only for females (Brummett et al., 2008; Eley et al., 2004; Hammen, Brennan, Keenan-Miller, Hazel, & Najman, 2010). Nevertheless, other work which has formally tested three-way interactions involving gender, 5-HTTLPR and an environmental factor has failed to detect sex-differentiated GxE patterns taking the form of differential susceptibility (Pluess et al., 2010, 2011). Finally, GxE-related gender differences emerged in work that composited putative plasticity genes, finding that it was only adolescent boys whose self-control proved related to the parenting they experienced in a for-better-and-for-worse manner (Belsky & Beaver, 2011). In summary, although gender differences in the operation of differential susceptibility emerge in a number of investigations, one is hard pressed to discern order in the empirical chaos. Perhaps if the issue is addressed more systematically and consistently—and theory as to why such should be expected emerges to motivate such inquiry—future research will tell a different story.

Competitive Evaluation of Models of Person–Environment Interaction

Much of the evidence cited in our earlier reviews of differential susceptibility-related evidence (Belsky et al., 2009; Belsky & Pluess, 2009a), as well as herein, was selected for consideration based on eyeball tests of graphed interactions between an environmental predictor and developmental outcome moderated by a plasticity factor. The limits of this approach to testing for differential susceptibility led Belsky et al. (2007) to propose explicit empirical criteria which we summarized earlier, while calling attention to the fact that much of the research cited in this chapter does not meet such seemingly rigorous evidentiary standards. Indeed, Kochanska and associates (2011) extended this effort to establish standards for distinguishing differential susceptibility from diathesis stress using the regions-of-significance approach (Preacher, Curran, & Bauer, 2006; Takane & Cramer, 1975) to evaluate, separately, the for-better and for-worse sides of the differential susceptibility hypothesis upon documenting the required cross-over interaction.

Roisman and associates (2012) recently offered an even more demanding approach for evaluating differential susceptibility by providing two new quantitative metrics in combination with the regions-of-significance analysis: the *proportion of interaction* index, which represents the proportion of the total area of an interaction plot that is uniquely attributable to differential susceptibility; and the *proportion affected* index, which quantifies the proportion of people in the sample who fall above the crossover point

(i.e., proportion of sample in the for-better condition). In addition, Roisman et al. (2012) recommend testing for nonlinear relationships between predictor and outcome and correction for multiple comparisons.

All the approaches offered to date to evaluate differential susceptibility have involved conducting essentially *exploratory* tests of organism–environment interactions as a first step before further interrogating the data at hand. Widaman and associates (Belsky, Pluess, & Widaman, 2013; Widaman et al., 2012) recently advanced a strategy which sidesteps such approaches, moving directly to test competing theoretical models. In a first step the cross-over point between high- and low-susceptible individuals is estimated with the help of a re-parameterized regression equation (Widaman et al., 2012). If the estimated cross-over point lies within the observed range of the predictor, four additional re-parameterized regression models are applied, two constrained to reflect a weak and a strong version of diathesis–stress and two to reflect a weak- and a strong-version of differential susceptibility. Fit indices of the four models are then compared to evaluate whether the data fits better with a diathesis–stress or differential susceptibility model (Belsky et al., 2013). The strong version of differential susceptibility presupposes that there are those who are susceptible to both positive and negative contextual conditions and others who are not, whereas the weak version presupposes that while many may be susceptible to environmental influences to some extent, some are more affected than others.

The time has thus come to move beyond exploratory tests of organism–environment interaction in regression and ANOVA designs, and more formally evaluate in a competitive manner the a-priori hypotheses central to diathesis–stress and differential susceptibility models of environmental action.

Variation in Environmental Cue Reliability

Whether children develop in a generally supportive or unsupportive environment, it is likely that the reliability of environmental cues indicative of the valence of the rearing milieu will vary. One can imagine in this regard two different hostile environments, one in which conflict is constant and thus highly predictable and another in which conflict is episodic and unpredictable. Frankenhuis and Panchanathan (2011) have insightfully observed that highly plastic individuals growing up in these two environments may differ in terms of when they commit to a developmental strategy, with the former deciding to specialize early, having high confidence about the state of the environment, but the latter deferring commitment and choosing to keep sampling the environment until a better estimate of the environment can be established. Whether this is actually the case or not is an issue that should be pursued empirically in the future. Indeed, Frankenhuis and Panchanathan's (2011) intriguing ideas lead us to wonder whether it is when cue reliability is low that individuals call upon the epigenome to infer from markings passed down across multiple generations what past environments were like and thus what is the best developmental pathway to pursue. Such a process would be consistent with Kuzawa's (2005) notion of intergenerational phenotypic inertia that highlights the fact that it is not just the experiences of the immediately preceding generation that developing organisms are sensitive to, but even ones preceding that.

Parent–Child Conflict of Interest

Like all-too-many developmental scientists lacking foundational knowledge about evolutionary theory, virtually all our thinking and writing about differential susceptibility to date has presumed that malleable children will have their development regulated by their rearing experiences. But as Trivers (1974) pointed out more than four decades ago, the fact that parents and children share, on average, 50% of their genes means that their biological interests are not one and the same and thus that they often experience a conflict of interest (see also Schlomer, Del Giudice, & Ellis, 2011). In discussing the influence of prenatal stress on development, Del Giudice (2012) recently pointed out that it is because of this fact that children, even highly malleable ones, may not simply take instructions from their parents. What are the implications of this observation for understanding developmental plasticity?

Family Dynamics

However intrigued we have become with theory and evidence pertaining to differential susceptibility and the notion that there exist individual differences in developmental plasticity, one issue has always caused us concern: We have *never* heard a parent characterize one of their children as more susceptible to their influence than another, which we regard as distinct from their saying that their children are temperamentally different, with perhaps one being more sensitive to challenging or stressful situations than others or even being more difficult to care for. Why is that? Evolutionary reasoning would seem to imply that parents should detect for whom their socialization efforts, be they implicit or explicit, pay off and for whom they

do not and so adjust those efforts accordingly. Yet we are aware of no evidence suggesting, much less indicating this to be the case. Indeed, should not more malleable siblings seek to alert their parents to the fact that they are more responsive to rearing inputs to obtain more attention and other resources? Might it be the case, however, that such children do engage in such efforts, but that they do not prove effective because less malleable children employ tactics to camouflage in some way this characteristic of theirs? Perhaps it is such children who prove most likely to claim it's not fair within families when siblings are perceived as being treated better as a way of throwing their parents off track. At the very least, it would be interesting to study parental awareness or perception of variation in susceptibility across siblings within a family.

Timing of Susceptibility

It is widely assumed by many developmentalists that it is during the early years of life when human development is most susceptible to environmental influences, for better and for worse (e.g., Blair & Raver, 2012; Ganzel & Morris, 2011), as plasticity is presumed to be greatest when biological systems are being laid down. But even if this is true in general, does it mean that it is true in the case of each and every individual? It certainly seems conceivable that at times in the ancestral past that individuals who were especially susceptible to environmental influence at some later point or points in the life span might have experienced an adaptive advantage, leading perhaps to the selection of genes for later rather than earlier plasticity. If this is so, it implies that variation should exist in terms of *when* children and even adults are especially developmentally plastic. And if this is the case, does it not imply that those who appear not to be especially malleable may simply not be so at the developmental point in time when developmental experiences and environmental exposures are measured? In fact, might it be the case that some are especially susceptible to contextual regulation early, others later, others at all times and still others more or less never?

For Better and For Worse—or Just for Better?

One important unknown in the differential susceptibility equation is whether some individuals could be especially susceptible to just adversity, some to just environmental support and enrichment, some to both, and some to neither. Of note in this regard is that whereas the English language has terms to characterize those highly susceptible to both positive and negative conditions (i.e., plastic/malleable) and highly susceptible to adversity (i.e., vulnerable), it is difficult to find a term that would characterize those disproportionately responsive to supportive conditions only. Indeed, the only term that Belsky and Pluess (2009b) could identify—in tongue-and-cheek fashion—to characterize those disproportionately likely to benefit from positive experiences and exposures was *lucky*. And this was after asking speakers of diverse languages, including French, German, Italian, Chinese, Czech, Spanish, Korean, and Polish, whether there was a word or term in their native tongue that captured the for-better side of differential susceptibility. The fact that there did not seem to be such a term in any of these languages raised the intriguing possibility that one reason variability in response to positive—as opposed to negative—experiences went unnoticed, or at least unheralded, for so long was that we simply lack terminology to direct attention to it.

Recently, Manuck and associates (2011a; Sweitzer et al., 2013) introduced the term vantage sensitivity to characterize the for-better side of differential susceptibility and more generally variability in response to *positive* experiences. *Vantage* is short for *advantage*, but in addition to implying benefit, gain or profit, it is also defined as a position, condition, or opportunity that is likely to provide superiority or an advantage (HMCO, 2000). In Manuck's own words (Manuck, 2011b), *vantage* bespeaks a position conferring advantage, benefit, or gain without bearing the singularity of a particular advantage. We embrace and promote the term vantage sensitivity to describe the notion that some individuals are more sensitive and positively responsive to the environmental advantages to which they are exposed to, but not especially susceptible to adverse experiences, as is presumed in the case of differential susceptibility. These advantages may take the form of security of attachment derived from sensitive parenting, academic achievement resulting from high-quality child care, prosocial behavior due to supportive friendship networks, and life satisfaction stemming from positive life events, as well as sense of efficacy following psychotherapy, to name just a few possibilities.

In hopes of stimulating work which would distinguish vantage sensitivity from differential susceptibility, Pluess and Belsky (2013) proposed the following concepts to characterize variability in response to positive experiences: (1) vantage sensitivity reflects the general proclivity of an individual to benefit from positive and presumptively well-being– and competence-promoting features of the environment, just as vulnerability depicts the tendency to succumb to negative effects of adversity in the diathesis–stress framework; (2) the degree

of vantage sensitivity is a function of the presence of vantage-sensitivity factors (i.e., promotive factors), just as vulnerability/risk factors increase vulnerability to negative effects of adversity in the diathesis–stress framework; (3) vantage resistance describes the failure to benefit from positive influences, just as resilience characterizes resistance to negative effects of adversity in the diathesis–stress framework; and (4) the degree of vantage resistance is a function of the presence of vantage-resistance factors or absence of vantage-sensitivity ones, just as protective factors increase resilience to negative effects of adversity in the diathesis–stress framework. In summary: vantage-sensitivity factors increase vantage sensitivity to the beneficial effects of positive experiences and exposures, whereas vantage-resistance factors diminish or even completely eliminate positive response to the same supportive conditions (Figure 2.4 for graphical illustration).

Having delineated the nature of vantage sensitivity, some evidence consistent with the notion merits consideration. Testing the a priori hypothesis that children characterized by a high sensitive personality (Aron & Aron, 1997) would show vantage sensitivity to psychological intervention, Pluess and Boniwell (2015) investigated variation in the anticipated positive effects of a school-based resilience-promoting program administered to a sample

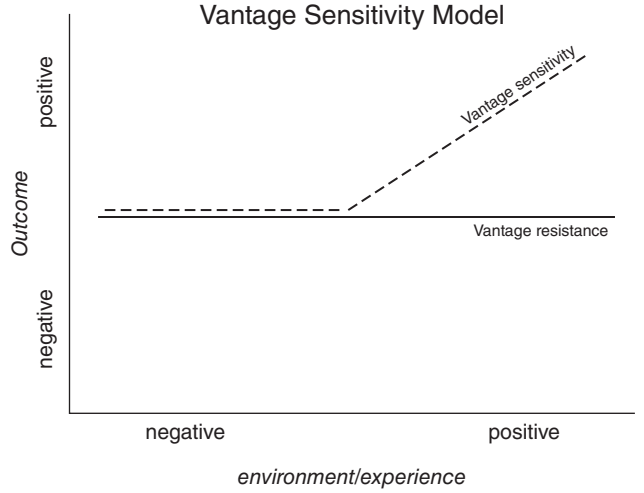


Figure 2.4 Graphical illustration of vantage sensitivity. Vantage sensitivity describes the propensity to respond favorably to positive experiences as a function of individual characteristics, whereas vantage resistance reflects the inability to benefit from supportive influences. No differences are predicted in response to negative influences. *Source:* Adapted from M. J. Bakermans-Kranenburg & M. H. van IJzendoorn, Gene–environment interaction of the dopamine D4 receptor (DRD4) and observed maternal insensitivity predicting externalizing behavior in preschoolers. *Developmental Psychobiology, 48*(5), 2006, Figure 1.

of 200 11-year-old girls in one of the most deprived areas in London, United Kingdom (Pluess, Boniwell, Hefferon, & Tunariu, submitted). The intervention led to a decrease of depression symptoms observable up to the 12 month follow-up assessment, but, consistent with vantage sensitivity, exclusively among children who scored in the upper quartile of the highly-sensitive-child questionnaire. All other children failed to benefit from the intervention, at least regarding changes in depression symptoms.

An example of vantage sensitivity as a function of a physiological moderating factor emerged recently in Eisenberg et al.'s (2012) work of 213 toddlers and their families. Baseline RSA moderated effects of the home environment (based on a composite of maternal and paternal education, family income, and marital quality) in early childhood on repeatedly assessed child aggression. For children with high RSA activity, high environmental quality was associated with less aggression at 54 months, whereas children characterized by low RSA activity—displaying vantage resistance—did not benefit from high-quality environments at all.

Eley et al.'s (2012) evaluation of whether 5-HTTLPR moderated effects of cognitive-behavioral therapy for anxiety disorders provides an example of genetic vantage sensitivity. Clinical diagnoses of anxiety disorders and symptom severity were assessed before and after treatment as well as 6 months after treatment ended. Although all children appeared to benefit from the treatment, the positive effect of the intervention was particularly pronounced in the case of those children carrying the short allele in this work with 6–13-year-old boys and girls ($N = 359$). More specifically, those homozygous for the 5-HTTLPR short allele showed a significantly greater reduction in symptom severity from pre-treatment to follow-up assessment, so much so, in fact, that they proved 20% more likely than others to be free of anxiety disorder at the 6-month follow-up assessment.

FUTURE DIRECTIONS IN RESEARCH ON DIFFERENTIAL SUSCEPTIBILITY

Here we highlight a number of issues that future research should prioritize to advance knowledge regarding individual differences in developmental plasticity. Following this, we draw some general conclusions.

Differential susceptibility is a rather new concept with most empirical work having emerged in just the past few years. Although already an influential framework, particularly within the fields of developmental and clinical psychology, providing answers to some long-standing

questions regarding individual differences in response to environmental influences, differential susceptibility reasoning actually appears to raise more new questions than answering old ones.

1. *Mechanisms of differential susceptibility*. Among all the unknowns in the differential susceptibility equation that have been discussed in this chapter as well as in previous publications (Belsky & Pluess, 2009a, 2009b, 2013a; Pluess & Belsky, 2013), that regarding *mechanisms* underlying individual differences in susceptibility seems especially important to apply differential susceptibility in practice, a thorough understanding of *how* susceptibility gets instantiated will be crucial. Future work should therefore endeavor to identify specific mechanisms and related processes across different levels of analysis from genetic and molecular, to neurological and hormonal, to behavioral.
2. *Domain specificity*. Are some individuals generally more and others less susceptible to all kinds of developmental experiences and environmental exposures, or are they more susceptible to certain influences compared with others? For example, might some be especially sensitive to peer influence and others to parental influence; or some especially susceptible to the effects of punishment and others to the effects of reward? Empirical investigation of this important question will require studies testing whether the same susceptibility factor increases plasticity of the same individual across different environmental influences and with respect to different phenotypic characteristics.
3. *Nature and nurture of susceptibility*. Is an individual's degree of susceptibility biologically fixed or can it be influenced through intervention or particular experiences? As discussed earlier, susceptibility seems to have a genetic basis. The question of determinants of susceptibility is particularly important regarding potential intervention efforts to foster both resilience and vantage sensitivity. Future studies with large longitudinal prospective samples that include molecular genetic measures are required to investigate the genetic and environmental determinants of susceptibility as well as the interaction of the two.
4. *Development of developmental plasticity*. Closely linked to the question of whether susceptibility is a fixed or malleable trait is a developmental question: Does susceptibility evolve during development or is it established early in life, perhaps even by the time of birth? Future research should seek to illuminate, for example, whether an individuals' propensity for vulnerability to environmental adversity may increase in response to accumulated negative experiences (i.e., diathesis–stress) and whether susceptibility to positive experiences (i.e., vantage sensitivity) may increase over time as a result of exposure to positive influences. Evidence of such would prove consistent with the notion of upward spiral dynamics (Fredrickson & Joiner, 2002).
5. *Susceptibility to what?* There appear to be three general models of person–environment interaction today: diathesis–stress (i.e., variability in response to exclusively negative experiences, Monroe & Simons, 1991), vantage sensitivity (i.e., variability in response to exclusively positive experiences, Pluess & Belsky, 2013), and differential susceptibility (i.e., variability in response to both negative *and* positive experiences, Belsky & Pluess, 2009a), with the latter reflecting the combination of both diathesis–stress and vantage sensitivity as a function of the same moderating variable. Empirical evidence for each of these models suggests that whereas some individuals may be disproportionately susceptible to negative experiences others may be disproportionately susceptible to positive environmental conditions and still others may be disproportionately susceptible to both—or to neither. Future research should investigate whether these four different types of environmental sensitivity exist in the population (Pluess, 2015).
6. *Susceptibility versus vulnerability versus vantage sensitivity factors*. Susceptibility, Vulnerability and Vantage Sensitivity have often been associated with the same psychological, physiological and genetic characteristics. Future research should aim to determine whether there are, in fact, specific factors for vulnerability, vantage sensitivity, and differential susceptibility and associated specific mechanisms and related processes.
7. *Sensitive periods*. Is an individual's susceptibility constant across development or are there sensitive periods where susceptibility to environmental influences is more pronounced compared with other developmental periods? Furthermore, do different susceptibility factors increasing susceptibility to environmental influences during different developmental periods? Addressing these questions requires studies testing interactions between putative susceptibility factors and environmental influences within the same person repeatedly across different developmental periods.
8. *Measures of susceptibility*. To apply differential susceptibility to psychological and educational services, it will be important to develop measures of susceptibility that are both reliable and easily applicable. Measures of

physiological reactivity or genetic susceptibility are currently not suited for that purpose. Future efforts should be directed toward the development of rating scales and observational indices of susceptibility. Although some existing self-report measures have been found to predict differential susceptibility as well as vantage sensitivity (for example, sensory-processing sensitivity, Aron & Aron, 1997; Pluess & Boniwell, 2015) more specific measures—validated rigorously in empirical studies—are required.

9. *Ethical considerations*. Give the potential application of differential susceptibility reasoning in clinical, educational, child care and other settings, it will be important to consider ethical challenges before applying differential susceptibility thinking to these services. Besides the mere identification of ethical challenges (e.g., systematic screening for high and low susceptibility, stigma of being found high or low in susceptibility, treating individuals differently given their susceptibility) it will be important to explore solutions for dealing with these potential problematic issues (e.g., offering alternative treatments rather than no treatment to low susceptible individuals).

GENERAL CONCLUSION

One of the most striking features of the empirical work reviewed in this chapter is how diverse the evidence base for differential susceptibility is, involving a myriad of developmental experiences and environmental exposures (e.g., parenting, child-care quality, life events, rural vs. urban residence, birth season), numerous phenotypic outcomes from different developmental periods (e.g., disorganized infant attachment, externalizing problems in childhood, antisocial behavior in adolescence, depression throughout adulthood), and distinct susceptibility factors (e.g., temperamental and other behavioral attributes of children, physiological and genetic characteristics).

Beyond highlighting empirical evidence for differential susceptibility, we have sought to emphasize the utility of thinking about development from an evolutionary perspective, without which the differential susceptibility framework seems unlikely to have emerged. Indeed, what is striking is how simple a concept differential susceptibility appears to be. It thus seems likely that failure to appreciate that there are individual differences in developmental plasticity, whether general or specific in nature, has been due, at least in part, by the general lack of an evolutionary orientation among many students of human development and related disciplines.

Beyond documenting the utility of an evolutionary perspective, one great benefit of differential susceptibility reasoning is its generativity—in stimulating new thinking and thus new avenues of research about the human development process. We thus feel confident that differential susceptibility thinking will continue to inspire, stimulate, and guide empirical and theoretical research efforts in human development and look forward to the scientific progress this should occasion.

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CHAPTER 3

Differential Sensitivity to Context: Implications for Developmental Psychopathology

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INTRODUCTION

A History of the Nature–Nurture Culture Wars

Modern technology is advancing and refining scientific knowledge at an unprecedented pace. In the three decades between the graduate academic training of this chapter's authors, significant shifts in the nature vs. nurture debate have occurred. And now, as we write this chapter, trainees are being steeped in a more-evolved formulation, representing yet another qualitative shift in understanding. While quickly paced paradigm shifts are somewhat commonplace in science, these nature–nurture debate shifts are particularly striking when one considers the centuries that passed with little progress in this argument before these more recent, rapid advancements.

Students of philosophy will note that the *nature versus nurture* debate is centuries old. The debate rose to popular public awareness in the seventeenth century, when French philosopher René Descartes proposed that individual humans each possess certain innate ideas that underpin our approach to the world—a stance that was later strongly contested by British empiricists, exemplified by John Locke's claim that humans were blank slates upon which experience marks its influence, fully shaping behavior. In 1874, Francis Galton, a second-cousin to Charles Darwin, presented a more integrated view of the influence of genetics and environment on a person's development, stating: "[Nature and nurture are] a convenient jingle of words, for it separates under two distinct heads the innumerable

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elements of which personality is composed. Nature is all that a man brings with himself into the world; nurture is every influence that affects him after his birth" (Galton, 1874, p. 12). Although this latter approach considered both nature and nurture when describing development, both were presented as separate, unique entities with different time courses of effect. This type of dual conceptualization was carried forward into the study of disease over the next century. Few trains of thought were more integrative than the predominant dual conceptualization allowed, though historians note that Freud was one of the first to integrate contrasting conceptualizations of psychiatric disease as both hereditary and environmentally acquired through childhood experiences, which is one likely reason for the endurance of his thinking (Sulloway, 1992). However, by and large, the leading investigators and scholars within the field of developmental psychopathology were academically reared within a scientific generation marked by a confluence of two distinctive views of the origins of human disorders. Within this single generation, physicians, clinical and developmental psychologists, social workers, and laboratory investigators were steeped in the twin agendas of environmental and biological determinism.

In the environmental determinism view, prominent in the scientific world of the 1960s and 1970s, disease and disorder were held to be products of contextual exposures and adversities. Human afflictions, it was believed, were due almost exclusively to the acute and chronic, cumulative influences of environmental agents of disease. Such agents included psychological stressors, impoverished living conditions, physical toxins, infectious pathogens, and inadequate or malevolent parenting. In the field of psychopathology, disease formulations were particularly influenced by behaviorist theories of B. F. Skinner and John Watson, who famously claimed, "Give me a dozen healthy infants . . . and my own specified world to bring them up in and I'll guarantee to take any one at random and train him to become any type of specialist I might select—doctor, lawyer, artist, merchant-chief and yes, even beggar-man and thief, regardless of his talents, penchants, tendencies, abilities, vocations, and race of his ancestors (Watson, 1930 p. 82)." Within this nurture framework of behavior and disease, schizophrenia was misleadingly viewed as the product of psychological double-binds within dysfunctional family units, autism was regarded as the legacy of cold, distant mothers, and maternal overprotectiveness figured prominently in the presumed etiology of childhood anxiety disorders. Thus, prevention and treatment were taken to require alterations in the range of causative environmental exposures.

Within a second canonical view, emerging at the pinnacle of the first by virtue of a revolution in molecular biology, human disorder was thought principally to be the result of biological frailties built into the structure of the heritable genome. Individual genetic differences, occurring on average in one of every thousand nucleotide base pairs, became seen as likely biological substrates for many human disorders, and quantitative trait loci (QTLs) were thought to constitute the multiple gene systems that, in isolation, code for variation in complex behavioral traits (Plomin & Crabbe, 2000). Most if not all disease, it was posited by some, would one day become explicable within the frameworks of evolutionary biology and human genetics, and eagerly anticipated gene therapies would transform the treatment and prevention of disordered biology. Thus, Alzheimer disease would one day be accounted for by mutations in the gene coding for apolipoprotein E4; a polymorphism in the promoter region of the serotonin transporter gene would eventually elucidate anxiety disorders and phobias; and the long repeat allele of the DRD4 dopamine receptor gene would explain the etiology of ADHD and other externalizing behavior problems. Within 3 decades' time, two opposing and mutually exclusive causal orthodoxies captured and held the high ground of scientific discourse on the genesis of human disease.

Early Evidence for Biology–Context Interactions

Vulnerabilities in both positions first became evident as three bodies of research findings emerged in the final years of the twentieth century. First, the nascent field of behavior genetics increasingly documented shared genetic and environmental accounts for variance in the incidence and severity of a broad array of behavioral and psychopathological disorders (Plomin, DeFries, McClearn, & McGuffin, 2001). Using heritability statistics derived from genetically informative research designs, behavioral geneticists became able to decompose phenotypic variance into genetic and environmental components. The genetic component was further subdivided into additive and nonadditive effects, and the environmental component was parsed into shared and nonshared influences (Goldsmith, Gottesman, & Lemery, 1997). While the neuroscience of schizophrenia provided compelling evidence for a heritable disorder of the brain, epidemiological studies revealed that, even among monozygotic twins, the concordance rate for a diagnosis of schizophrenia never exceeded 50%. Schizophrenia was demonstrably a biological disorder with heritable components, but as much as half of the variance in its rate of occurrence was attributable to environmental exposures. The science of behavior and development thus faced a Kierkegaardian dilemma (Kierkegaarad, 1986 (1843)), in which an uncompromising either–or became a more illuminating both–and. Schizophrenia, like

virtually all forms of human behavior (Rutter et al., 1997), became understood as a product of both biological and contextual etiologies.

A second set of findings revealed the previously unsuspected bidirectional influences of biology and context, each on the other. While it had become apparent that genes affected both normative and disordered human behavior, new evidence indicated: (1) the heritability of environmental experience, and (2) the potentially profound regulatory effects of social environmental exposures on the transcription of DNA. Discoveries of such bidirectional effects led to a recognition of genotype-environment correlations and to the categorization of such correlations into passive, reactive, and active forms (Plomin, DeFries, & Loehlin, 1977). Studies by Plomin and colleagues demonstrated heritable influences on parental behavior and the home environment (Braungart, Fulker, & Plomin, 1992; O'Connor, Hetherington, Reiss, & Plomin, 1995), and other work showed that even random misfortune, such as stressful events (Kendler, Neale, Kessler, Heath, & Eaves, 1993) and the loss of friends (Bergeman, Plomin, Pederson, McClearn, & Nesselroade, 1990), were partly attributable to genetic variation. Animal research by Meaney and colleagues demonstrated that brief maternal separations among rat pups alter maternal behavior, leading to down-regulation of the CRH system and diminished adrenocortical reactivity extending even into adult life (Anisman, Zaharia, Meaney, & Merali, 1998). Other studies in mice found that disruption of social hierarchies led to viral infection-related mortality, which was attributable to an over-expression of genes for cytokine proteins (Sheridan, Stark, Avitsur, & Padgett, 2000), and that caloric restriction prevented aging-related alterations in the expression of genes governing protein metabolism (Lee, Klopp, Weindruch, & Prolla, 1999). While both environmental and biological determinism assumed impenetrable divisions between contexts and genes, new evidence revealed a capacity for the genome to influence environmental experience and for social and physical environments to switch on and off the decoding of genetic material (Cacioppo, Berntson, Sheridan, & McClintock, 2000). Social experience became a heritable predisposition, and the transcription of genes became a process governable by the character of social experience.

The third source of vulnerability in the twin dogmas of biological and environmental determinism at the turn of this century was the accelerating emergence of evidence for biology–context interactions in studies of disease etiology. Much of the work examining biological and contextual contributions to pathogenesis was initially preoccupied with partitioning variance into the two distinctive categories of causal factors. Other studies began to illuminate how the interplay between biology and context serves a central etiologic role. Mednick, Gabrielli, and Hutchings (1987), for example, found that a child's rearing by an adoptive parent with a criminal conviction did not increase the likelihood of criminality in the child, unless one of the child's biological parents had also been convicted of a crime. Similarly, a polymorphism in the promoter region of the gene encoding corticotrophin releasing hormone (CRH) was shown to moderate the association between maternal stress and preterm birth (Wang et al., 2001). Self-perceived maternal stress was associated overall with pregnancies that were an average of 1.3 weeks shorter, but when a mother possessed a variant allele of the CRH gene, perceived stress was associated with a 2.9-week shortening. Another example was the finding that a polymorphism in the monoamine oxidase A (MAOA) gene promoter moderated the association between early life trauma and increased risk for antisocial behavior, such that the increased risk for individuals abused as children was higher for those carrying the genotype that confers lower levels of MAOA expression but those carrying the genotype that confers higher levels of MAOA expression were somewhat buffered from this maladaptive effect (Caspi et al., 2002). Even in so-called monogenic diseases, such as phenylketonuria, phenotypic expression of the disease depends upon dietary exposure to phenylalanine, suggesting environmental factors influence disease severity and course (Scriver & Waters, 1999). Common to each of these examples is a biogenetic vulnerability that amplifies the pathological effects of a social or physical environmental exposure.

Taken together, those emerging lines of evidence constituted a convincing empirical threat to a monodeterministic view of pathogenesis, and a race to integrate biology and context into a coherent model ensued. Accumulating evidence from the past few decades has made real the current position that, while human morbidities will undoubtedly be identified that have their origins in solely genetic or environmental causes, variation in the onset and course of *most* human disorders will be most likely ultimately explained by interactions among biological and environmental forces (Rutter, 2006; Weatherall, 2001).

As a field, we have moved past the simple partitioning of developmental variance into genetic and environmentally determined components and into the examination of more complex and potentially rewarding questions of genetic change and continuity, relations among dimensional symptoms and diagnosable psychopathology, and the interplay between biology and context (Meaney, 2010; Plomin & Crabbe, 2000). This chapter will outline some of the theories and empirical evidence for biology and context interactions in the etiology of healthy and pathological psychosocial development, with an eye toward highlighting

the conceptual and methodological controversies in this work and translational implications. We also describe the challenges awaiting a new generation of investigators and theorists poised to bring the nature–nurture discussion into its next evolutionary form.

SENSITIVITY TO CONTEXT WITHIN A DEVELOPMENTAL PSYCHOPATHOLOGY FRAMEWORK

Within the field of developmental psychopathology, as well as in the broader fields of medicine and biology, there is a strong focus on discovery of the mechanisms by which environmental forces get under the skin to affect health. Using the term *biological embedding* (Hertzman & Wiens, 1996) to describe the process whereby differential human experiences systematically affect health across the life cycle, Hertzman (1999, 2012) provided an articulation of the range of potential processes for these effects. Placing special emphasis on early development, he offered a hypothesis that systematic differences in early environment quality, including emotional and physical support and stimulation, will affect the neurochemistry and shaping of the central nervous system in ways that will adversely affect cognitive, social, and behavioral development. Although myriad biologic processes may be affected by social experience, some candidate systems are more likely to transduce social environmental factors into aspects of human biology with the capacity for embedding and influencing mental or physical health throughout the rest of the life course. Hertzman and Boyce (2010) identified four systems that are influenced by daily experience, respond to experience throughout an organism's development, have meaningful impacts on health/learning/behavior, and are known to function differentially in response to variations in early experience. The four systems comprise: (1) the hypothalamic-pituitary-adrenal (HPA) axis and its expression of the glucocorticoid, cortisol; (2) the autonomic nervous system and its neurotransmitters, epinephrine and norepinephrine; (3) the prefrontal cortex, subserving memory, attention, and other executive functions; and (4) systems for social affiliation involving connections between the amygdala, locus coeruleus, and higher order cerebral connections, which are mediated by serotonin and other neurohormones. Other systems, such as the mesolimbic dopamine system, which mediates attentional processes, reward seeking, learning and behavioral engagement, and biological processes such as epigenetic modifications of neuroregulatory genes and telomerase activity are emerging as likely processes by which biological embedding occurs. Despite the plausibility of biological embedding and the champions behind it, and that nationally representative studies have shown that adverse experiences early in life predict nearly 45% of childhood-onset and 30% of adult-onset psychopathology (Green et al., 2010), there is surprisingly little research on the early life effects of social environment on biology. Thus, the increasing attention to this gap in the empirical literature is merited. However, while understanding the mechanistic (i.e., mediation) processes by which an environmental exposure is linked to disordered development can be a powerful aid to elucidating pathogenesis and imagining novel interventions, understanding of mechanistic linkages, although perhaps necessary, is insufficient for a comprehensive understanding of causation. The quest for accurate determination of the mechanisms underpinning associations across early social contexts, stress, development, and psychopathology necessitates elucidation of the effects of modifiers (i.e., moderators) that reveal when, at what ages, or in what subgroups such associations hold (Baron & Kenny, 1986; Kraemer, Kiernan, Essex, & Kupfer, 2008; Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001).

NEUROBIOLOGICAL SENSITIVITY TO CONTEXT THEORIES AND EVIDENCE

Contexts and experiences do not have universal influence across individual organisms, and the parsing of populations into subgroups of varying exposure susceptibility, through the discovery of moderator variables, can advance comprehension and the tractability of a given association between experience and pathology outcome. Indeed, the modern movement toward precision medicine (National Research Council, 2011) is, in part, motivated by the clinical advantage of identifying patients who are more susceptible to certain diseases, who will respond to treatments differently, and whose diseases or conditions may progress on a different course than others in the general population. Psychology has paid particular attention to understanding organismic factors (e.g., gender, IQ, and impulsivity) that place some individuals at greater risk for development of problems in adverse environments. This diathesis–stress or stress–vulnerability model (Figure 3.1) has been a prevailing view within medical and psychological frameworks since the 1960s, and emphasizes how individuals possessing biological vulnerabilities are most likely to develop functional impairments when exposed to particular stressors (for a review, see Ingram & Luxton, 2005). This framework is often conceptualized as a multicausal developmental model that proposes multiple risk factors across levels interact over the course of development, which has been remarkably useful in advancing

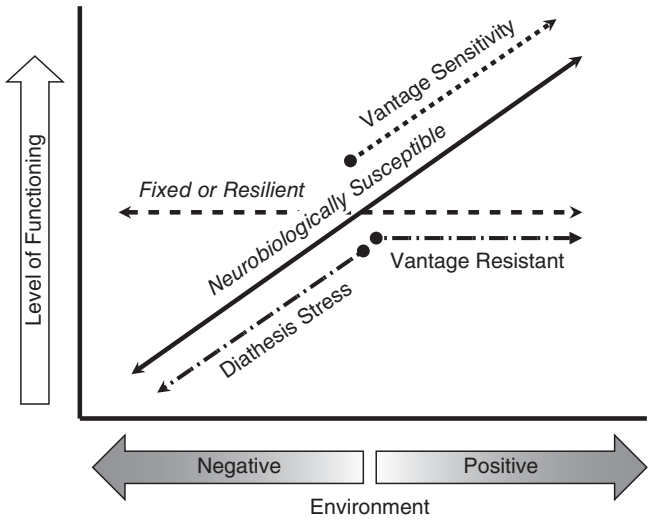


Figure 3.1 Visual model of various theoretical concepts of sensitivity to environment.

understanding of individual variability in stress response and risk for pathology. Perhaps the most famous case of biologic sensitivity to adversity is the 2003 finding of Caspi and Moffitt's group (Caspi, Sugden, Moffitt, Taylor, Craig, Harrington, McClay, et al., 2003), who pioneered longitudinal family gene–environment (GxE) research using their Dunedin study of roughly 1,000 individuals tracked over 40 years. Their 2003 paper linked experiences of childhood maltreatment with higher levels of adult depressive symptoms, but only among those possessing one or two copies of the short allele in the promoter region of the 5-HTT serotonin transporter gene—the gene that regulates transport of serotonin to the brain. They further found that possession of the longer allele was protective against those harmful effects. This first evidence demonstrating that one allele could lead to exacerbation or buffering of the stress–illness association was received with considerable scientific and media attention, and launched a gold rush of sorts into a quest for GxE interactions in mental health. This finding has been the source of considerable debate ever since, which we describe below, but nevertheless marked a major turning point in the conceptualization of and public awareness of the manner in which individual differences in a biological marker could confer varying sensitivity to harmful contexts.

More recently, emphasis has shifted from the predominant diathesis–stress conceptualizations to a pursuit of understanding the individual difference factors that reliably allow some individuals to be anomalously resilient in the face of adversity (see Luthar & Lyman, in press; Masten, 2012; Rutter, 2012; Werner, 2012). In particular, an individual's stress reactivity appears to be an important individual difference variable that influences the manner in which an organism responds to environmental experiences (Bush & Boyce, 2014; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011; Obradović, Bush, Stamperdahl, Adler, & Boyce, 2010). Although heightened stress reactivity has traditionally been considered to be a factor that uniformly increases risk, burgeoning empirical evidence suggests instead a differential neurobiological susceptibility to environmental conditions among some individuals who show exaggerated sensitivity or permeability to both negative and positive environmental conditions (Belsky, 1997, 2005; Boyce & Ellis, 2005; Boyce et al., 1995; Ellis et al., 2011). Specifically, a theory known as biological sensitivity to context (BSC) suggested that higher levels of physiologic stress reactivity may promote adaptation in settings characterized by support, predictability, and protection, but exacerbate risk for maladaptive outcomes in stressful childhood environments characterized by adversity (Boyce, 1996, 2007; Boyce et al., 1995; Boyce & Ellis, 2005; Ellis, Essex, & Boyce, 2005b). Such individuals thus show either the least or most adaptive outcomes within the population, depending on the character of the proximal social contexts in which they are reared. BSC theory had clear parallels with Belsky's differential susceptibility theory, which emphasized the manner in which behavioral reactivity made individuals particularly susceptible to both positive and negative experiences (Belsky, 1997, 2005). Although originally devised separately, through separate streams of thought and literature, the two theories shared considerable features and are now frequently presented together and referred to as *differential neurobiological susceptibility* (DNS; see Figure 3.1; Boyce, Obradović, et al., 2012; Ellis et al., 2011; Pluess & Belsky, 2013), which is inclusive of multiple levels of endogenous susceptibility factors. Thus, in this chapter when referring to findings applicable to this integrated framework, we hereafter use this DNS term.

A range of factors across multiple levels of biology have been thought to represent or subserve neurobiological sensitivity to social contexts, including genetic variation, chromatin modification, gene transcriptional control, ANS and HPA activation, and differences in brain structure and functions. The dominant lines of DNS research have tested differential susceptibility models by demonstrating interactive effects between various types of contextual stress (e.g., marital conflict, financial stress, parental psychopathology) and psychobiological reactivity in the prediction of health outcomes (e.g., Belsky & Pluess, 2009; Boyce et al., 1995; Obradović et al., 2010). Such research finds support for the claim that associations between risky and

supportive environmental exposures and adaptation vary across different levels of stress reactivity.

In one of our lab's early empirical examinations of the DNS theory using the Peers and Wellness Study (PAWS) longitudinal community sample of 328 kindergarten children, we found support for DNS within two different biological systems and across multiple outcomes of adaptive functioning. Specifically, although children demonstrating high parasympathetic nervous system (PNS) reactivity (assessed via respiratory sinus arrhythmia) to a set of standardized challenges had the worst outcomes when they lived in families with high levels of family adversity, high parasympathetically reactive children demonstrated the highest levels of prosocial behaviors and school engagement and the lowest levels of externalizing behavior when they lived in contexts with low levels of family adversity. High parasympathetically reactive children also showed improvement in academic competence from fall to spring of the kindergarten year in the context of low adversity but declines in competence in the context of high adversity; whereas the inverse was true for low reactive children. In a similar fashion, children demonstrating high HPA axis reactivity (assessed via salivary cortisol) to the challenge protocol had the highest levels of prosocial behavior in the sample when they were in family contexts with low levels of adversity but the lowest levels of prosocial behavior when they were in family contexts with high adversity. The results of this study provided strong support for DNS in that the findings were relatively robust, particularly for parasympathetic reactivity, which emerged as a significant moderator of family environment across four domains of child adaptation—each pattern of which was consistent with BSC or DNS theory. Moreover, the DNS interactions were found for both positive and negative indices of adaptation, which are rarely examined simultaneously in empirical reports and allow for the test of the theory across a continuum of adjustment. These findings within a typically developing sample were also exciting because they suggested that, if stress reactivity moderated the effects of adversity on development in a community sample of children, who on average do not face extreme disadvantage or show clinical levels of problem behavior, the interactive effects are likely to be larger at the extreme ends of such distributions.

Essex, Armstrong, Burk, Goldsmith, and Boyce (2011) tested DNS theory in a longitudinal sample of children to understand the roles of physiological and behavioral reactivity to the environment of classroom climate in the prediction of mental health symptoms across a 6-year period of childhood. Measuring both positive (teacher–child closeness) and negative (teacher–child conflict) aspects of the classroom environment in first grade, they found that both autonomic (mean arterial blood pressure) and behavioral (objectively coded temperamental inhibition) reactivity moderated the impact of classroom climate on mental health problem severity in seventh grade, after adjusting for mental health problem severity in first grade. It is striking that all four biological sensitivity to context × teacher–child relationship interaction terms were statistically significant demonstrating DNS moderated associations of both adverse and supportive aspects of the early teacher–child relationship on the development of early adolescence symptom severity.

Even within samples of children reared in poverty, wherein all study children are experiencing significant socioeconomic disadvantage, Conrad and colleagues found clear evidence that phenotypic reactivity can confer sensitivity to the risks and advantages conferred by other environmental factors such as objectively coded attachment security. In their study of infants born into disadvantaged conditions, infants with high baseline respiratory sinus arrhythmia (RSA) who were raised in contexts of high security had lower levels of problem behavior (actually below community norms), and infants with high baseline RSA who were raised in caregiving environments that fostered disorganization had the greatest number of problem behaviors at 17 months. Attachment security did not relate to problem behavior for infants with low RSA. These differences were also evident in the large effect sizes for these varying associations. These findings bolster evidence that poverty is not a uniform risk for problem behavior, particularly for children raised by nurturing caregivers; but they also reveal that children high in basal RSA are best able to take advantage of such opportunities and most at risk for harm if not provided with sensitive, responsive caregiving environments. Raver, Blair, and Willoughby's (2013) work also demonstrates that even in low-income populations, variation in temperamental reactivity can confer sensitivity to variations in the stressors of poverty. Although chronicity of poverty shows a negative linear association with young children's effortful control, their study found that it had no association for children low in reactivity. However, children high in reactivity demonstrated the highest levels of effortful control when they were not from families with chronic financial strain but the lowest levels of effortful control when they resided in the most chronically poor families—thus, demonstrating the *for-better-or-for-worse* effect even within a population with a restricted range of income.

Researchers using sophisticated modeling techniques on data from the Caucasian subsample of 1,030 adolescents and young adults from the nationally representative National Longitudinal Study of Adolescent Health have recently provided a compelling example of how sensitivity via a polymorphism in the serotonin transporter gene (5-HTTLPR) can convey DNS (Li, Berk, & Lee, 2013). Despite the widely demonstrated effects of high-quality family support on depression, they found that level of family support (cohesion, communication, and warmth) had little to no effect on depression scores in male individuals with the ll genotype. However, male s-carriers in families with high levels of support had the lowest levels of depression in the sample while s-carriers in families with the lowest levels of support had high levels of depression. This interaction was only marginally significant for females. Findings within this large representative sample, and across a broad range of environmental exposure (low to high quality of family support), have added support for DNS theories.

Studies demonstrating this greater susceptibility of neurobiologically responsive children to both positive and negative aspects of their environments have now included a wide variety of the following:

Stressors and adversities: peer victimization and aggression (Rudolph, Troop-Gordon, & Granger, 2010, 2011); parental depression and antisocial behavior (Cummings, El-Sheikh, Kouros, & Keller, 2007; Shannon, Beauchaine, Brenner, Neuhaus, & Gatzke-Kopp, 2007); marital conflict (El-Sheikh, 2005; El-Sheikh, Keller, & Erath, 2007); overall family distress (Obradović et al., 2010); child maltreatment (Grazioplene, DeYoung, Rogosch, & Cicchetti, 2013)

Positive environments: parental warmth (Ellis, McFadyen-Ketchum, Dodge, Pettit, & Bates, 1999); supportive child-care settings (Phillips et al., 2012); supportive interventions (Bakermans-Kranenburg, Van, Pijlman, Mesman, & Juffer, 2008)

Defining behavioral and biological parameters: temperament (Lengua, 2008; Pluess & Belsky, 2009) and personality (Grazioplene et al., 2013); physiologic reactivity (Alkon et al., 2006; Boyce et al., 1995); structural and functional differences in brain circuitry (Whittle et al., 2011); gene polymorphisms (see Belsky & Pluess, 2009 for a review; Knafo, Israel, & Ebstein, 2011; Manuck, Craig, Flory, Halder, & Ferrell, 2011)

Further, there is evidence for differential susceptibility across positive and negative types of environment as described previously but also for differential susceptibility to experience across the variety of characters that play important roles in children's lives, including mothering (Conradt, Measelle, & Ablow, 2013; Davies & Cicchetti, 2014), fathering (Boyce et al., 2006), quality of child-care settings (Pluess & Belsky, 2009), and teacher relationships (Essex et al., 2011). Most importantly, this body of literature reveals that highly susceptible children show bidirectional effects on outcomes in contrasting low- and high-stress settings, not simply an attenuation of negative effects in low-stress circumstances.

Implications for Conditional Adaptation

Within the Biological Sensitivity to Context Theory body of work, Boyce and Ellis (2005) also argued, in the second, less extensively explored component of the theory, for the importance of considering U-shaped associations, predicted from evolutionary principles, between the stressful versus supportive character of early rearing environments and the proportion of individuals evincing highly reactive phenotypes. The second of the 2005 papers advancing the BSC theory provided provisional evidence from two studies supporting the postulated U-shaped association between adversity and the prevalence of high reactivity phenotypes (Ellis, Essex, & Boyce, 2005a). The character of early contextual experiences likely plays a role, through conditional adaptations, in *shaping* the development of children's physiology. Those raised in stimulating and nurturing contexts may disproportionately acquire heightened biological sensitivity as a means of maximizing the advantages of resources and opportunities therein. On the other hand, children reared in harsh, threatening environments might also develop greater biological sensitivity to enhance vigilance to threats and other hazards. In contrast, the majority of children, raised within species-typical environments falling within these two extremes, may acquire diminished, more normative biological sensitivity, as the environments to which they are exposed are neither highly nurturing nor highly threatening (see Ellis & Boyce, 2011; Ellis et al., 2011 for the full argument in this regard). More recently, the concept of differential susceptibility has been usefully elaborated in a more detailed evolutionary framework referred to as the adaptive calibration model (ACM; Del Giudice, Ellis, & Shirtcliff, 2011). The ACM is a theory of developmental programing that focuses on calibration of organismic stress response systems and life history strategies in response to local environmental conditions. The ACM framework emphasizes a model of highly variable inter-individual patterns of stress responsivity

across life stages, prototypical responsivity patterns, the emergence of sex differences, and the primacy of the adaptive nature of long-term changes in biobehavioral systems, which its authors suggest promotes cross-field theoretical and research integration.

Boyce, Ellis, and colleagues thus suggest that high-reactivity phenotypes will be most prevalent in the contexts of low and high adversity exposure. In accordance with this theory, a U-shaped association between adversity and physiologic reactivity could provide for diverging trajectories of subsequent mental health over time. For example, although high reactivity may be adaptive across very low and very high stress contexts in the short term, as high reactivity becomes established (i.e., canalized), subsequent exposures to adversity over time would predispose the highly reactive individual to disorders of mental health. However, only longitudinal studies of the interplay between environmental effects and stress reactivity, starting with prenatal development and within broadly variable social contexts, can provide credible empirical evidence for this hypothesis. Moreover, to date, research has rarely considered U-shaped associations despite the value to be gained from understanding with greater precision the shape of associations between contextual stressors and the biological systems that contribute to psychopathology.

Three papers specifically explore curvilinear influences of early environmental stressors on the development of physiologic systems, specifically the HPA axis. Gunnar and colleagues (Gunnar, Frenn, Wewerka, & Van Ryzin, 2009) reported that children with moderate levels of early life adversity demonstrated lower cortisol reactivity to laboratory stressors than did children with either low or high levels of adversity, providing additional evidence for curvilinear associations between early life stress and HPA axis regulation. A second study, using a sample of young adults, found a curvilinear effect in the opposite direction from that proposed by BSC theory and found in Gunnar et al.'s study. Engert and colleagues (2010) found evidence for an inverted U-shaped relation between retrospective self-report of levels of maternal care received in childhood and young adults' cortisol stress reactivity, such that stress-induced cortisol levels for low- and high-maternal care groups were lower than for those in medium-care group. Such divergent patterns found between studies may result from meaningful differences in developmental timing of physiological assessment, intensity of the stressors, and factors such as retrospective reporting of stressors vs. concurrent or prospective assessments. Both studies examine effects on reactivity to laboratory stressors, which may not generalize to daily levels of physiologic load that are more relevant to allostatic load. A third paper, a review by Macri et al. (Macri, Zoratto, & Laviola, 2011), summarizes evidence from laboratory rodent studies and suggests that the link between neonatal stress exposures and adult phenotypic reactivity follows a U-shaped, curvilinear relation. The conclusions of these three papers support, at the very least, further consideration of curvilinear associations between early life stress and HPA axis regulation.

Recent work from our laboratory provides some additional evidence. Using an ethnically diverse longitudinal sample of 338 kindergarten children, we examined the effects of cumulative contextual stressors on children's developing HPA axis regulation (Bush, Obradovic, Adler, & Boyce, 2011). Chronic HPA axis regulation was assessed using cumulative, multiday measures of cortisol in both the fall and spring seasons of the kindergarten year. Hierarchical linear regression analyses revealed that contextual stressors related to ethnic minority status, SES, and family adversity each uniquely predicted children's daily HPA activity and that some of those associations were curvilinear in conformation. Results showed that the quadratic, U-shaped influences of family SES and family adversity operate in different directions to predict children's HPA axis regulation such that children from both the low and high SES families demonstrated higher levels of daily cortisol than their peers from middle-SES families and children from families with moderate adversity demonstrated higher daily cortisol than did those at either end of the adversity continuum. Results further suggested that these associations differed for white and ethnic minority children, with the opposing patterns of findings potentially reflecting different biological responses to environmental adversity by subgroup or different ranges of exposure to the stressors within subgroups. In total, this study revealed that early childhood experiences contribute to shifts in one of the principal neurobiological systems thought to contribute to allostatic load, and findings suggested that analyses of allostatic load and developmental theories accounting for its accrual would benefit from an inclusion of curvilinear associations in tested predictive models.

A further consideration is that the preponderance of differential susceptibility research has examined the manner in which biology and context interact to predict psychopathology symptoms or diagnoses. More recently, we have investigated the manner in which "stress sensitive" alleles moderate the effects of early life adversity on stress physiology early in development—a phenotypic predictor of later development across a broad array of health outcomes. Exploring the established negative association between SES and chronic cortisol arousal in children,

Bush and colleagues found that both 5-HTTLPR and BDNF genotype moderated the effects of early life family SES on children's chronic daily cortisol arousal (Bush, Guendelman, Adler, & Boyce, 2013a, 2013b), such that children with the l/l genotype of the serotonin transporter or who are carriers of the BDNF met allele had the highest chronic cortisol levels when growing up in low SES homes, but the lowest levels when growing up in high SES homes. Strikingly, for s carriers and Val/val genotypes, SES did not affect chronic daily cortisol levels. Beyond providing additional examples of DNS (and contributing to the small literature demonstrating that l/l genotypes are most sensitive to some environments (see, for example, Davies & Cicchetti, 2014), this work highlights how susceptibility via one biomarker (genes) can influence stress sensitivity in other systems (HPA axis arousal).

Evidence of Differential Susceptibility Within Positive Environments

As a result of the field's focus on contextual risk for pathology over contexts that promote optimal development, the majority of studies reviewed above emphasize the negative impacts of adverse exposures or deprivation on children's neurobiology. These studies tell us little about whether enriched environments produce optimized neurobiological development of the same magnitude as that negatively affected by adverse environments. A few studies, however, do point to enhanced sensitivity to positive environments. One excellent example is the work by Knafo and colleagues (Knafo et al., 2011) who used a sample of 168 twin pairs of Israeli preschool-aged children to parse genetic and environmental effects and investigate whether the 7-repeat allele of the dopamine receptor D4 (DRD4) would confer enhanced sensitivity to positive parenting. They found that positive parenting predicted maternal-rated prosocial behavior, but only for 7-repeat carriers. Similar findings occurred in a Dutch study in which 7-year-old children who were securely attached to their parents had higher rates of experimentally induced sharing assessed by willingness to donate their recently earned money to charity, but only for 7-repeat carriers (Bakermans-Kranenburg & van IJzendoorn, 2011). Additional evidence can be found from a study that found that the highest levels of social integration within objectively coded high-quality childcare settings was demonstrated by the most temperamentally reactive toddlers (Phillips et al., 2012). Together, these studies suggest that a variety of indices of sensitivity allow for increased sensitivity to enriched or optimal environments, yet many more studies in this area are needed to discern whether the sensitivity to both positive and negative environments is similar in magnitude and frequency.

Studies of differential susceptibility to adversity also do not help us ascertain whether extremely enriched contexts might counteract detrimental effects of adversity. However, a new literature is pointing to evidence for enhanced sensitivity to interventions, which represent positive environments designed to ameliorate negative effects of context on trajectories of mental health.

The Bucharest Early Intervention Project, for example, is a novel study where institutionally reared Romanian children who had been abandoned in the first few years of life were randomized to either remain under institutional care or be placed in (relatively) enriched environments via in-home foster care placements (Nelson et al., 2007). It has provided compelling evidence for differential susceptibility to adversity and intervention effects (i.e., both negative and positive environments). Specifically, children with one of the more sensitive genotypes (in this study, the 5-HTTLPR s/s or BDNF Val66Met met-carriers) demonstrated the *lowest* levels of indiscriminate behavior in the enriched foster care environment and the *highest* levels in the continued institutionalization context (Drury et al., 2012). Children with either of the less sensitive alleles (in this study, 5-HTTLPR l-carriers or of BDNF val/val) demonstrated little difference in levels of indiscriminate behaviors over time and no group × genotype interaction. Strikingly, this pattern was amplified when GxGxE tests were conducted, revealing that the DNS effect was largest for children with both sensitive genotypes, relative to those possessing just one, and children with no plasticity alleles demonstrated no intervention effect on levels of indiscriminate behavior over time.

Additional evidence can be found in more typically developing samples in the United States. In a randomized controlled trial of 169 families, only highly irritable infants showed positive benefit from an intervention designed to improve attachment security (Cassidy, Woodhouse, Sherman, Stupica, & Lejuez, 2011). Likewise, in a randomized controlled trial of 985 low birth weight infants from the Infant Health and Development Program, Blair (2002) found that a comprehensive compensatory education intervention had a substantially stronger effect on cognitive functioning and externalizing behavior outcomes for infants with greater temperamental negativity (Blair, 2002). In addition, preliminary analyses of a longitudinal evaluation of a clinical intervention for school-aged boys with disruptive behavior disorder found that only those with high cortisol reactivity prior to treatment showed decreases in parent-rated aggression and oppositional behavior after

treatment (van de Wiel, van Goozen, Matthys, Snoek, & van Engeland, 2004). Bakermans-Kranenburg and colleagues (2008) also found that DRD4 7-repeat carriers were more sensitive to an intervention designed to increase maternal positive discipline within families struggling with or at risk for child externalizing behavior problems; not only were the intervention effects on decreasing externalizing behavior strongest for 7-repeat carriers, but the association was also graded such that the effects were largest when mothers had better adherence to the goals of increased positive parenting.

Particularly compelling is recent evidence from two randomized alcohol use prevention trials involving more than 900 African American youths presented by Brody and colleagues (Brody, Chen, & Beach, 2013). This group found that variation in dopaminergic (DRD2, DRD4, and ANKK1) and GABAergic (GABRG1 and GABRA2) genes predicted alcohol use across a 2-year period of adolescence such that genetically at-risk youth within the control condition displayed greater levels of alcohol consumption but genetically at risk youth assigned to the prevention condition showed the lowest levels of consumption. Strikingly, when adolescents were coded based on how many of the risk genes they possessed (a multilocus genetic score in this study) an interaction predicting longitudinal change in alcohol use revealed that youth carrying greater numbers of the risk genes showed the greatest increase in alcohol use if in the control condition but greater responsiveness to prevention (smaller increases in use) than carriers of zero or one risk gene. The large sample size and randomization increase confidence in these findings.

Intervention Effects on Susceptibility

In addition to thinking about differential susceptibility to interventions, it is important to consider how interventions might improve risk-associated phenotypic reactivity or sensitivity in a manner that affects later susceptibility to environment. Prospective research has found that parental responsivity during early childhood predicts adolescent cortisol reactivity to social stressors, even after adjusting for subjective appraisals of the stressor, other environmental risk factors, and current psychosocial functioning (Hackman et al., 2013). This points to interventions targeting parental behavior as potentially important for the shaping of neurobiological susceptibility to environment. Thus far, the limited empirical investigation of intensive interventions suggests that, although they may not be entirely reversible, some harmful effects of biological embedding of early adversity can be overcome. For example, promise for recovery through intervention can be found in the recent results of primate rearing experiments. Although peer-reared monkeys exhibited higher cortisol levels in infancy and in response to stress, relative to mother-reared monkeys, 16 months after monkeys were relocated to a large social environment consisting of infants from all experimental rearing conditions, rearing groups were indistinguishable from one another physiologically and behaviorally (Dettmer, Novak, Suomi, & Meyer, 2012), suggesting transition to more normative environments can allow for recalibration of systems over time. The Bucharest Early Intervention Project has also shown that early intervention to correct a deeply impoverished early environment can improve brain structure and function as well as cognitive and emotional capabilities (Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012), suggesting the potential for catch-up brain growth in human children, even following extreme deprivation. Further results point to behavioral improvements as well, indicating that children in the foster care intervention demonstrated higher levels of positive affect and attention at both 30 and 42 months of age, and improved cognitive outcomes at age 42 and 54 months, compared with children who remained institutionalized (Ghera et al., 2009; Nelson et al., 2007). Children who were transitioned to foster care at earlier ages demonstrated the most marked improvements, suggesting sensitive periods for brain development. Studies of foster care children living in the United States have similarly provided evidence that psychosocial interventions may indeed modify children's disrupted biological systems, such as cortisol diurnal rhythms (Dozier et al., 2006; Fisher, Stoolmiller, Gunnar, & Burraston, 2007) and cortisol reactivity (Nelson & Spieker, 2013). For example, Nelson and Spieker found that an attachment promotion program with toddlers experiencing transitions in foster care placement led to increased cortisol reactivity (improvement in this context) in response to an experimental separation paradigm. There is also evidence that psychoeducation mixed with cognitive behavioral stabilizing group treatment can lead to decreases in levels of dorsal anterior cingulate cortex and left anterior insula activation to the Stroop task (thought to reflect selective attention and emotional regulation) for child abuse-related complex PTSD patients who previously demonstrated activation higher than that of matched controls (Thomaes et al., 2012). Together, these observed associations suggest some negative effects on neurobiology can be reversed or compensated for with early interventions, emphasizing the importance of both enrichment and adversity-reduction interventions in creating good

developmental environments for all children. Continued examination of intervention efforts with children exposed to early adversity and possessing stress reactivity phenotypes will broaden evidence for how contextual experience can shape the development of children's physiology and which phenotypes might be most capable of reversing ill effects on biology.

Vantage Sensitivity

In contrast to the diathesis–stress framework's emphasis on vulnerability to risk, Pluess and Belsky (2013) recently promoted a new construct of vantage sensitivity, which they argue can be distinguished from theoretically related concepts of differential-susceptibility and resilience, because it reflects variation in response to *exclusively* positive experiences as a function of individual endogenous characteristics (see Figure 3.1). They use this term to refer to the "bright side" of differential susceptibility in that some individuals are more sensitive and positively responsive to the environmental advantages to which they are exposed, be it security of attachment derived from sensitive parenting, prosocial behavior derived from supportive, healthy friendship networks, or academic achievement stemming from high-quality preschool or child care. This theoretical framework addresses some of the challenges that arise when attempting to examine certain combinations of individual characteristics and environments within a DNS framework. For example, from a DNS stance, a highly intelligent child might profit exceptionally from a high-quality education, but she may suffer disproportionately in a low-quality educational setting (perhaps due to being so smart that she disengages in the classroom and fails to learn); however a vantage sensitivity framework might allow for that child to have advantage in a good environment and no harm (unresponsive) to the adverse school environment, or even show protection from the adverse environment (increased resilience to adversity). In their review of recent empirical evidence for vantage sensitivity, they provide compelling examples featuring behavioral, physiological, and genetic factors as moderators of a wide range of positive experiences ranging from family environment and psychotherapy to educational intervention. We provide two illustrative examples here. First, in a large British cohort study, temperamentally reactive girls were more prosocial at age 6 if their fathers were highly involved in their care during early childhood, but nonreactive girls did not show any benefit of early father involvement on that outcome (Ramchandani, IJzendoorn, & Bakermans-Kranenburg, 2010). Second, Eisenberg and colleagues (Eisenberg et al., 2012) found that children high in baseline RSA activity reared in high quality home environments displayed lower aggression, whereas children characterized by low RSA levels did not benefit from the high quality environments. Pluess and Belsky pointed out in their review that much of the empirical work to date does not allow for true determination of whether individual phenotypes make one differentially susceptible to positive environments alone, because most studies with evidence for vantage sensitivity are not positioned to test whether those individuals are also more responsive to negative contexts. This situation of leaning on available data to support portions of a theory is a challenge for differential susceptibility more generally and improved study designs with breadth of measurement of contextual predictors and adjustment outcomes across negative and positive ends of those spectrums will greatly advance the field.

Cumulative Sensitivity to Environment?

Although research has spanned biological systems and often tests for DNS effects across several sensitivity markers concurrently, only recently have scientists begun to examine how sensitivities might be additive to create cumulative risk or advantage to environmental experience. In particular, Belsky and colleagues (Belsky & Beaver, 2011) have made efforts to advance this body of work through multigenic studies within larger samples, to test whether there are additive effects of purported plasticity genes. In the Add Health nationally representative sample of 1586 adolescents, they examined whether maternal parenting quality (including involvement, disengagement and attachment) predicted concurrent adolescent attentional, emotional, and behavioral self-regulation, assessed by questionnaires. Children in the sample were assessed for five gene polymorphisms with known associations with behavior and mood, including genes affecting dopamine availability and processing (DAT1, DRD2, and DRD4), the serotonin transporter gene (5-HTTLPR), and the MAOA gene, to test for cumulative sensitivity to parenting. Findings revealed that possessing increasing numbers of plasticity variants was associated with increasing sensitivity to parenting quality, such that maternal parenting quality was not associated with attentional and behavioral self-regulation for those carrying zero or one sensitivity alleles but predicted more and less self-regulation under, respectively, supportive and unsupportive parenting conditions, for those carrying two or more alleles. The pattern of findings suggested an additive effect such that the strength of the interactive association was greater with an increasing

number of sensitivity alleles. However, this effect was only found for males, and was not significant for females in this sample.

Of note, preliminary findings from our longitudinal sample of kindergarten children partially parallel this unique pattern of findings. Specifically, our findings (Allison, Bush, Adler, & Boyce, 2013) suggest that cumulative genetic sensitivity across several dopamine polymorphisms (DAT1, DRD2, and DRD4) predicts increasing severity of inattention and ADHD symptomatology later in the kindergarten school year, but only in males. However, this cumulative dopamine sensitivity variable did not significantly interact with family adversity to predict those symptoms. DAT1 alone, however, did interact with family adversity to predict inattention and ADHD symptoms in a manner consistent with the DNS theory. The variation in patterns of findings between the Belsky and Beaver analyses and those resulting from our preliminary analyses may be due to a variety of factors—a discussion of which highlights the complex challenge of establishing a body of evidence for cumulative sensitivity. First, we did not include two of the additional two sensitivity genes (5-HTTLPR and MAOA) used in their cumulative plasticity variable, as our interest was specifically in testing for cumulative effects within the dopamine pathway. Because studies rarely have exact replicates of variables for attempts at replications of findings, this sort of discrepancy will make it difficult to discern whether a specific genotype was driving the cumulative effect in a particular study and having multiple "risk" genotypes may just increase the odds that an individual possessed that particular variant. Second, we utilized different environmental variables (parenting vs. family adversity); although each are relevant exogenous influences on pathology, one measure may be more proximal for an individual child or more potent, and thus provide a better test of sensitivity to context. Third, our environmental variable had a limited positive range (lack of adversity does not necessarily imply a positive environment), and the parenting variable in the Belsky and Beaver study may have better reflected a broad range of experience in which to detect variability in response to environment. Fourth, there was an important difference in the ages assessed; the apparent cumulative sensitivity in adolescence may not manifest in a detectable manner by age 5, at least not in terms of ADHD symptomatology, which was relatively low in our community sample of young children.

Although not framed as cumulative plasticity, new findings from a sample of 120 preschool-aged children also appear to reveal how polygenic effects may add together to make individuals sensitive to environmental influences, for better or for worse. Pagliaccio and colleagues (2014) found crossover interactions such that children with greater numbers of genetic polymorphisms associated with risk of depression or higher cortisol had low hippocampal volume when they had histories relatively free of adversity but the highest hippocampal volumes when they had significant histories of adversity. The complex patterns of findings on children's hippocampal volume and risk for adjustment in the literature to date prevent us from interpreting this finding in terms of which children are better off, yet the crossover interactions found in that study provide additional data for consideration in the quest for understanding DNS.

Taking this cumulative plasticity approach is quite new, and additional work is needed to determine whether such conceptualizations and analyses will advance understanding of the etiology of developmental psychopathologies. Work such as that conducted by Brody and colleagues described above (Brody, Chen, et al., 2013), which revealed possession of greater numbers of susceptibility genes conferred increased risk for alcohol use across adolescence but greater sensitivity to a preventative intervention, is promising in this regard.

Although theoretically and statistically distinguishable from cumulative additive effects, three-way interactions among biological sensitivities and context, such as the GxGxE differential susceptibility findings reviewed earlier in this chapter, may also reflect a cumulative sensitivity or plasticity. Another example of this GxGxE effect can be found in additional work published by Brody and colleagues (Brody, Yu, et al., 2013). Within a sample of 315 African American youth, they found that those who possessed both the short (s) allele of the 5-HTTLPR gene and an allele of DRD4 with 7 or more repeats were most sensitive to the effects of the family environments on biology; whereas family environment had no effect on those who possessed none or just one of those sensitivity alleles. Specifically, individuals who experienced low levels of family support in adolescence were more likely to demonstrate high levels of allostatic load (a compilation of measures of HPA axis activity, blood pressure, and other biological markers of health) if they were both s-carriers and 7-repeat carriers. Cicchetti and colleagues have also found GxGxE effects in allostatic load models within a large multiethnic sample of 10-year-old children. Their findings revealed that maltreatment and CRHR 1 (corticotropin releasing hormone receptor 1) genetic variation affect cortisol regulation but that maltreatment and the joint effects of CRHR 1 TAT haplotype and 5-HTTLPR moderated

the effect of child maltreatment to predict internalizing symptoms (Cicchetti, Rogosch, & Oshri, 2011). Neither of these GxGxE studies presents findings that reveal the full spectrum of for-better-or-for-worse effects on adjustment due to their lack of differential susceptibility findings in better off family contexts or positive adjustment outcomes. However, they do reveal the ways multiple genes may simultaneously confer sensitivity to disadvantage via synergistic effects and point to the need for further multigene examination of sensitivity to context, particularly across positive and negative contexts and outcomes.

CONCEPTUAL AND METHODOLOGICAL ISSUES FOR EXAMINATIONS OF DIFFERENTIAL NEUROBIOLOGICAL SUSCEPTIBILITY

Impediments to Discovery

Given the difficulties of discovering biology–context interactions (Wachs & Plomin, 1991), and that the challenging factors discussed in the above section apply not only to searches for replication of cumulative sensitivity effects, but to replication of interaction findings more generally, it is all the more remarkable that such interactions are being increasingly identified and characterized in studies of human disease. GxE interactions are assessed as the differential risk effects of an exposure among individuals with different genotypes, or as the differing effects of a genotype among those who are heterogeneous with respect to exposure (Kraemer et al., 2001). As noted by McClelland and Judd (1993), field studies tend to underestimate the magnitude of interaction effects due to the nonoptimal distributions of the component variables, as the power to detect GxE interactions depends on the distributions and frequencies of the genotypes and exposures in the sample (for a discussion and examples see Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). Interactions accounting for as little as 1% of outcome variance in field research may conceal a true R^2 many times that size that would be found using an optimal, experimental design. When demonstrated, biology–context interactions in human populations may disproportionately exist at the extremes of genetic and environmental variation (McGue & Bouchard, 1998). Mathematically, analyses of variance and related statistical tests often fail to identify nonadditive effects because they have much less power in tests of interactions than in tests of main effects (Wahlsten, 1990). Improved genetic research designs (Andrieu & Goldstein, 1998; Caspi et al., 2010; Dunn et al., 2011), along with statistical approaches that are more sensitive to interaction effects (Kraemer et al., 2001) and can simultaneously consider multiple genetic markers within an entire targeted region (e.g., Belsky, Moffitt, & Caspi, 2013; Yu et al., 2012), are abetting the discovery of complex interactions between and among biologically and environmentally based factors.

Single studies are likely to be capable of capturing only a portion of the underlying paradigmatic DNS interaction. As illustrated in Figure 3.2, which is adapted from a figure in our previous publication (Obradović et al., 2010), the observational window (indicated by the area within the lightly shaded square) for DNS effects shifts from study to study, and even within a particular study depending on the focus of specific publications. The observational window can shift depending on a variety of factors, including: *characteristics of the sample*, such as intentionally oversampling impoverished children or unintentionally having greater success enrolling and retaining upper SES families, which greatly influences the range and qualities of environmental exposures; *the outcomes of interest* and whether they have a positive or negative valence (such as prosocial behavior and externalizing problems respectively) or more of a continuum such as with effortful control, or whether studies are examining early phenotypic risk factors for later

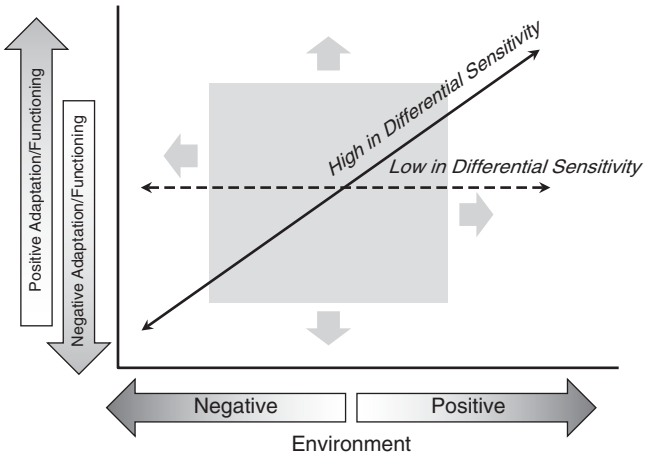


Figure 3.2 Conceptual model of the interactive effects between DNS and environmental influences, and the window of observation allowed by any one study design. Solid shaded gray area represents the window of observation by which any single study is capable of capturing a paradigmatic DNS interaction. The window can move in any direction, depending on study design and sample characteristics. *Source:* Figure adapted from previous work from our lab published in J. Obradović, N. R. Bush, J. Stamperdahl, N. E. Adler, & W. T. Boyce, Biological sensitivity to context: The interactive effects of stress reactivity and family adversity on socioemotional behavior and school readiness, *Child Development, 81*(1), 270–289, 2010. Adapted with permission from the authors.

pathology or examining extreme psychopathology (which can affect the strength of associations or the variability in your outcomes); *the measure of reactivity*, because some indices may have greater inter-individual variability, and some indices may be quite difficult to ethically elicit reactivity in, (such as purely sympathetic preejection period response in young children) which restricts the ability to detect highly reactive children; *the type of challenge or stressor used to elicit reactivity,* since some individuals may be particularly reactive to some types and not others (for example, perhaps highly stressed in contexts of social threat but not in those evaluating math performance); *developmental timing factors*, such as ways children's age or cognitive or biological development affect the capacity for studies to detect differences in phenotypic reactivity or adjustment outcome (e.g., some measures of physiological reactivity may not be appropriate early in development as the early development and functioning of those systems is not well understood); and a host of other possibilities.

For example, the observational window may shift to the left in studies of highly disadvantaged child populations or to the right in intervention studies. The window may shift downwards and flatten in studies of children with severe behavioral problems but cover more of the y axis in community samples of typically developing children with a broad range of functioning. Similarly, the slopes of the two component lines may be determined by the researchers' ability to capture the full range of stress reactivity responses, such as by truly activating the stress response system for reactive children or adequately sampling reactive and nonreactive genotypes, and thus distinguish between high and low reactive children. Failure to consider these factors in presentation of DNS findings, or in contexts when results fail to support DNS theory is an impediment to discovery, as it can lead to erroneous conclusions. It is critical, therefore, that developmental researchers examine and compare the interactive effects of stress reactivity and context across a range of outcomes and environmental influences and that the full scope of existing theories and literature be taken into account in the interpretation of such effects.

GxE Debate

As the cost of DNA testing has plummeted, an increasing number of tests of differential susceptibility are examining genetic polymorphisms as key biological plasticity factors. It is important to note that as enthusiasm for GxE studies in psychopathology has increased over the past decade, this has not occurred without controversy. The vast majority of GxE studies to date use the candidate gene approach, which focuses on associations between allelic variation within prespecified genes of interest and phenotypes or disease states. Candidate genes are most often selected for study based on a priori knowledge of the gene's biological functional impact on the phenotype or disease state being investigated. Strengths of these study designs often include: selection of both gene and environmental variables with plausible interactive biologic pathways; selection of an environmental variable with known association with the phenotype of interest; prospective and retrospective measurement of the environmental risk factor; and accepted and validated measures of the phenotype, based on *DSM-IV* (American Psychiatric Association, 2000; now *DSM-V*) criteria. Such an approach is thought to lead to accurate determination of true GxE effects.

On the other hand, candidate gene analyses, examining either main effects or a specific polymorphism's moderation of an environmental effect as in DNS models, have received criticism of late. GxE studies are notoriously difficult to replicate, and depending upon the methodology and comprehensiveness of an approach, meta-analyses have shown mixed evidence for GxE effects for even the most-studied candidate genes in psychopathology, such as the serotonin transporter polymorphism 5-HTTLPR (e.g., Karg et al., 2011; Risch et al., 2009). Such contrasting findings have advanced a robust debate among scholars, although studies with stronger methodological rigor appear more likely to replicate the original (Caspi et al., 2003) effects on depression. Additional rigorous work has extended these findings, suggesting that 5-HTTLPR confers sensitivity in the prediction of a variety of disease-related phenotypes such as hormone and inflammatory responses, brain wave patterns, and brain imaging results (Caspi et al., 2010). Recent years have led some from the field of genetics to argue that significant GxE results are likely to be the result of artifact or chance (see Rutter, Thapar, & Pickles, 2009), and that the smaller sample sizes required for these rich biological and environmental data analyses, inconsistency in which environments are selected for models, selective presentation of results, or publication bias may be inflating the appearance of a true effect. Proponents of this position often argue that genome-wide association studies (GWAS), which scan the entire genome for common genetic variation, are superior in that they avoid some of the bias problems within candidate-gene studies. Rather than beginning with a specific hypothesis about a candidate gene and psychopathology, as GxE researchers often do, whole-genome researchers typically begin with consideration of a particular disease, then examine the genomes of hundreds or thousands of people

exhibiting that disease to determine whether they possess specific genes or gene variants absent in disease-free individuals (The Psychiatric GWAS Consortium Steering Committee, 2008). This atheoretical approach is viewed by some to be more scientific, and when no genes materialize in GWAS analyses it is asserted that no genetic association exists for that disorder. However, in the decade following the decoding of the human genome, the mass of large-scale GWAS have found many promising leads, yet no clarity about causes or cures for the most prominent, heritable psychopathologies facing our society. Although genome-wide approaches to identify loci involved in GxE interactions have recently begun to appear, they have yet to establish significant GxE interactions in common or well-documented sensitivity alleles (Aschard et al., 2012), leading to increased skepticism for the GxE framework.

A crucial problem in this debate is that GWAS research is not able to test properly for DNS for a variety of reasons:

1. It is quite common that no significant main effects are found when true interactions exist, because crossover effects are masked due to the average level of outcome resulting from some individuals with the gene having very poor outcomes and others, also with the gene, having very good outcomes (see Rutter et al., 2009 for a discussion),
2. GxE effects of interest are not typically detectable in population-based whole-genome studies because such studies rarely examine environmental factors, and when they do it is often with one item, retrospective reporting, or other limiting methodologies, and
3. Very large surveys typically conducted for GWAS generally assess a particular categorical disease outcome, rather than a full continuum of positive and negative behaviors (such as emotion regulation), which is the hallmark of DNS (see Caspi et al., 2010 for a discussion of some of these and other issues).

Even well-designed genome-wide environmental interaction (GWEI) studies face a broad range of methodological and statistical challenges (see Aschard et al., 2012, for a review) before they can begin to unravel the complexities of GxE effects in human disease and behavior. Advancement in this debate will require a variety of approaches from all sides, including increased appreciation for replication, and inclusion of rich environmental variables in genome-wide association studies. As is crucial in all scientific endeavors, multiple research strategies are needed, and it is likely that both the GWAS approach and the candidate GxE approach will be informative and ultimately result in a synergistic or complementary understanding of these phenomena.

Is Reactivity or Susceptibility Maladaptive?

The identification of factors contributing to the activation and dysregulation of physiological systems designed to maintain the allostatic balance has been thought of as essential for the design of prevention and intervention efforts (Lupien et al., 2006). Indeed, the term *dysregulation* is widespread in the stress–reactivity and regulation literature—often without reference values for normative or healthy levels, and without consideration of the adaptive function of those organismic systemic changes. This promotes confusion about the meaning of physiologic resting and reactivity levels, the sources for variability in these measures, and interpretation of variability or changes in these values. However, in recent years, scholars have begun to consider that the alterations in individual biological systems in response to environmental adversity, although sometimes seen as harmful or maladaptive, may actually be an appropriate physiologic coping response to the organism's physical or social context. Thus, rather than being interpreted as a pathogenic response to negative experience, high reactivity would index heightened biological sensitivity to the quality of the environment, a characteristic with demonstrable adaptive features in certain rearing environments. Studies in rats and monkeys, for example, have revealed that negative neurobiological effects of low quality maternal care can actually contribute to adaptive physiologic and behavioral responses under future stressful conditions (Lyons, Parker, & Schatzberg, 2010; Oomen et al., 2010). Human children exhibiting muted or augmented reactivity in adverse contexts might be responding adaptively to chronic stressors, and although such physiological system modifications may do harm in the long run (e.g., allostatic load effects on pathology), they likely allow for improved functioning over the short term. Modifications such as enhanced amygdala reactivity to neutral stimuli (Tottenham & Sheridan, 2010) may also be a favorable response for children living in a high crime neighborhood, protecting one from physical harm albeit increasing risk for affective dysregulation. As such, variation in physiological outcomes sometimes found for minorities (e.g., Bush et al., 2011), relative to majority population levels, may be legitimately adaptive to contextual demands and might also reflect unique population characteristics that have other value for those populations (Garcia-Coll, Akerman, & Cicchetti, 2000).

Particularly when considering the evolutionary perspective of differential susceptibility, which we describe in more detail below (see also Belsky & Pluess, 2013), it may not be appropriate to think in terms of positive or negative outcomes, but rather alternative strategies by which organisms attempt to enhance their capacity for survival, given the ecological conditions in which they find themselves. Such a reactivity profile may work well in some setting but not others (e.g., crime-ridden neighborhood vs. classroom) and at some points in time but not others (e.g., successful in early childhood, but problematic as a child is expected to gain independence). Readers may also be interested in a new manuscript by Ellis and Del Giudice (2014) in which they outline the similarities and differences between the adaptive calibration model (ACM) and allostatic load models and articulate the value of long-term adaptive changes in biobehavioral systems, such as high reactivity phenotypes, that might otherwise be seen as dysregulated. Increased effort to discuss susceptibility factors and phenotypes with less deterministic wording and more context- and time-specific contingencies will likely prove to advance knowledge and prediction.

Evolutionary Thinking About Variation in Sensitivity

The origins, dimensions, and consequences of individual differences in phenotype are emerging as essential components in a full understanding of the biology of experience. Biology is teeming, of course, with both between- and within-species variation that bears convincing witness to the evolutionary uses of diversity, and elegant ethological and epigenetic work, such as that by Meaney (2010), McGowan and Szyf (2010), and Suomi (2006), reveals the adaptive benefits of phenotypic diversification. For example, the maternally and epigenetically regulated differentiation of rat pups' adrenocortical responsivity produces a range of low- to high-reactivity phenotypes, each of which may maximize survival and fitness within particular early life and later life environments (Weaver et al., 2004). Similarly, neither the aggressively uninhibited nor the shy, neophobic phenotypes of young rhesus macaques can be warranted as normal or optimal; rather, each has adaptive value within specific social and physical contexts (Cirulli et al., 2009; Stevens, Leckman, Coplan, & Suomi, 2009). What is salient and important about phenotypic variants is their capacity for enhancing fitness within the diversity of species-typical environments encountered. Human variation in sensitivity to social environmental influence is but one illustrative case.

Evolutionary arguments for the importance of these sensitivity polymorphisms or phenotypes suggest that the DNS gene variants with the greatest empirical support thus far (e.g., s/s allele of SERT, the 7-repeat of DRD4, and the Met allele of BDNF) appear to have emerged (most likely through mutation) and then rapidly expanded through humankind only within the past 100 millennia, now existing in up to 1/3 of the population (most likely through natural selection). It is thought that, due to population dynamics, the adaptive edge of some variants only holds if the trait remains within a minority of the population, as they become nonadaptive when common. For example, although the high sensation seeking and risk taking found in 7R DRD4 carriers in many studies may have helped drive human expansion around the globe, these traits are expensive in evolutionary terms, increase risk for negative outcomes, and would likely lead to societal failure if all members shared this phenotype (Matthews & Butler, 2011; Wilson, 1998). Thus, populations of individuals possessing the fullest range of phenotypic variation, at both the individual and group levels, are likely to have the best odds of adapting to the constantly varying social, physical, and chemical environment of our world. However, it is also important to note that evolutionary frameworks emphasize adaptations that will improve fit in terms of survival and ability to successfully reproduce into the next generations. Other fields interested in understanding human experience and life course trajectories emphasize the impact of those adaptations on mental and physical health, which may have a different time course (e.g., occurring well beyond reproduction) or occurring and affecting well-being despite not significantly changing reproductive trajectories. Thus, although evolutionary frameworks are quite important to a deepening understanding of DNS, they are only part of the equation when considering the broad range of processes and outcomes related to DNS.

Developmental Timing and DNS

It is clear that the relevance and strength of these interactive associations depend very much upon the developmental time at which they are examined. Thus, examination of this DNS phenomena is enhanced when one considers the central role of time—evolutionary, historical, developmental, neurogenomic, and neurophysiological—in determining phenotypic variation and whether it is adaptive (Boyce, Sokolowski, & Robinson, 2012). Much of the biological sensitivity to current social contexts has resulted from response predispositions established, selectively and epigenetically, through adaptations to the temporally distant environments of early hominids (Dubos, 1965; Nesse & Young, 2000). Social disparities in health—products, in part, of the social, economic, and health policies of

contemporary societies—wax and wane within historical time according to the era's dominant sociopolitical philosophies (Beckfield & Krieger, 2009; Krieger, 2001). Developmental time is uneven in its potency, intensity of change, and accessibility to environmental influence. Thus, for example, critical or sensitive periods exist for the acquisition of language and the discrimination of speech sounds in human infants (Weikum, Oberlander, Hensch, & Werker, 2012), and exposure to music can change auditory preferences in young mice through changes in prelimbic and infralimbic medial prefrontal cortex during an early critical period (Yang, Lin, & Hensch, 2012). It also appears that early trauma and early SES have a greater effect on adult pathology than does later experience of those phenomena (see, for examples Adler, Bush, & Pantell, 2012; Heim, Plotsky, & Nemeroff, 2004; Kittleson et al., 2006), because of both the increased biological sensitivity to experience that exists early in development and because of the greater impact on trajectories of experience that early experiences can have (see Cicchetti & Toth, 2009; Gunnar & Vazquez, 2006; Meaney, 2010).

Findings from animal research reveal evidence for the importance of neurogenomic time and neurophysiologic time, in that honey bees encode spatiotemporal mappings of foraging sites through differential gene expression signatures, allowing them to remember not only geographic locations of food but the circadian patterning of food availability (Naeger et al., 2011), and even fleeting social interactions between fish can trigger changes in neural firing and secretory action (Robinson, Fernald, & Clayton, 2008). Thus, at strikingly different levels of temporal resolution, time and timing appear to play crucial but not yet fully explored roles in guiding societal, organismic, and neurobiological responses to the conditions of early life (Boyce, Sokolowski, et al., 2012).

Work within the multidisciplinary field of developmental psychopathology requires the use of multiple levels of analysis, considered simultaneously, and the outcomes under study generally result from transactional, interdependent co-determination among multiple levels of influence (Gottlieb & Halpern, 2002). Of course, human development is more than an interaction term between a biological and an environmental variable, as it is dynamic and ever-changing (we now know, for example, that epigenesis continues throughout the life course). As we have tried to illustrate throughout this chapter, biological sensitivity to context is not just a cause but is an outcome as well, shaped by previous social contextual experiences. This critical latter element is not yet fully appreciated, especially outside of the field of developmental psychopathology. The cumulative history of the person determines in part the environmental contexts he or she finds him- or herself engaging with, reacting to, eliciting, or processing. Indeed, the organism reacts differently to the same environmental circumstance uniquely at different points in development, because it carries forward its history and the biological, cognitive and behavioral shaping that resulted from that history—thus engendering a slightly (or in some cases dramatically) different response to the same circumstances.

Prenatal Exposures

The prenatal environment is a relatively underexplored context and period that increasing evidence suggests plays a major role in DNS. As described already, susceptibility or plasticity can be shaped by the environment, and an organism's first environmental exposure occurs at conception. Although *nurture* is often thought of as a postnatal experience, animal and human studies building upon Barker's prenatal programming hypothesis (Barker & Sultan, 1995; Gluckman & Hanson, 2006) demonstrate that maternal stress hormones, nutritional cues, and other biological signals cross over the placental barrier to influence offspring phenotype, with the assumption that such information transfer is designed to support the optimal adaptation to the world into which the fetus will be born (for a review see Pluess & Belsky, 2011). For example, maternal psychosocial stress and stress hormone levels during pregnancy have been shown to predict infant birth weight (Worthman & Kuzara, 2005) (which has been linked to numerous neurodevelopmental outcomes, including difficult temperament (Pluess & Belsky, 2011)), child temperament (Davis et al., 2005) and behavioral recovery to a stressor (Davis, Glynn, Waffarn, & Sandman, 2011), HPA-axis regulation (Davis et al., 2011; Owen, Andrews, & Matthews, 2005) and stress-related gene methylation (Oberlander et al., 2008). Davis and colleagues (Davis et al., 2011) provide an excellent example of these effects in their finding that exposure to higher levels of maternal plasma levels of cortisol during the second and third trimesters of pregnancy predicted larger infant cortisol responses to the painful stress of a heel-stick procedure 24 hours after birth. Additionally, elevated levels of maternal cortisol early in pregnancy as well as prenatal maternal psychosocial stress throughout gestation predicted a slower rate of behavioral recovery to the heel-stick. Importantly, these findings could not be explained by socioeconomic status, child race or sex, or medical factors such as prenatal medical history, mode of delivery, or birth order.

These prenatal programming effects appear to last across development. For example, a prospective, longitudinal study of healthy mother-child dyads found that higher maternal cortisol in early pregnancy was associated

with larger right amygdala volume in female offspring at age 7 and that this effect partially mediated the association between maternal stress during pregnancy and girls' affective problems at age 7 (Buss et al., 2012). Additionally, these prenatal programming effects appear to last across development (e.g., Entringer, Kumsta, Hellharnmer, Wadhwa, & Wust, 2009). Such programmed physiological and behavioral phenotypes then moderate environmental effects on those offspring's developmental trajectories. It is intriguing to note that a fetus' own genetic sensitivity to environmental experience may make one fetus more sensitive to the uterine environment than another, adding a layer of DNS complexity to the understanding of the programming of DNS.

Researchers have begun to hypothesize about individual difference characteristics that make some more or less susceptible to the prenatal environment. For example, in a first examination of EEG data within a DNS framework, Fortier and colleagues (Fortier et al., 2014) recently postulated that asymmetry in alpha-activation of the frontal lobe may be a marker of DNS. They highlight that frontal EEG alpha-activation asymmetry has a moderately heritable basis, is present in utero, and fairly stable across the life course. Although the increased risk for negative affectivity in those with greater activation of the right hemisphere (right frontal asymmetry; RFA) might be seen as the more sensitive phenotype, the authors posited that the variability in positive and negative outcomes across the literature for those with greater activation in the left hemisphere (left frontal asymmetry; LFA) was evidence for that phenotype being the more susceptible to context. Indeed, the authors found that LFA individuals were sensitive to prenatal environment (reflected in low vs. normal birth weight) whereas RFA individuals were not. Specifically, LFA individuals who were normal birth weight (presumably reflecting optimal intrauterine conditions for development) evidenced the best mental health outcomes a decade later, and those who were extremely low birth weight (presumably reflecting adverse intrauterine conditions) evidenced the highest attention problems and withdrawn behaviors. Prenatal conditions reflected in birth weight had no association with later life problems for RFA individuals. The patterns of interaction found in this study reflect DNS for better and for worse outcomes.

New research is also attempting to span the prenatal programming of offspring reactivity literature with the DNS hypotheses. For example, a Swiss study examined the interplay between the prenatal environment, as indicated by maternal blood plasma cortisol levels in response to the Trier Social Stress test conducted late in pregnancy, and neonates' temperamental reactivity, as assessed by behavioral coding of newborns' neurological and behavioral reactivity to stimulation 10–14 days after birth (Bolten et al., 2013). Consistent with DNS theories, newborns that were most reactive demonstrated the best emotion regulation during the stressful Still Face Paradigm, if they had gestated in mothers with lower HPA axis reactivity, but they had the lowest emotion regulation scores if they were born to mothers with high HPA axis reactivity during pregnancy. Although newborn reactivity has been linked to maternal HPA axis functioning during gestation, these results point to the possibility that variability in newborn reactivity (presumably stemming from reactivity developed during the fetal stage) may also serve as a susceptibility factor to maternal reactivity in utero (and presumably her reactivity phenotype postnatally), in the prediction of developing emotion regulation. Another research group has also explored similar associations and find that infant's carrying the sensitive polymorphism of the 5-HTTLPR gene had higher levels of emotional dysregulation in early childhood if their mothers were depressed during gestation but the lowest levels of emotional dysregulation if their mothers had lower levels of prenatal depression (Babineau et al., 2015). These interaction findings held across multiple longitudinal time points and were robust to adjustments for postnatal factors such as maternal postnatal depression, but they are still limited by the shared reporter of maternal mood and offspring emotional regulation. Although both sets of these findings require replication and careful consideration of the timing of exposures and effects, they provide fodder for discussion of the complexity of the development and manifestation of DNS and highlight the opportunities for discovery when the prenatal period is examined.

BIOLOGICAL PATHWAYS LINKING EARLY LIFE DIFFERENTIAL SUSCEPTIBILITY TO LATER PSYCHOPATHOLOGY

Throughout this chapter, we have focused on the accumulating evidence for the manner in which biological sensitivity can moderate the effects of context on developing physiology and behavior. These findings add to the growing body of literature supporting a differential susceptibility model of biology × environment interactions in developmental psychopathology. It remains to be seen whether the differential effects on behavior are mediated by individuals' neurobiological changes, given the far less empirical evidence for biological processes linking early

adversity with subsequent psychopathology (Pollak, 2005). In rat and nonhuman primate studies, adverse early life exposures, such as maternal separation or low quality maternal care, have been shown to result in subsequent HPA axis, autonomic, and immune system changes in response to stress, as well as marked behavioral changes in adulthood such as anxious behavior, anhedonia, social dysfunction, predisposition to alcohol abuse, decreased appetite and sleep disruptions (Dettmer et al., 2012; Liu et al., 1997; Plotsky & Meaney, 1993; Provencal et al., 2012; Sanchez, Ladd, & Plotsky, 2001). Although animal research lends itself to the rigorous study of causal environmental effects on biology, it has limitations in its ability to model human experiences of early life stress or developmental psychopathology. On the other hand, researchers studying children with mental health problems find it challenging to incorporate biological assessment into their studies and to follow individuals for the long periods of time required to assess these life course processes. Burghy and colleagues provide a particularly useful study that bridges several of the concepts reviewed above (Burghy et al., 2012). Their findings suggest that stress exposure during infancy increases adolescent depression and anxiety and decreases amygdala-vmPFC resting-state connectivity via cortisol elevations in childhood. In a parallel fashion, the Buss et al. work reviewed above (Buss et al., 2012) found that stress exposure during gestation, via maternal circulating cortisol levels, was associated with greater affective problems, and this association was mediated in part by amygdala volume. Both studies also reveal important gender differences for this vulnerability to dysregulated affect, as well as developmental sensitive periods for these effects. The relatively small sample sizes of youth in both studies merits caution for generalization of the findings, but the rich breadth of longitudinal data, strong theory-driven hypotheses, and sophisticated statistical modeling in those studies make them exemplars of the advances being made in this area.

A Closer Consideration of Epigenetic Pathways

The work just reviewed spans several biological systems and levels of inquiry into neurobiological susceptibility. However, given the tremendous increase in attention given to the field of epigenetics over the past decade, and the promise it holds for understanding human development and disease, we examine that literature in more detail here. In short, epigenetics (from the Greek root *epi,* meaning upon or over) has been defined as "the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered [gene] activity states" (Bird, 2007, p. 398). Epigenetic mechanisms change gene expression or activity through alterations in chromatin organization, but they do so without changing the genetic code of the DNA (Meaney, 2010). Thus, the epigenome can be viewed as a responsive overlay on the genome itself, and it possesses the potential to moderate the effects of genetic variation through up- and down-regulation of gene transcription.

Before we review evidence for such processes, it may be helpful to review some of the basic biology involved. Chromatin configuration is controlled by a physicochemical process in which chemical tags (i.e., epigenetic marks, such as methyl, acetyl, phosphate, or ubiquitin groups) are placed on or removed from the DNA or histone proteins. DNA methylation is the most highly studied and best characterized epigenetic mark. Methylation involves a direct covalent, chemical modification of a cytosine base lying sequentially adjacent to a guanine base (thus a *CpG dinucleotide*), and is catalyzed by a group of enzymes called DNA methyltransferases (DNMTs). CpG methylation can occur during any stage of the cellular life cycle and, depending upon genomic context, can impede or foster gene expression or leave it unchanged (Klengel, Pape, Binder, & Mehta, 2014).

Promoter DNA methylation (often in CpG islands, areas of the genome with comparatively high numbers of CpG dinucleotides) and gene body DNA methylation typically have contrasting associations with gene expression. High levels of promoter DNA methylation are frequently linked with diminished gene expression, but high levels of methylation in the gene body are more typically associated with increased gene expression (Jones, 1999; Kass, Landsberger, & Wolffe, 1997). DNA methylation is a relatively stable epigenetic tag, yet it has just recently become viewed as reversible and thus a potential mechanism of developmental plasticity (Wu & Zhang, 2014).

Epigenetics and the Mediation of Differential Susceptibility to Environmental Influence Interactions

All disorders of health and development can be seen as uniformly both genetic and environmental, in the sense that virtually all endpoints depend upon mutually interactive influences of both (Rothman & Greenland, 2005). The epigenetic marks and modifications controlling gene expression are gaining recognition as the molecular mechanisms underlying GxE interaction effects on developmental and mental health outcomes. Accordingly, these mechanisms constitute a tangible, physical nexus between environments and genes, between nurture and nature, between the exogenous and endogenous determinants of human development and psychological well-being.

Several recent leading edge discoveries support the perspective that *epigenetic processes* are molecular mechanisms for GxE at the population level. In a sample of 192 adults, Klengel and colleagues (Klengel et al., 2013) found that a functional polymorphism in the FK506 binding protein 5 (FKBP5) gene, an important functional, cytoplasmic regulator of the glucocorticoid receptor complex, interacted with childhood trauma exposure to predict the risk of developing stress-related psychiatric disorders in adulthood in a manner consistent with DNS. Although the interaction between FKBP5 and childhood maltreatment was known, their findings provide the first molecular evidence in humans that this type of GxE effect may be mediated via allele-specific, childhood trauma–dependent DNA demethylation in functional glucocorticoid response elements of FKBP5. Specifically, this research group found that demethylation was linked to increased stress-dependent gene transcription, followed by a long-term dysregulation of the stress hormone system and a global effect on the function of immune cells and brain areas associated with stress regulation. The authors suggest that, when occurring during developmentally sensitive periods, these epigenetic changes remain stable over time and further amplify the differential susceptibility to environment that the individual's genetic makeup originally bestowed upon it—particularly through long-term changes in the stress hormone system regulation and alterations in neuronal circuits. In turn, the early life demethylation event results in a consequent augmentation of risk for PTSD across the life course. Although gene expression is likely controlled by a variety of molecular mechanisms, only one of which is epigenetic marks, this empirically driven intersection of the fields examining genetic and epigenetic variation offers one groundbreaking account of how and under what conditions GxE interactions arise.

Work from the Holbrook lab (Teh et al., 2014) approached examination of this complex phenomena from the opposite direction. Their results demonstrate how neonatal human methylomes are affected by both unique intrauterine exposures and fixed genetic variation, resulting in GxE interactions during gestation. Specifically, within a sample of more than Singaporean newborns, the investigators found over 1,400 punctate genomic regions that were highly variable in methylation status across individuals—locations termed variably methylated regions (VMRs). Using birthweight as a proxy for environmental factors (e.g., nutrition, smoking, maternal depression, and maternal body mass index during gestation), they examined genetic and GxE origins of VMRs. Strikingly, GxE interactions were found to account for 75% of VMRs, through a combination of intrauterine environmental signatures on the fetal epigenome and the physicochemical effects of sequence variation on a CpG site's propensity for methylation. Of note, no VMRs were best accounted for by environmental linkages alone, independent of gene sequence variation. Allowing essentially the same inference as that made by Klengel and colleagues (2013), Teh et al.'s results reveal an increasingly convergent picture of how DNA sequence variation interacts with naturally occurring (and sometimes pernicious) variation in social environmental exposures at the molecular level, through chromatin modifications and other transcription regulatory processes, to produce complex developmental and health trajectories.

Kobor and colleagues provide additional recent data that sheds light on these complex epigenetic processes. Their series of studies examining allelic and epigenetic variation within human populations demonstrates that human populations possess highly divergent DNA methylation profiles and that the sources of divergences between populations involve differences in allelic frequencies and complex GxG and GxE interactions (Fraser, Lam, Neumann, & Kobor, 2012). Examining over 14,000 genes in 180 different cell lines from European and African samples, they found population-level differences in DNA methylation near transcription start sites in over a third of genes. Further analyses indicated that these methylation differences were mostly attributable to differences in allele frequencies. The Kobor lab's work augments the existing small evidence base for epigenetic dissimilarities between human populations (Krushkal, Tylavsky, & Thomas, 2011; Heyn et al., 2013; Moen et al., 2013) and points to the need for considering population heritage in epigenetic analyses but also for recognizing the manner in which population-level genetics drive variation in the epigenome.

Considered together, these three recent studies and related observations suggest that considerable developmental variation, particularly when it places individuals at risk for developmental psychopathology, may be linked to interactions between genetic and environmental differences. Moreover, they add to the emerging evidence implicating epigenetic processes as molecular-level mechanisms by which GxE interactions may occur. In light of these findings, it seems that the increasingly apparent *statistical* interactions identified between allelic variants and risk-engendering early social environments may be rooted in and attributable to differences in DNA methylation, post-translational histone modifications, or other epigenetic marks, which contribute to inter-individual

variation in the transcription of genes linked to pathological phenotypes or endophenotypes.

Variation in Epigenetic Marks as a Result of Differential Susceptibility to Context

A related, important question is whether epigenetic modifications, acquired as a consequence of early environmental signaling, might also be linked to differentially susceptible phenotypes. For example, researchers have studied large, differentially methylated regions centered upon the *NR3C1,* GR gene in the hippocampi of both rats and humans experiencing substantially different levels or forms of early parental care (Suderman et al., 2012). Suderman and colleagues found that the methylation profiles of both species were extensively different in individuals receiving high vs. low level (rats) or abusive vs. nonabusive (humans) early parental care. They also found many between-species commonalities in the specific, differentially methylated sites. Examining stressors associated with socioeconomic environment within a sample of African American youth from working poor communities, Beach and colleagues (Beach et al., 2014) found that cumulative socioeconomic adversity and the S-allele of the 5-HTTLPR, serotonin transporter gene interactively predicted promoter region methylation within a group of more than 200 genes associated with depression. Youth who were S-allele carriers demonstrated either the highest or lowest levels of depression-related gene methylation, depending upon levels of exposure to poverty-related stress. Recently, researchers have argued that the increased susceptibility of infants to infectious agents of disease may be due to differential methylation of immune-regulating and other developmentally salient genes (Strunk, Jamieson, & Burgner, 2013). Finally, the Binder laboratory work (Klengel et al., 2013) demonstrated a differential susceptibility of individuals bearing the AG/AA risk allele of the FKBP5 gene in that such individuals have either higher or lower rates of adult PTSD, conditional upon childhood exposures to sexual or physical abuse. Further, their work demonstrated that the molecular process by which this epidemiologically observed interaction occurs is mediated through DNA demethylation in the glucocorticoid response elements of FKBP5. These observations are among the first to show how chromatin modification and epigenetic marks may constitute the actual molecular mechanisms for a differential susceptibility to environmental conditions, yet much remains to be elucidated.

The proliferation of epigenetic publications and reports represents an epidemic of interest in this area, although the tremendous initial enthusiasm with which the work was greeted by the scientific community has more recently been tempered by increasing awareness of the limiting realities that commonly characterize the rapid emergence of new fields and technologies. Not only is it inappropriate to expect epigenetic processes to explain all biological phenomena, but sometimes they also fail to reliably explain phenomena within systems or questions it is most reasonable to assume they should. Yet, despite the need to face these scientific realities, the research domain holds at least implicit promise for illuminating one of the oldest and deepest mysteries of human experience (i.e., how individual susceptibility and social conditions work together)—at the behavioral, physiologic, neural, cellular and molecular levels—to initiate and sustain disorders of development, behavior, and health.

FUTURE DIRECTIONS

The body of work reviewed in this chapter is advancing at a rapid pace, and the opportunities for new research are vast and compelling. Although the developmental sequelae of early experience are well documented, current understanding of the individual-specific (moderated) manner in which those experiences get under the skin to affect psychopathology is quite limited, leaving much for the next generation to uncover.

A recent, potentially transformative shift in conceptualization of developmental psychopathology and funding for discovery may provide stimulus for this work. The National Institute of Mental Health's recent promotion of Research Domain Criteria (RDoC; Cuthbert & Insel, 2013; Insel et al., 2010) focuses on investigating the etiology and treatment of mental disorders as biological disorders that require advanced understanding of breakthroughs in genetics, physiology, and molecular, cellular and systems neuroscience. This movement away from diagnostic symptom criteria brings about additional reasons to increase attention to the range of ways variation in biology confers sensitivity to environment. As it is more likely that differential susceptibility to environments affects a broad range of physical and mental health phenotypes and outcomes (i.e., multifinality; Cicchetti & Rogosch, 1996), investigation of DNS is likely to benefit from this greater focus on intermediate phenotypes (heightened physiologic reactivity, patterns of epigenetic methylation, reactivity in regions of the brain, etc.) for a range of health outcomes, rather than predicting disease classifications.

As the fields reporting various forms of interactions between biologic predispositions and environments exponentially grow, what is now critically needed are programs of research examining the questions of how and by what mechanisms genes and early social contexts codetermine trajectories of behavioral and biological development. With respect to differences in complex behavior and its disorders, a focus on proximal, neurobiological processes must come strongly to the fore. With advances in neuroscience and human molecular genetics, next steps include identifying common variation in the genes and their expression that influence the functioning or availability of components in these stress–disease pathways. Illustrations of such approaches can be found in recent work within emerging imaging genomics (e.g., Hariri et al., 2005; Pezawas et al., 2005). A particularly groundbreaking example of progress in this realm that is specific to differential susceptibility research is the epigenetic work reported by Klengel and colleagues (Klengel et al., 2013) described earlier. Such sophisticated identification of molecular mechanisms for genotype-directed, long-term environmental reactivity is particularly informative, and further determination of how early in life such epigenetic modifications occur may elucidate the molecular origins of differential susceptibility and the deeper etiologies of developmental psychopathology.

Future work must also advance theory. For example, there is the need for research to determine whether these behavioral, physiological, and genetic markers of susceptibility to context constitute the same phenomena expressed at different levels of scale or complexity or represent different forms of susceptibility (Obradović & Boyce, 2009). To date, DNS studies typically focus on sensitivity in one level or system (albeit sometimes across various markers in that level), making it difficult to answer this question. Exceptions include work from our lab, such as that examining reactivity in both the HPA axis and within the parasympathetic nervous system to assess sensitivity to family adversity in the prediction of a variety of adjustment outcomes (Obradović et al., 2010). Although the patterns of findings in that study were cohesive across the biological systems and various outcomes, DNS interaction findings were not exactly replicated across the two biological systems. Although this might be the result of measurement or sample variability, such discrepancies suggest unique roles for sensitivity in each system, or at least unique timing for the role of sensitivity to context. In parallel, Belsky and Pluess's (2013) recent theory describing individuals as possessing plasticity phenotypes, rather than just system- or gene-specific plasticity, or acquiring cumulative plasticity, are important ideas demanding empirical testing and expansion.

A major impediment to uncovering the relations among adversity, biological sensitivities, and psychopathology is that the majority of behavioral and emotional pathologies are likely to result from constellations of aberrant biological systems, and multisystem studies and longitudinal analyses are rare. Considerable recent attention has been given to early adverse experience effects on the complex and varied neurobiology of depression (Bogdan & Hariri, 2012; Heim et al., 2004). For example, progressive effects on developing stress physiology might explain findings supporting the kindling hypothesis, in which an increase in spontaneous dysregulation or a lowering of the threshold for experiencing life stressors leads to easier triggering of depressive episodes (Monroe & Harkness, 2005). As precise, biologically plausible and multisystem models of psychopathology are developed (Pollak, 2005), our ability to seek and understand the manner in which early experience manifests as health and pathology will be greatly enhanced, as well.

To this end, some work from our laboratory and those of colleagues is beginning to indicate ways we might use simultaneous measurement of reactivity across the HPA, sympathetic and parasympathetic systems to better understand developmental psychopathology (Alkon et al., 2003; Bauer, Quas, & Boyce, 2002; Quas et al., 2014). In particular, Quas et al. found six distinctive patterns of cross-system reactivity in a multicohort sample of 664 children with anticipatory and stress reactivity measures across the parasympathetic and sympathetic nervous systems and the hypothalamic-pituitary-adrenal axis. Although the majority of children in their samples displayed moderate reactivity indicated by an average level of cross-system reactivity, five other patterns also emerged: parasympathetic-specific reactivity, anticipatory arousal, multisystem reactivity, hypothalamic-pituitary-adrenal axis specific reactivity, and underarousal. Of note, groups meaningfully differed in socioeconomic status, family adversity, and age, suggesting important roles for developmental timing and contextual exposures in the shaping of these anticipatory and reactivity profiles. Surprisingly little attention has been given to delineating precisely how these systems interact with each other when confronted with stress, and the Quas et al. findings highlight the importance of attention to this issue. The lack of attention to date may be due to the difficulty and cost associated with cross system data collection, particularly in children; however, it is likely also the result of the dearth of theory addressing this issue. For example, although much

argument has been made for the importance of multisystem models, theoretical models that argue for the existence and importance of cross-system patterns of physiological reactivity to challenge or stress have yet to elaborate on how more than two biological systems operate in conjunction with one another. For example, the influential work of Berntson, Cacioppo, and colleagues (e.g., Berntson, Cacioppo, Quigley, & Fabro, 1994) does not comment on the role of HPA axis activation in their detailed account of autonomic nervous system indices, despite the importance of the HPA axis arousal and regulation in the activation of other stress-response systems. Similarly, the work by Bauer and colleagues (Bauer et al., 2002) did not consider the regulatory function of the parasympathetic system. The Adaptive Calibration Model (ADM) described above (Del Giudice et al., 2011), makes progress in this regard in that it theorizes about varying patterns of baseline arousal and stress-induced activation of both branches of the ANS as well as the HPA axis; however data examining the 3-system patterns they propose is lacking. A primary reason for the varied findings across DNS studies (those published and those left in the file drawer) may be the lack of attention to responses across multiple systems. Increased theoretical and empirical attention to these simultaneously occurring physiological phenomena is likely to clarify DNS and will certainly advance understanding of the development of psychopathology given the importance of both main and interactive effects of physiological arousal on pathology.

Successful pursuit of advancement in the science of differential susceptibility within developmental psychopathology will surely also involve advanced methodology and more complex analyses. One example is that of Davies and Cicchetti (2014), who utilized structural equation modeling to test mediated moderation models to reveal that children's angry reactivity to maternal negativity partly accounted for the greater susceptibility of homozygous L carriers of the 5-HTTLPR polymorphism to variations in maternal responsiveness. Additional sophisticated approaches include those incorporating the perspective of complex adaptive systems (Galea, Riddle, & Kaplan, 2010). Traditional epidemiological strategies for understanding the health effects of social environmental factors involve the ascertainment of such factors' independent influences on a health end point through the use of multiple hierarchical regression models (Diez Roux, 2007). Although such an approach allows estimation of the isolated effects of single independent variables, it belies the reality that most human disorders are etiologically complex, with multiple interacting causes. Even detecting GxE interactions likely underserves the true complexity of pathogenic processes, because allelic variation in a single gene likely interacts with polymorphisms in several other genes and multiple dimensions of the environment may also interactively influence outcomes. In such circumstances—circumstances that may eventually prove to predominate in disease causation—the use of more sophisticated models and analytical tools will be required to understand the multiply interactive networks of risk factors involved in the ontogeny of disordered development and health. If so, one such approach with increasingly demonstrable efficacy is the use of complex systems analysis, involving descriptive inventories of system components, nonlinear mathematical modeling, and the construction of agent-based models of causal networks (Diez Roux, 2007; Galea, Hall, & Kaplan, 2009).

The apparent interaction between biological processes and contextual influences reviewed here points to the value of integrating biological measures into the design and evaluation of preventive interventions (Cicchetti & Gunnar, 2008). Moffitt (2013) elegantly articulated the need for and value of bringing stress–biology research and clinical intervention science together in the case of children exposed to violence, but the review and advocacy for the addition of a range of biomarkers to the study of violence-exposure interventions applies well across a variety of clinical contexts. Increasingly, the literature points to the potential for the inclusion of measures of HPA axis activation, inflammation, telomere length, gene expression, and epigenetic methylation. Given their increasing ease of collection and decreasing cost for assay, biological markers such as genotype and hair cortisol are beginning to prove useful for detecting who is most affected by interventions and whether those interventions affect biological systems related to later susceptibility. As costs go down for other neurobiological assessments, feasibility of using sophisticated biomarkers to advance our crafting and evaluation of interventions for psychopathology will improve, and the field will advance. Additionally, these endeavors, and the others described in this section should take account of the breadth of positive environments and buffering factors that operate across the life span, which will take us a step further in understanding healthy behavioral and emotional development.

Just as use of genetic information has played a major role in certain aspects of precision medicine (National Research Council, 2011), determination of sensitivity to context in conjunction with advances in technology, methodology, and biological discovery will enable a level of personalization in the prediction and treatment of psychopathology that was not previously feasible or

practical. It is likely that failure to assess for differential susceptibility in most environmental intervention trials (e.g., parenting, family, classroom, neighborhood) has led to erroneous or blunted conclusions about the efficacy of certain approaches and a misestimation of treatment effects. Although it would be ideal to provide all children with optimal or enriched environments, practicality often demands targeted interventions to those at greatest risk and those most likely to be sensitive to intervention, as well as clarity about which types of contextual interventions are most beneficial for whom, which is made more feasible as we better understand differential susceptibility. On the other hand, there are circumstances in which understanding sensitivity to environmental factors mandates a public health intervention that improves well-being for the entire population. For example, the discovery that certain individuals possess genetic variants that make them particularly susceptible to the harmful effects of lead exposure (Astrin et al., 1987) led to improved federal guidelines and regulations for lead-safe practices, thereby reducing exposure and toxicity risk for everyone. One can imagine how identifying individuals who are particularly susceptible to toxic effects of a variety of chemical and social exposures might promote public attitudes and policies that would limit risk for these individuals and their fellow community members.

CONCLUSIONS

A remarkable diversity of early, social environmental dimensions has been linked to important differences in mental and physical health, trajectories of development, and individual differences in behavior. As attention to differential susceptibility to those environmental dimensions grows, the capacity to place a finer, more exacting point on the specific kinds of environments that interact with particular variants of biological sensitivity will be important and likely illuminating. Indeed, studies examining the developmental biology of social experience show that we are on the cusp of providing deep mechanistic explications of the important, earlier insights of Waddington (1966), Gottlieb (1991) and others that organismic development is guided by the combined, interactive influences of biological predispositions and experiences.

Conducting scientific inquiry related to interactions between individually varying sensitivity variables and the range of environments we are exposed to requires consideration of a broad range of theoretical and analytic possibilities for those patterns of association. Such openness improves our ability to determine the true nature of these associations and better predict outcomes and optimal interventions. Rather than approaching these analyses with post hoc explanations for patterns of findings, researchers should endeavor to strongly consider the existing evidence base, evolutionary theories, and biological processes involved prior to developing hypotheses. However, if appropriate methods and statistics are used, post hoc analyses can disaggregate variability in responses to experiences and environments attributable to diathesis stress, differential susceptibility, vantage sensitivity, or some other form of host response singularity (e.g., Belsky, Pluess, & Widaman, 2013; Roisman et al., 2012). This approach has rarely been taken to date, but would greatly advance theories and evidence in this realm.

In conclusion, the information presented in this chapter supports several main points. First, the data support reframing the conventional focus on individual risk and resilience factors toward a conceptualization of developmental psychopathology that considers whether certain neurobiological factors confer differential susceptibility to both positive and negative environmental experiences. Second, there is a remarkable convergence among theories and supporting evidence from fields (e.g., pediatrics, developmental psychology, evolutionary anthropology, biological psychology) and scientific laboratories originally unknown to each other (e.g., the compelling work of Klengel et al. 2013, was conducted by researchers largely unfamiliar with the DNS literature) toward this same conclusion, suggesting a shared scientific value of this reframing. Additionally, beyond aiding an understanding of etiology of psychopathology, a DNS framework expands the possibilities for understanding biological and environmental factors contributing to the full range of behaviors across the life course as well as individual difference variables that predict intervention success. In reviewing this literature, we have hoped to stimulate a new generation of research illuminating the manner in which early life contexts interact with children's biological proclivities and biases to shape development and predict health and disorder. We hope that this work will support powerful insights into children's typical and atypical development, highlight clear opportunities for the prevention of psychopathology, and play a formative role in newly individualized approaches to precision medicine.

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CHAPTER 4

Understanding Developmental Psychopathology: How Useful Are Evolutionary Perspectives?

JAMES F. LECKMAN

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INTRODUCTION

What is the most fruitful perspective from which to view developmental psychopathology? At present a major vantage point of our field, as embodied in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5;* American Psychiatric Association, 2013), is largely atheoretical and descriptive. Conceptually, it reifies psychopathological states as categorical entities that are modeled after discrete medical disorders (Kendler, 2012). To some extent this has been a serviceable and generative approach, well suited to today's medical marketplace. Leaving aside the inelegant unspecified designations, *DSM-5* also has a certain bureaucratic appeal with every disorder neatly in its place. The weaknesses of *DSM-5* are also readily apparent. Many of the criteria are no more than a reflection of the conventional wisdom of a committee of experts with limited empirical justification. Being categorical in nature, it largely ignores the dimensional properties of many syndromes and their intimate relationship with environmental factors and the individual's antecedent developmental history.

Perhaps most disappointing is its failure to provide a dynamic framework that would allow for a sensible dialectic with burgeoning areas of science including evolutionary biology, molecular genomics, environment-dependent epigenetic alterations of gene expression, systems and developmental neurosciences, neuroimmunology, ethology, child development, and cognitive and social neuroscience—to name a few. Despite these shortcomings there is an increasing recognition that there is a need to look beyond the proximal mechanisms that underlie specific disorders and to consider the distal evolutionary mechanisms that give rise to psychopathology (Stein & Neese, 2011). In this chapter the primary focus is on these emerging perspectives on how evolutionary processes may support the preservation of various forms of psychopathology.

GOALS OF EVOLUTIONARY EXPLANATIONS

The principal goal of an evolutionary perspective of psychopathology is to provide a coherent framework from which to view patterns of maladaptive behavior that are

persistent in human populations (Leckman & Mayes, 1998). In such an evolutionary framework, the issue of persistence appears to be paradoxical given the editing power of natural selection. Darwin's (1859) principle of natural selection posits (1) the existence of variation among individuals, (2) differential reproductive success for those individuals who exhibit traits that are useful in the struggle for life, and (3) differential inheritance of those factors that gave rise to the favorable traits. Why then would particular variations persist that place individuals at a reproductive disadvantage in the struggle for life? We also need to consider whether various forms of psychopathology are not truly maladaptive when viewed from an evolutionary perspective. As pointed out by Belsky and Pluess (2013), some forms of behavior that are generally considered to be psychopathological and maladaptive (e.g., impulsive, risky, antisocial) can be considered adaptive within certain conditions of adversity to the degree that they enhance an individual's reproductive fitness.

Before reviewing the proposed mechanisms, this chapter's position should be made clear. A major thesis of this review is that the improbable cascade of evolutionary events that has led to the emergence of our species and our particular set of conserved behavioral and mental capacities has also left us vulnerable to certain forms of psychopathology. By conserved behavioral and mental capacities, we refer simply to adaptive capacities that have contributed to our evolutionary success as a species. On reflection, this set of capacities includes such behaviors (and associated mental states) as purposive reaching and holding, feeding, locomotion, grooming, communication (gestures, species-specific vocalizations and language), alarm systems activated by perceived threats such as separation from an attachment figure, courtship and pair bonding, reproductive and parental behaviors, the formation of social dominance hierarchies, and our capacity to be resilient and adapt and thrive in novel and challenging environments—among many others.

Another fundamental aspect of this approach is to consider the developmental course of these conserved behavioral and mental capacities over the lifetime of the individual. Consideration of continuities and discontinuities between normality and psychopathology is a hallmark of developmental psychopathology (Cicchetti, 2006; Zigler & Glick, 1986). Consequently, in our examination of specific forms of psychopathology we will consider the developmental time course for the emergence of these conserved behavioral and mental capacities.

In line with this developmental perspective, it is becoming increasingly clear that changes in the transcriptional regulation of key developmentally expressed genes are major contributors to the evolution of our human species—especially the evolution of our brain and the emergence of brain-related disorders (Vallender, Mekel-Bobrov, & Lahn, 2008; Varki, Geschwind, & Eichler, 2008). Indeed, variation in regulation of gene expression during development, rather than variation in protein sequence, is almost certainly the dominant factor in human brain evolution (King & Wilson, 1975). Such changes are thought to have led to the creation of new combinatorial expression patterns during development and ultimately to the formation of distinct neuronal circuits. In this context the field of evolutionary psychology and psychopathology needs to take into account our rapidly expanding knowledge of the human genome and the organ specific transcriptomes (Barbosa-Morais et al., 2012; ENCODE Project Consortium, 2012), and the complexity of the neurodevelopmental programs required for cellular proliferation and circuit formation within the human brain (Kang et al., 2012).

Current estimates suggest that at least 80% of the human genome is functional. Our genome contains more than 20,000 protein-coding genes, more than 18,000 RNA genes as well as protein-bound regions, regions of histone modification and DNA methylation, and chromosome interacting regions (ENCODE Project Consortium, 2012). Many of these recently discovered regulatory elements are physically associated with one another and with expressed genes. A more complete understanding of their role should provide new insights into the specific mechanisms of gene regulation associated with neural development. A significant portion of these regulatory elements are likely to be associated with environmentally sensitive alterations in region-specific gene expression mediated by epigenetic mechanisms that take place during specific periods of development (Caldji, Hellstrom, Zhang, Diorio, & Meaney, 2011; Keverne, 2011; Pujadas & Feinberg, 2012).

Another advance in understanding how species with similar repertoires of protein-coding genes differ so markedly in their biobehavioral repertoires has come from an in-depth analysis of organ transcriptomes from vertebrate species spanning ~350 million years of evolution. These events likely have further contributed to the diversification of splicing and other transcriptomic changes that underlie the emergence of our species-specific bio-behavioral repertoire. For example, significant differences in alternative splicing complexity between vertebrate lineages has been documented with the highest complexity found in primates (Barbarosa-Morais et al.,

2012). However, other investigators have found that much of our uniqueness as a species comes from variations in regulatory elements in mammalian aligned regions rather than from primate-specific regions (Ward & Kellis, 2012).

The emerging picture of the intricate and dynamic complexity of the genetic programs associated with the development of the human brain is also worthy of note. Recent analyses of exon-level transcriptome and associated genotyping data, from multiple brain regions including several neocortical areas of developing and adult postmortem human brains, have found that over 80% of the more than 17,000 mostly protein-coding genes studied were expressed, and that 90% of these genes were differentially regulated at the whole-transcript or exon level across brain regions and/or time (Kang et al., 2012). Notably, many of the spatiotemporal differences detected were differently present prior to birth and included a number of genes that were sexually dimorphic in their patterns of expression (Kang et al., 2012). This study also identified in the developing and the adult human brain core gene co-expression networks associated with cellular proliferation, synapse and dendrite formation, and myelination. Moreover, because of functional redundancy of gene families in divergent biological processes, it is clear that the genetic and evolutionary origins of developmental disorders affecting behavior and emotions may be more systemic and polygenic in nature than is generally appreciated.

Ongoing studies comparing genomes across species as well as comparing spatiotemporal differences of gene expression should provide a clearer understanding of the transcriptional foundations of human brain development and evolution of language and other uniquely human traits (Johnson et al., 2009). Future studies of human postmortem brain material that include recently discovered regulatory elements in the human genome should allow investigators to generate expression trajectories of genes commonly associated with specific mental disorders. Likewise, large-scale experimental assays in multiple individuals, cell types, and populations have the potential to identify the role of the regulatory elements that are key to both human evolution and disease.

In an effort to integrate an interdisciplinary perspective on developmental psychopathology Killeen, Tannock, and Sagvolden (2012) have suggested that we consider Aristotle's four causes to explain how things come to be (Hocutt, 1974). The *formal cause* describes the pattern or form which is necessary for us to recognize something as a particular something. At present, criteria contained in the *Diagnostic and Statistical Manual* (DSM) and *International Classification of Diseases* (ICD) identify the specific requirements needed to diagnose mental disorders. The *material cause* is equivalent to the nature of the raw materials out of which something is made. Here it will be important to consider aspects of neural and somatic development occurring within specific environmental contexts—from the intrauterine environment to the social ecology of the caregivers and of the developing child (Rutter, 2008; Werner & Smith, 2001). The *efficient cause* identifies the triggers that cause something. Here again the individual's interactions with multiple environments is key. Examples include the unfolding complex somatic and emotional environment associated with child birth leading to postpartum depression or the recreational use of certain drugs—leading to addiction. Last, but not least, is the final cause, or *telos*, which is defined as the purpose, end, aim, or goal of something, and here we return to evolutionary accounts. With this Aristotelian perspective in mind the focus of this chapter is to understand why the evolution of our species' conserved behavioral and mental capacities has also left us vulnerable to certain forms of psychopathology. Although we focus on the final cause, it will also be important to consider the other three causes as well.

EVOLUTIONARY MECHANISMS THAT MAY ACCOUNT FOR THE EMERGENCE OF PSYCHOPATHOLOGY OVER THE COURSE OF DEVELOPMENT

As reviewed elsewhere in this volume (Chapter 1), evolutionary reasoning has played an increasingly prominent role in theoretical models that have been proposed to explain individual differences in behavior that emerge over the course of development. Several of these theoretical models were initially prompted by the limitations of biopsychosocial stress-diathesis models (Ingram & Luxton, 2005). While the concepts of resilience and adaptation remain useful concepts (Panter-Brick & Leckman, 2013; Chapter 6, Volume 4), other evolutionary-based theoretical models, including differential susceptibility and biological sensitivity to context, are gaining widespread use in both theoretical formulations and empirical studies of child development (Chapters 2 and 3, this volume). Likewise, efforts to integrate evolutionary science and neuroscience are being proposed that leave aside the prevailing taxonomy of mental disorders altogether and focus instead on the therapeutic importance of attachment solutions to the existential separation challenges that are inherent in life (Fricchione, 2011).

Stress–Diathesis Models: Resilience and Allostasic Load

In the early 1970s, Garmezy and his team at the University of Minnesota were focused on the risk and protective factors associated with the development of schizophrenia (Garmezy & Streitman, 1974). In this context, the concept of resilience emerged to describe the dynamic process involving positive adaptations within the context of significant adversity (Luthar, Cicchetti, & Becker, 2000). While adaption and resilience can be readily seen from an evolutionary perspective (Lasker, 1969), the initial formulations of these constructs in the field of developmental psychology typically did not explicitly invoke evolution as being an important determinant (Rutter, 1979). By the time McEwen and his colleagues introduced the term allostasis in the 1990s to describe how organisms can adapt to environmental challenges and obtain stability through change, an evolutionary perspective was firmly in place (McEwen & Stellar, 1993).

Differential Susceptibility and Biological Sensitivity to Context

The emergence of an evolutionary perspective led Belsky and colleagues to ask uncomfortable questions. For example, why would natural selection lead to the emergence of an individual that would respond to adversity by becoming putatively disturbed and dysregulated (Belsky, Steinberg, & Draper, 1991; Daly & Wilson, 1981)? Belsky et al.'s (1991) psychosocial acceleration theory was advanced to explain why behaviors such as early pubertal development, promiscuous sexual behavior, adolescent pregnancy, and limited parental investment in multiple offspring might make biological sense as a way to prepare for and insure the passage of genes from one generation to the next despite the likelihood of growing up in the context of environmental adversity. Subsequent work by Belsky, Boyce, and Ellis has led to several theoretical concepts including differential susceptibility and biological sensitivity to context (Belsky, 1997; Boyce & Ellis 2005). This evolutionary perspective has enriched the field of child development and led to a rich and expanding body of work that seeks to integrate scientific advances from a broad range of disciplines, from genetics and epigenetics to developmental neurobiology and neuroimaging to neuroimmunology. Although a comprehensive and critical exploration of this multifaceted field is well beyond the scope of this chapter, readers are referred to other chapters in this volume as well as to recent special issues of *Development and Psychopathology* (Ellis & Boyce, 2011) and *Developmental Psychology* as well (Ellis & Bjoklund, 2012). There are also several other excellent reviews and editorials (Belsky & Pluess, 2013; Leckman, 2014; O'Conner, Moynihan, & Caserta, 2014). It is also becoming increasingly clear that early adversity can have enduring detrimental effects on physical as well as mental health over the life course (Danese et al., 2009) and that early interventions have the potential to alter this unfortunate, but evolutionarily understandable, trajectory (Campbell et al., 2014; Heckman, Moon, Pinto, Savelyev, & Yavitz, 2010).

Separation Challenges and Attachment Solutions

Fricchione (2011) provided one of the most detailed and compelling accounts of biological foundations of the evolutionary need for attachment solutions, from the earliest single cellular organisms that appear to our vertebrate and humanoid lineage leading to the emergence of our species and our incredibly complex and plastic biobehavioral systems. Fricchione's conceptual framework relies heavily on attachment theory initially advanced by Bowlby (1969, 1973, 1980). In contrast to many evolutionary accounts that focus on the processes at work that lead to psychopathology, Frichonne relied on his evolutionary perspective to provide a theoretical foundation for his compassionate clinical care across the life span including the separation challenges that occur at the end of life.

EVOLUTIONARY MECHANISMS THAT MAY ACCOUNT FOR THE PERSISTENCE OF DISCRETE FORMS OF PSYCHOPATHOLOGY

In this section five evolutionary-based mechanisms that may account for the persistence of some forms of psychopathology are presented. Table 4.1 presents a list of these mechanisms along with short descriptions and putative examples. Interested readers may also wish to consult anthologies and book-length reviews of evolutionary psychology and psychopathology (Barkow, Cosmides, & Tooby, 1995; Baron-Cohen, 1997; Brüne, 2008; Buss, 2011; Marks & Nesse, 1994; McGuire & Troisi, 1998; Tooby & Cosmides, 1990).

Failure of *Conserved Patterns of Behavior* to Develop Normally

If we depend on the normal expression of specific genes at the correct time and place in the developing brain, then we remain vulnerable to events that can disrupt the

TABLE 4.1 Proposed Evolutionary Mechanisms

Proposed evolutionary mechanism	Description	Examples
Failure of conserved neurobehavioral systems to develop normally. If we depend on the normal expression of specific genes at the correct time and place in the developing brain, then we remain vulnerable to events that can disrupt the development of these neural circuits.	Any failure of a conserved neurobehavioral system will set an individual apart. Although most of the proximal causes for such deficit states are accidental or stochastic, these events (mutations or untoward epigenetic events) occur early and constrain subsequent CNS development. Many of the mutations that have been identified involve regulatory regions of the human genome and not conserved protein-coding regions per se. These mutations often affect an entire cascade of neurobiological systems	Disorders associated with intellectual disability (e.g., fragile X, Prader-Willi syndrome, Angelman syndrome), learning disorders and communication disorders; autism spectrum disorder; and childhood-onset schizophrenia
Dysregulation of conserved neurobehavioral systems	Some conserved neurobehavioral systems are highly plastic and only appear in response to particular environment perturbations or at particular points in development. Some of these are behavioral alarm systems. Inappropriate or expressive activation in response to potential threats or failure to shut down such systems following loss may lead to psychopathology.	Mood and anxiety disorders, obsessive-compulsive disorder
Differential susceptibility	In response to chronic adversity during prior generations as well as during embryonic, fetal and postnatal life, individual differences may emerge that promote putative maladaptive behaviors (impulsivity, poor inhibitory control, and antisocial acts). However, these maladaptive behaviors may be adaptive in the context of chronic environmental adversity by enhancing an individual's reproductive fitness despite the negative effects on the mental and physical health. The precise stochastic genetic, and epigenetic mechanisms that result in these individual differences and their impact of biobehavioral plasticity over the course of development have yet to be fully determined.	Increased susceptibility to develop behaviors associated with attention-deficit/hyperactivity disorder (ADHD); conduct disorder; antisocial behavior; and substance use disorders
Environmental shifts and the value of diversity at the population level	Historical shifts in the environment away from the primeval environment of adaptation may make some individuals stand out by displaying previously adaptive behaviors that are now out of place. Alternatively, there may continue to be advantages in reproductive fitness at the group level for the presence of individuals in the group who are drawn to novel stimuli, adventurous, variable in their response to the same stimuli and willing to take risks despite the potential negative impact on their own reproductive fitness.	ADHD
Co-optation of conserved neurobiological systems	Conserved neurobehavioral systems are highly dependent on specific neurobiological substrates. Some of these pathways can be co-opted or hijacked by exogenous substances, leading to addiction, behavioral dysfunction, and impairment.	Substance use and addictive disorders
Evolutionary arms races	Some conserved biobehavioral systems may have evolved in relationship to other species (e.g., parasites, predators) that were important members of the primeval environment of adaptation.	Some forms of acute onset obsessive-compulsive disorder: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

Source: Adapted in part from J. F. Leckman & L. C. Mayes, Understanding developmental psychopathology: How useful are evolutionary perspectives? *Journal of the American Academy of Child and Adolescent Psychiatry, 37*, 1998, Table 1 (Leckman & Mayes, 1998).

development of these neural circuits which in turn can lead to the emergence of certain forms of psychopathology. In association with certain genetic mutations, characteristic phenotypes appear which reflect the loss or breakdown of *conserved patterns of behavior*. In some cases the reasons for persistence are clear; however, in many others the molecular mechanisms remain obscure. For many of these disorders there is a clear loss of reproductive fitness (Power et al., 2012). Four examples are briefly considered: fragile X syndrome, Prader-Willi and Angelman syndromes, autism spectrum disorder (ASD), and childhood-onset schizophrenia (COS).

Fragile X Syndrome

Fragile X syndrome serves as a good example of a single-gene disorder with a characteristic profile of strengths and weakness that generally follow a specific course over development (Hagerman & Hagerman, 2002; Chapter 2, Volume 3). Typically, males with fragile X syndrome have a characteristic phenotype with both physical

stigmata (long face, large ears, hyperextensible joints, and large testes) and cognitive-behavioral features (mental impairment with sequential processing deficits, dysarthric speech, motoric hyperactivity, anxiety and unstable mood, and social difficulties). Fragile X syndrome is the single most common cause for heritable intellectual disability. In addition, it is also the most widely diagnosed form of intellectual disability that leads to ASD (Hatton et al., 2006). This X-linked disorder is caused by an expansion of a trinucleotide CGG repeat (>200) on the promoter region of the *fragile X mental retardation* 1 gene (*FMR1*). As a result, the promoter region often becomes methylated which leads to a deficiency or absence of the expression of the FMR1 protein (FMRP) (McLennan, Polussa, Tassone, & Hagerman, 2011). The transcription failure is usually due to the presence of an unstable region of DNA in which a trinucleotide repeat sequence, (CGG)n, is amplified from fewer than 54 repeats in typically developing individuals to more than 200 repeats in affected males (Fu et al., 1991). Individuals in these families with more than 52 but less than 200 repeats have a premutation. Curiously, a premutation expands to a full mutation only when it is transmitted by a female so that daughters of a male with a premutation have only a premutation and remain unaffected. The genetic anticipation (progressively more individuals in a kindred are affected in successive generations) associated with this mutation accounts in large part for the persistence of this mutation in the population. Similar DNA amplification abnormalities and associated patterns of genetic anticipation within large kindreds have also been documented in several other autosomal disorders including Huntington disease (Walker, 2007). These disorders provide a clear example of how a mutation in a regulatory region can have a major impact on neural development.

Recent evidence suggests that the neuronal deficits in fragile X syndrome may occur in part due to the loss of translational constraint imposed by FMRP on transcripts for a number of synaptic proteins including neuroligin-3, neurexin-1, SHANK3, PTEN (Cowden syndrome), TSC2, and NF1 (neurofibromatosis type 1) (Darnell et al., 2011). Several of these genes including SHANK3 and NRXN1 have also been linked with ASD (State & Sestan, 2012). Also of note is that there are species-specific differences in the expression of FMR1 in the neocortex (Kwan et al., 2012) which in turn points to the potential limitations of animal model systems to explore the neuropathology of some neurodevelopmental disorders. From an evolutionary point of view this finding is consistent with the emerging knowledge that many of the genetic mutations responsible for human diseases occur in regulatory regions of the genome that are not conserved across other mammalian or primate species (Ward & Kellis, 2012).

Prader-Willi and Angelman Syndromes

Prader-Willi syndrome in conjunction with Angelman syndrome perhaps represents the best example of genomic imprinting in humans. Genomic imprinting is a phenomenon by which certain genes are expressed in a parent-of-origin-specific manner. It is independent of the classical Mendelian inheritance. Genomic imprinting is an epigenetic process that involves DNA methylation and histone modifications to achieve monoallelic expression without altering the protein-coding sequence. These epigenetic marks are established in the germline and are maintained throughout the somatic cells of an organism. Forms of genomic imprinting have been demonstrated in mammals as well as insects and flowering plants.

Prader-Willi syndrome is characterized by mild mental retardation, obesity, short stature, hypogonadism, and small hands and feet (Cassidy, Schwartz, Miller, & Discoll, 2012). Most commonly Prader-Willi syndrome is understood to involve the loss of a *paternally* imprinted stretch of five genes that encode polypeptides (MKRN3, MAGEL2, NECDIN, and SNURF-SNRPN) and a family of six paternal-only expressed small nucleolar RNA genes located on the proximal long arm of chromosome 15 (15q11.2-q13). There are three main molecular mechanisms that result in Prader-Willi syndrome: paternal deletion, maternal uniparental disomy and an imprinting defect. In 65–75% of the cases there is an interstitial microdeletion of the paternally inherited region on chromosome 15. In another 20–30% of cases, Prader-Willi is due to maternal uniparental disomy when the affected individual has two copies of chromosome 15, both of which are inherited from the mother. Maternal uniparental disomy has been shown to be associated with advanced maternal age (Gillessen-Kaesbach, Robinson, Lohmann, Kaya-Westerloh, Passargem, & Horsthemke, 1995). Finally, several forms of imprinting defects have been reported (Cassidy et al., 2012). Most of these defects arise from epigenetic causes while other individuals have a very small deletion (7.5 to >100 kb) in the promoter region of the SNRPN gene.

In contrast to Prader-Willi syndrome, Angelman syndrome is characterized by a severe intellectual impairment as well as a speech impairment characterized by the absence or the minimal use of words, epilepsy, puppet-like ataxic movements, prognathism, tongue protrusion, paroxysms of laughter, abnormal sleep patterns, and motoric

hyperactivity (Williams et al., 2006). Individuals with Angelman syndrome frequently exhibit socialization and communication deficits that meet the diagnostic criteria for ASD (Steffenburg, Gillberg, Steffenburg, & Kyllerman, 1996). Unlike Prader-Willi, Angelman's syndrome is due to the loss of expression of two *maternally* imprinted genes (*UBE3A* and *ATP10A*). These two loci are immediately adjacent to the Prader-Willi region on chromosome 15. UBE3A encodes an E3 ubiquitin ligase that is expressed biallelically in most tissues but is *maternally* expressed in almost all neurons (Mabb, Judson, Zylka, & Philpot, 2011).

One well-characterized substrate for UBE3A is the immediate early gene, Arc (activity-regulated cytoskeleton-associated protein). Arc is brain-specific and is rapidly upregulated in response to increases in neuronal activity. It is also required for learning and long-term memory (Greer et al., 2010). Angelman syndrome model mice, which carry a maternal Ube3a null mutation, recapitulate major features of Angelman syndrome in humans, including enhanced seizure susceptibility (Mabb et al., 2011). Interestingly, seizure or learning protocols induce abnormally elevated Arc expression in Ube3a knockout mice relative to wild-type controls (Greer et al., 2010), suggesting that UBE3A is required for Arc turnover in the brain during periods of increased synaptic activity. Excitatory neurotransmission onto neocortical pyramidal neurons has also been shown to be diminished (Wallace, Burette, Weinberg, & Philpot, 2012). These findings have resulted in an accelerating interest in UBE3A and its role in neural transmission. However, a number of critical gaps remain in our knowledge concerning UBE3A imprinting and its role in synaptic and circuit function.

A deeper understanding of Prader-Willi and Angelman syndromes will likely shed light on why mammalian development is characterized by the nonequivalence of parental genomes. There are a few hints from the animal literature that genomic imprinting has allowed mammalian species to alter the dosage of particular genes and sculpt their patterns of expression using non-Mendelian mechanisms. For example, results from mouse chimera studies suggest that the accumulative effects of paternally derived imprinted genes differentially influence hypothalamic and septal structures but not the cerebral cortex. Conversely, the accumulative effect of maternally derived genes is evident in the cortex, striatum, and hippocampus, but not the hypothalamus (Keverne et al., 1996). Perhaps the most compelling argument is that monoallelic expression (either maternal or paternal) provides a clear source of stability amidst the temporal and spatial complexity that characterizes the programming sequence associated with human CNS development (Keverne, 2011).

Autism Spectrum Disorder

Autistic behaviors have emerged as recognizable syndromes in the twentieth century based on the initial work of Kanner (1943), Asperger (1944), and Heller (1908). The current *DSM-5* diagnostic criteria for ASD focus on two symptom dimensions: (1) persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays; and (2) restricted, repetitive patterns of behavior, interests, or activities (American Psychiatric Association, 2013).

At first glance ASD provides a clear example of a form of developmental psychopathology that involves a failure of conserved cognitive and emotional capacities to develop normally. Specifically, individuals with ASD are profoundly impaired in understanding the motives and mental states of other individuals. This impairment in their theory of mind extends into an understanding of one's own mental states as well as the mental states of others (Baron-Cohen, Leslie, & Frith, 1985; Chapter 4, Volume 3). Yet there are perplexing issues. Why does ASD persist in the face of such a potentially negative effect on reproductive fitness? What is the evolutionary explanation for why these two dimensions (social communication and highly restrictive interests or repetitive behaviors) co-occur together? Intuitively these aspects of behavior do not seem to be closely interrelated.

Some evolutionary explanations have approached this question. Most notably Baron-Cohen (2002) focused on the preponderance of males affected with ASD and proposed the extreme male brain theory of autism. This theory is based on the perspective that females on average have a stronger drive to empathize while males on average have a stronger drive to systemize. This theory is controversial, but it has led to an expanding body of empirical data focused on sex differences in brain structure and function and the potential role of fetal testosterone in influencing aspects of early brain development (Baron-Cohen, Lombardo, Auyeung, Ashwin, Chakrabarti, & Knickmeyer, 2011).

More recently, Reser (2011) examined the hypothesis that some genes associated with ASD did in fact enhance reproductive fitness due to the adaptive benefits of being cognitively suited for solitary foraging. According to this theory, individuals with subclinical ASD included ecologically competent individuals that could have been adept at learning and implementing hunting and gathering skills on their own. During times when nutritional resources were sparse, human groups may have had to

periodically disband. In such circumstances individuals adept in solitary foraging were at an advantage. Reser also speculated that the most severe cases of ADS may be due to assortative mating.

Evolutionary explanations also need to account for why children with ASD are much more commonly affected by a broad range of neurologic (e.g., epilepsy), neuropsychiatric, gastrointestinal and endocrine disorders (Chen, Chen, Liu, Huang, & Lin, 2009; Gurney, McPheeters, & Davis, 2006). The common neuropsychiatric and psychiatric comorbidities include stereotypic movement disorder, attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), Tourette's syndrome, and mood and anxiety disorders and sleep disorders (Gurney et al., 2006; Matson & Nebel-Schwalm, 2007). Ultimately, many of these questions will be answered by our rapidly expanding knowledge of the genetic and epigenetic factors that regulate the spatiotemporal development of the human brain.

The neuropathogy associated with idiopathic ASD is variable although some structural and functional consistencies are emerging (Abrahams & Geschwind, 2008, 2010). Structurally, one well-replicated finding is that of accelerated postnatal growth in defined brain regions (Courchesne et al., 2010). There is also evidence of disrupted connectivity and laterality involving the frontal and temporal cortices, cerebellum, and amygdala (Eyler, Pierce, & Courchesne, 2012). Likewise, in response to viewing biological motion movements, children with ASD show differential patterns of activation compared with their unaffected siblings and typically developing controls (Kaiser et al., 2010). Biological motion refers to our evolutionarily conserved and robust visual sensitivity to the movements of other individuals (Blake & Shiffrar, 2007). The differential patterns of activation included prefrontal and temporal cortical regions as well as the amygdala and the fusiform gyrus (Kaiser et al., 2010). Intriguingly the unaffected siblings of the children with ASD also had unique patterns of functional activity in ventromedial prefrontal cortex and the right posterior temporal sulcus in response to biological motion. The authors speculate that since these regions have been previously implicated in aspects of social perception and social cognition (Adolphs, 1999), these regional activations may be *compensatory* in character such that these differential patterns might reflect a process through which brain function was altered over development to compensate for an increased genetic risk to develop ASD. In any case the social brain in its normal and dysfunctional states must be understood not in terms of specific structures but rather in terms of their interaction in large-scale networks (Kennedy & Adolphs, 2012)

Based on twin and family genetic studies, it is clear that ASD is highly heritable (Abrahams & Geschwind, 2008). A number of genetic mutations affecting single genetic loci have been described, including fragile X and Angelman syndromes. The number of single gene mutations associated with ASD phenotypes is increasing. One of the most well characterized disorders include Rett syndrome (Rett, 1966). Rett syndrome is one of the most common causes of ASD and intellectual disability in girls. It is characterized by early neurological regression that severely affects motor, cognitive and communication skills and is often associated with a seizure disorder. It is a monogenic X-linked dominant disorder related to mutation in MECP2, which encodes the methyl-CpG-binding protein MeCP2 (Smeets, Pelc, & Dan, 2012). Of interest MeCP2 deficiency in Rett syndrome causes epigenetic aberrations at the PWS/AS imprinting center that affects UBE3A expression (Makedonski, Abuhatzira, Kaufman, Razin, & Shemer, 2005). Among other single gene disorders, Novarino et al. (2012) recently identified inactivating mutations in the gene BCKDK (branched chain ketoacid dehydrogenase kinase) in consanguineous families with ASD, epilepsy, and intellectual disability. The encoded protein is responsible for phosphorylation-mediated inactivation of a branched-chain ketoacid dehydrogenase, causing individuals with homozygous mutations to display reductions in plasma branched-chain amino acids. Although the mechanism by which abnormal brain amino acid levels lead to autism, intellectual disability, and epilepsy is not fully understood, it likely involves the various biogenic amine pathways that underlie the dopaminergic, noradrenergic, serotonergic, and histaminergic pathways.

It is also becoming clear that in addition to single gene disorders that impact multiple neurodevelopmental pathways, rare and de novo point mutations and submicroscopic variations in chromosomal structure *contribute*, but in isolation do not cause, a considerable number of ASD cases. To date more than 100 susceptibility genes have been identified (Betancur, 2011; State & Sestan, 2012). They include synaptic adhesion molecules and postsynaptic density proteins including FMR1, SHANK3, and NRXN1 as well as chromatin modifiers (MECP2, CHD8), and DNA binding proteins (POGZ), ion channels (SCN2A), microtubule-associated proteins (KATNAL2), neurotransmitter receptors (GRIN2B), and phosphorylation-regulated tyrosine kinases (DYRK1A) (Jamain et al., 2003; Kwan et al., 2012; Neale et al., 2012;

O'Roak et al., 2011; Peça & Feng, 2012; Sanders et al., 2012; Sebat et al., 2007; Zachariah & Rastegar, 2012). In a recent exome sequencing of more than 340 children with ASD and one unaffected sibling Iossifov et al. (2012) estimated that there are at least 350 to 400 ASD susceptibility genes. In addition to rare and not so rare variants, it is also clear that common genetic variants likely account for substantial additive effects on ASD liability (Klei et al., 2012).

Returning to the question—why does ASD persist in the face of such negative effects on reproductive fitness—we can now say with certainty that the normal expression of many of these susceptibility genes at the correct time and place in the developing brain are crucial to our capacity to understand the mental states of the other. However, it is also clear that unaffected siblings who share some of these susceptibility genes also have modestly reduced fecundity as well. This is particularly true of brothers (Power et al., 2012). This raises further questions about the persistence of the disorder and perhaps the possibility that the presence of individuals with certain autistic-like traits might benefit society as a whole.

In addition, knowledge concerning the nature and timing of the relevant environmental insults that are associated with and increase the likelihood of ASD will also reveal further insights into the regulatory mechanisms that influence the emergence of our social and linguistic capacities over the course of development. For example, some of the strongest evidence indicates that advanced paternal age, especially for fathers over the age of 50 years; the immigrant status of the mother; prenatal nutrition; as well as pregnancy and birth complications, particularly gestational diabetes, can increase the risk of a child to develop ASD and related conditions including schizophrenia (Hamlyn, Duhig, McGrath, & Scott, 2013). The role of fetal levels of androgens (Lombardo et al., 2012) and events that can lead to activation of the fetal immune system early in life are also gaining increased attention (Crespi & Thiselton, 2011).

Schizophrenia, Particularly Childhood-Onset Schizophrenia

COS is variably defined by an onset of psychosis from age 12 to 18 years. Children with this condition have been identified and followed for decades (Asarnow, Tompson, & McGrath, 2004; Nicolson & Rapoport, 1999). The signs and symptoms of childhood/pediatric schizophrenia are nearly the same as adult-onset schizophrenia (Masi, Mucci, & Pari, 2006). Auditory hallucinations are the most frequent positive symptom, while visual and tactile hallucinations are rarer. The appearance of negative symptoms including emotional, cognitive, and behavioral abnormalities is often seen years before the onset of psychosis. In many instances the child has a history of delays in cognitive, language and motor development (Alaghband-Rad et al., 1995; Hollis, 1995). Indeed, cognitive abilities in the borderline to the intellectually disabled range have been reported in up to 20% of children with schizophrenia and ASD (Sporn et al., 2004).

A number of evolutionary theories have been advanced to account for the persistence of schizophrenia. For example, Brüne (2005) reviewed the available empirical evidence and concluded that, as in ASD, theory of mind is specifically impaired in schizophrenia and that many psychotic symptoms can be understood in light of a disturbed capacity in patients to recognize their own intentions, and to monitor others' intentions. Similarly, Burns (2006) advanced the hypothesis that the evolution of our social brain and other higher order cognitive abilities is also responsible for the evolution of schizophrenia. The overlap of the natural histories of COS and ASD as well as the overlap of the evolutionary theories advanced to account for the persistence of ASD and schizophrenia provides the rationale for the inclusion of COS and schizophrenia more broadly in this section of the chapter.

Structural brain imaging studies have documented an altered pace of neurodevelopmental trajectories in COS as well as in ASD. Specifically, in young adolescents with COS, there is increased velocity of gray matter thinning, which rectifies itself in parietal regions but partly persists in frontotemporal regions leading to the cortical deficit pattern similar to the one found in adult-onset schizophrenia (Gogtay, 2008; Rapoport & Gogtay, 2008). However, the trajectory of CNS development in COS differs from that seen in ASD.

Genetically, there is clear evidence that many of the same genes convey vulnerability for both ASD and schizophrenia (Talkowski et al., 2012). For example, Lin, Hrabovsky, Pedrosa, Wang, Zheng, & Lachman (2012) using transcriptome sequencing identified 801 genes in differentiating neurons that were expressed in an allele-biased manner. These genes included a number of putative schizophrenia and ASD candidate genes including several involved in synapse formation and function (NRG1, NRG3, NLGN1, NLGN4, and NRXN1). Overall, there was a modest enrichment for schizophrenia and ASD candidate genes among those that showed evidence for allele-biased expression. This again points to the possibility of parent-of-origin effects and the possible role of genomic imprinting in the transmission of schizophrenia and ASD in some families.

Knowledge concerning the nature and timing of the relevant environmental insults that are associated with the increased risk of developing schizophrenia also overlap with those implicated in ASD. There is strong evidence which indicates that advanced paternal age increases the risk for both disorders (Miller et al., 2011). Curiously this meta-analysis also documented a modestly increased risk for schizophrenia among the offspring of younger fathers (<25 years), but this increased risk was only seen among the male offspring. The immigrant status of the family as well as pregnancy and birth complications can increase the risk of a child to develop schizophrenia (Hamlyn, Duhig, McGrath, & Scott, 2013). Events that can lead to activation of the fetal immune system early in life are also gaining increased attention in schizophrenia research (Brown, 2011; Hsiao & Patterson, 2012).

Dysregulation of Conserved Behavioral Systems and Associated Mental States

Apart from developmental failure or distortion, another plausible mechanism that could account for the preservation of specific maladaptive phenotypes is the dysregulation of conserved behavioral patterns and associated mental states. Briefly, if normal behavioral patterns are initiated at an inappropriate time, are of too high an intensity, or are not turned off in a timely fashion, this could lead to a consistent phenotype of maladaptive behavior. A large number of psychiatric disorders have been suggested to be the result of such a mechanism. The list includes separation anxiety disorder (Bowlby, 1973), phobias (Marks, 1987; Mineka & Ohman, 2002), generalized anxiety disorder (Woody & Rachrnan, 1994), panic disorder (Klein, 1993; Nesse, 1989; Stein & Bouwer, 1997), OCD (Evans and Leckman, 2006), and major depression (Nesse & Williams, 1994). In many instances, these speculations rest on the plausible existence of innate alarm systems that are selectively activated when the brain detects danger in the environment (Marks & Nesse, 1994; Nesse, 1999). Here we consider mood and anxiety disorders as a general class. We then consider OCD as a specific example.

Mood and Anxiety Disorders

In *The Expression of Emotions in Man and Animals,* Darwin (1872) argued that anxiety and fear are evolved, adaptive responses evident in our mammalian ancestors. A strong case has been made that our ability to experience and outwardly manifest distress, fear, anxiety, and sadness provided selective advantages to our ancestors by altering aspects of appearance (including facial expressions and bodily cues), physiology, cognition, behavior and motivation. Key components of this conserved system appear very early in infant development and are distinctive elements of their behavioral repertoire (Gullone, 2000). Individual differences in the expression of distress, fear, anxiety, and sadness are closely linked to separation or the fear of separation from primary caregivers. For example, most infants experience a period of stranger anxiety around 8 to 12 months of age, marked by wariness or distress around new people (Waters, Matas, & Sroufe, 1975). Stranger anxiety is often followed by separation anxiety, which is usually evident by 10 to 18 months of age and is characterized by distress about being separated from the primary caregiver (Thompson & Limber, 1992). Here it is impossible to miss the fundamental importance of the infant's dyadic interactions with caregivers. Indeed, Bowlby's work from the 1950s on individual differences in human attachment behavior eventually led to a deep appreciation of the importance of evolutionary thinking about human development and the value of studying these phenomena across species (Bowlby, 1969, 1973, 1980; Hinde, 1987; Tinbergen, 2010).

Most anxiety disorders begin early in development, with a median age at onset of 12 years (Kessler, Avenevoli, Costello, et al., 2012; Merikangas et al., 2010). Almost one in three children suffers from an anxiety disorder at some point during childhood or adolescence (Merikangas et al., 2010). Mood disorders also affect a high percentage of adolescents and they are often preceded by an anxiety disorder (Merikangas et al., 2010; Silk, Davis, McMakin, Dahl, & Forbes, 2012). Epidemiological studies from across the globe also indicate that symptoms of anxiety and depression are not an all or none phenomenon; they have a dimensional character (Achenbach, Rescorla, & Ivanova, 2012). Indeed, a recent factor analytic study of the data from a population-based sample of adolescents found that mood and anxiety disorders are divided into two classes: (1) a *fear* class, including specific phobia, social phobia, panic disorder, and agoraphobia; and (2) a *distress* class, including separation anxiety disorder, posttraumatic stress disorder, generalized anxiety disorder, and major depression (Kessler, Avenevoli, McLaughlin, et al., 2012). High rates of comorbidity were seen within each of these two classes of disorders.

Viewed from an adult perspective a number of evolutionary hypotheses concerning mood and anxiety disorders have been advanced (Akiskal & McKinney, 1975; Andrews & Thompson, 2009; Forbes & Dahl, 2012; Hartley and Phelps, 2012; Nesse, 2009; Nettle, 2004; Price, Sloman, Gardner, Gilbert, & Rohde, 1994; Stein & Nesse, 2011;

Thornhill & Thornhill, 1989). Our capacity to detect and respond to potential threats and losses, customized to different developmental stages and differing social contexts are key elements of many of these hypotheses. Somatic symptoms of fever, pain, and coughing are presented as being analogous to the "psychic" pain and distress associated with depression and anxiety. In this model the psychic distress informs the sufferer that something needs to change in their interpersonal world and perhaps be avoided in the future. Nesse (2000) detailed the adaptive value of these symptoms in communicating to members of one's social group a need for help, a willingness to accept a lower social rank, as well as an increasing self-awareness that it may be useful to disengage from commitments to unreachable goals. In such situations, a depressed mood, pessimism, and lack of motivation may provide a fitness advantage by inhibiting otherwise futile or dangerous behavior. Similarly, Andrews and Thompson (2009) proposed the analytical rumination (AR) hypothesis that depression and related forms of mental distress are adaptive in that they provide a mechanism for the individual to engage in sustained analysis (rumination) of complex problems until a viable solution is reached. It is also worth noting that there is a fair amount of empirical evidence indicating an increased degree of assortative mating among individuals with mood disorders (bipolar disorder > major depression) which likely contributes to the persistence of some of these traits in the population (Mathews & Reus, 2001).

Most of these evolutionary hypotheses are not mutually exclusive. They also posit (or at least imply) that the neural mechanisms underlying these capacities can become dysregulated, leading to severe, chronic disabling and, at times, life-threatening symptoms and behaviors. The question then becomes how best to set the threshold for disorder and are there times when a "disorder" level impairment is normative and adaptive at a given developmental stage. While evolutionary theories may be useful in conceptualizing symptoms and disorders, population-based studies across age and gender groups and within diverse cultural and ethnic groups is a much more pragmatic and clinically useful approach.

Given their universality, it is likely that fundamental aspects of human neural development are closely interrelated with these unpleasant emotions. The available neurobiological studies of rodents, primates and humans have identified key components of the emotional regulation and fear circuitry that include the amygdala and regions of the prefrontal cortex (Blackford & Pine, 2012; Canteras, Mota-Ortiz, & Motta, 2012; Kupfer, Frank, & Phillips, 2012). Studies of depressed youth also have implicated these same brain regions as well as areas of the brain involved in reward processing, particularly in a social context (Silk et al., 2012).

Consistent with an evolutionary perspective, family, twin and adoption studies support an important role for genetic factors in the etiology of mood and anxiety symptoms and disorders (Hettema, Neale, & Kendler, 2001; Kendler, Gatz, Gardner, & Pedersen, 2006; Pawlby, Hay, Sharp, Waters, & O'Keane, 2009; Sullivan, Neale, & Kendler, 2000). These studies also consistently suggest that many of the genetic risk factors for mood and anxiety disorders are shared in common across these disorders (Kendler, Aggen, Knudsen, Roysamb, Neale, & Reichborn-Kjennerud, 2011; Kendler, Prescott, Myers, & Neale, 2003). However, efforts to identify specific genetic variants associated with an increased susceptibility to mood and anxiety disorders using large N genome-wide association studies (GWAS) have not been successful to date (Shyn et al., 2011). Despite this failure, it will be important to continue efforts to identify these susceptibility genes. Power et al. (2012) documented that siblings of patients with depression have significantly increased fecundity which more than compensated for the lower fecundity of affected individuals. This suggests that some of these susceptibility genes can increase an individual's reproductive fitness.

Efforts to identify gene by environment effects (GxE) with regard to mood and anxiety disorders have also been of great interest since the initial report by Caspi et al. (2003). They noted that a functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene (SLC6A4) moderated the influence of stressful life events on depression. In the initial report, individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele. These findings have not been universally replicated, but the preponderance of the data from quantitative population genetics, neurobiological studies, and experimental studies in animals confirms the plausibility of their initial findings although the overall effect size may be modest (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010).

Two approaches of considerable promise for future research are the emerging data from population-based samples of twins and efforts to begin to understand the role of epigenetic modifications that occur as a result of environmental adversities. First, the most convincing data concerning GxE effects have come from recent efforts

to examine the impact of environmental experiences on symptoms of anxiety and depression across the life span using longitudinal data from eight American and European population-based twin registries (Kendler et al., 2011). By modeling data from monozygotic (MZ) twin pairs of widely varying ages this group of investigators were able to reject the hypothesis that genetic influences alone can account for the relative stability of anxiety and depression across the life span. Based on their analyses of the individual trajectories, they determined that levels of symptoms increasingly diverged between the MZ twins from childhood to late adulthood based on their environmental experiences. Only in late adulthood (~70 years of age) did this divergence disappear.

Efforts to delineate the multiple and diverse epigenetic and neurobiological mechanisms by which environmental experiences shape the character and continuity of mood and anxiety disorders is also an important area for future study. It is increasingly evident that environmental experiences can lead to epigenetically mediated alterations in gene expression that likely influence an individual's vulnerability to depression and anxiety (Monk, Spicer, & Champagne, 2012). To date the strongest data from human and animal models concerns the epigenetic consequences of early adversity. For example, analysis of cord blood samples from infants born to depressed mothers indicated elevated levels of DNA methylation within the gene (NR3C1) that codes for the glucocorticoid receptor (Oberlander, Weinberg, Papsdorf, Grunau, Misri, & Devlin, 2008). At 3 months of age, these investigators assessed the infants' stress responsivity by examining their salivary cortisol levels. Levels of NR3C1 methylation in fetal cord blood were found to predict infant cortisol response to stress, suggesting a functional consequence of this epigenetic variation. Similar epigenetic changes have also been reported for the gene encoding the serotonin transporter (SLC6A4) (Devlin, Brain, Austin, & Oberlander, 2010). Although the meaning of these epigenetic changes in blood is unclear with regard to brain function, as epigenetic alterations can be tissue specific and even specific to particular brain regions (Provençal et al., 2012), animal models have convincingly demonstrated that exposure to prenatal stress can induce similar epigenetic changes in the most relevant brain regions as well as increased depressive-like behavior in adult animals (Mueller & Bale, 2008). Viewed from an evolutionary perspective these data suggest that we and our mammalian ancestors have evolved molecular mechanisms that permit some degree of programming so that the offspring may be better prepared for the environmental context in which their rearing will take place.

Obsessive-Compulsive Disorder

Dysregulation of otherwise adaptive behavioral patterns linked to specific environmental perturbations may also be readily evident in other forms of psychopathology. Although speculative, this list includes OCD. OCD has a lifetime prevalence of 2–3%, affecting all age groups across the globe (Ruscio, Stein Chiu, & Kessler, 2010). OCD is considered to be the fourth most common mental disorder and is frequently accompanied by family, social, school, and work dysfunctions (Ayuso-Mateos, 2006). Obsessive-compulsive (OC) symptoms, like symptoms of anxiety and depression are dimensional in character and evolutionary accounts for each of the symptom dimensions have been proposed (Evans & Leckman, 2006; Mataix-Cols, Rosario-Campos, & Leckman, 2005).

Obsessions are ego-dystonic, repetitive, and intrusive thoughts or images that are not simply excessive worries about real-life problems (American Psychiatric Association, 2013; Leckman et al., 2010). Classic examples include intrusive worries about cleanliness or about harm coming to close family members. Compulsions are repetitive behaviors (e.g., hand washing, checking, ordering) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession. These rituals usually need to be performed according to certain rules. Often there is a heightened sensitivity in the home environment to things not being "just right" in the way they feel, look, or sound (Leckman, Walker, Goodman, Pauls, & Cohen, 1994). This awareness that something is not just right is commonly associated with a sense of dread that something terrible is about to happen. Other OC symptom dimensions include preoccupations about symmetry and exactness and compulsions of ordering and arranging, doing and redoing, and counting (Leckman et al., 1997). Here again we may see the presence of an ancient alarm system that may have served well our hunter–gatherer ancestors as they struggled to survive in the face of predators and unsanitary conditions (Brüne, 2008; Feygin, Swain, & Leckman, 2006; Marks & Nesse, 1994).

Beginning in the second year of life, most normally developing children display a variety of intrusive thoughts, habits, and routines, some of which closely resemble the behaviors associated with OCD (Evans, Gray, & Leckman, 1999; Evans et al., 1997; Gesell, 1928; Leonard, Goldberger, Rapoport, Cheslow, & Swedo, 1990; Zohar & Felz, 2001). For example, in one large population-based study ($n \sim 1{,}500$), we found that parents reported that over half of the 2-year-olds were very aware of minute details, such as imperfections in toys and clothes (Evans et al., 1997).

Likewise, parents of 2-year-olds were also almost twice as likely to report that their child is very concerned with dirt, cleanliness, or neatness than were parents of 5-year-olds, and almost 7 times more likely than parents of children less than age 1. Finally, 63% of 2-year-olds were reported to arrange objects until they are just right compared with 4% of children less than 1 year of age and 41% of 5-year-olds.

For children less than 4 years of age, repetitive behaviors were positively related to the child's level of fearfulness in general as well as their fear of strangers (Evans et al., 1999). Interestingly, bedtime fears (fear of the dark, of monsters) were related to hoarding objects; fear of death was significantly associated with strong attachment to a specific object. For children older than age 4 years, a greater number of correlations emerged. Most notably, overall scores on the rituals inventory were related to bedtime fears. Just right behaviors were related to fears of contamination and fear of separation; and fear of death was positively related to repeats actions over and over, and arranges objects until they are just right (Evans et al., 1999).

As noted by Evans and Leckman (2006), these findings echo many of the theories of Erikson (1968), Werner (1957), and Winnicott (1958a) that children's rituals are associated with anxiety states brought on by the many fears and uncertainties that are common in childhood and that they bear some relationship to the presence or absence of attachment figures as a source of security and syncretic wholeness. These findings also emphasize the normal capacity that young children have to compare elements of the outside world with their existing mental representation to ensure that important aspects of their world are just right (Gesell, 1928; Piaget, 1962). This in turn recalls *les sentiments d'incompletude* (feelings of incompleteness) that Janet (1903) identified as the core problem for individuals with OCD at the end of the nineteenth century.

The initiation of parenting is another developmental stage that is normally characterized by intense harm-avoidant preoccupations and a heightened sense of responsibility accompanied by compulsive attention to issues of safety and cleanliness characterized by anxious intrusive thoughts and harm avoidant behaviors (Kim, Mayes, Feldman, Leckman, & Swain, 2013; Leckman, Mayes, Feldman, Evans, King, & Cohen, 1999; Winnicott, 1958a). The normally occurring emergence of these symptoms may well account for the increased risk of onset or exacerbation of OCD seen late in pregnancy and during the early postpartum period (Abramowitz et al., 2010; McGuinness, Blissett, & Jones, 2011). Viewed in the context of the historically high rates of infant mortality (Bideau, Desjardins, & Brignoli 1997) these observations are consistent with the hypothesis that the dysregulation of conserved behavioral patterns and associated mental states can contribute to the emergence of particular psychopathological outcomes.

Like the other anxiety disorders, OCD has been conceptualized as an imbalance between subcortical and cortical circuits. A relatively large and growing number of neuroimaging studies have examined both functional and structural correlates of OCD in both children and adults (Blackford & Pine, 2012). Functional imaging studies have consistently reported hyperactivity in the orbitofrontal cortex, anterior cingulate cortex, and caudate nucleus of individuals with OCD. Although these findings and the results of structural studies are not sufficient to establish causality, a relatively compelling case can be made that an imbalance in the cortico-basal ganglia-thalamo-cortical loops that specifically involve the orbitofrontal and the anterior cingulate cortices play a causal role in this disorder (Maia, Cooney, & Peterson, 2008).

Consistent with an evolutionary perspective, family, twin, and adoption studies have demonstrated that both genetic biological and environmental factors are important in the etiology of OCD (Pauls, 2010). Family-genetic studies published since the 1930s indicate that among first-degree relatives of OCD-affected children and adults there is a four- to tenfold OCD risk increase, respectively, as compared with relatives of controls. A review of twin studies concluded that obsessive-compulsive (OC) symptoms are heritable, with greater genetic influences in child-onset (45–65%), than in adult-onset OCD cases (27–47%) (Pauls, 2010). However, efforts to identify specific genetic variants associated with an increased susceptibility to OCD using large N GWAS have not been successful to date (Stewart et al., 2013).

In conclusion, the available data support the plausibility of the hypothesis that many OC symptoms appear normally during the course of development and confer some degree of reproductive fitness. It is only when there is some dysregulation of evolutionarily conserved neurobiological pathways that extreme variants appear and a diagnosis of OCD is warranted. While future genetic research, e.g., next-generation sequencing strategies, the study of rare variants), longitudinal epidemiological studies, particularly population-based twin studies (Kendler et al., 2011), and the development of valid animal models (Chen et al., 2010; Yaddanapudi et al., 2010) will continue to elucidate the relevant etiological pathways, it is difficult to imagine how specific evolutionary hypotheses concerning OCD can

be formally tested. Consequently, these hypotheses are best viewed as strategically important in the conceptualization of the study of psychopathology and the integration of data from across multiple disciplines.

Ancient Versus Current Environments and the Value of Diversity Within Populations

Another evolutionary explanation focuses on the changing nature of our environments. This viewpoint posits that much of our human behavioral equipment can be best understood in relationship to our primeval environment where we evolved as a species. As Bowlby (1969) pointed out, the property of being adapted entails a reference both to a specified outcome and to a specified environment. Thus as modern societies shift away from their agrarian pasts, certain behavioral traits might become less adaptive. That said, things never stay the same and the multiple environments in which we dwell are constantly changing. Global warming and climate change are emerging as a major challenge to our species while the near universality of virtual worlds via social media and the internet are now part of everyday life even for preschool children. Indeed, our capacity as a species to explore and adapt to novel environments is one of our most distinguishing traits—compared with other species (Morán, 2008). Work in this area also highlights another aspect of evolutionary theory—namely, in the struggle for life it is the reproductive fitness within societal groups that is selected for rather than any particular individual. With this perspective in mind, let us consider ADHD.

Attention-Deficit\|Hyperactivity Disorder

According to the *DSM-5*, ADHD is defined by a constellation of clinical features, including hyperactivity, inattention, and impulsivity (American Psychiatric Association, 2013). Children with ADHD are more likely to exhibit school behavior problems, academic underachievement, poor self-esteem, parent–child conflicts, and difficulties with peer acceptance (Abikoff, Gittelman-Klein, & Klein, 1977; Barkley, 1997; Erhardt & Hinshaw, 1994; Chapter 14, Volume 3). ADHD is a chronic disorder—as children age, become teenagers, and enter adulthood, they are more likely to engage in antisocial behaviors including substance abuse and criminal acts, as well as the persistence of attentional, familial, interpersonal, and occupational difficulties throughout their life span (Cherkasova, Sulla, Dalena, Pondé, & Hechtman, 2013; Klein & Mannuzza, 1991). These symptoms, and the compromised function they entail, should constitute strong evolutionary pressures that perhaps should have eliminated ADHD from the population within a few score generations. Yet ADHD is one of the most common psychiatric disorders in children and adolescents, with a worldwide prevalence above 5% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007).

So why does ADHD persist in the face of such a potentially negative effect on reproductive fitness? Several evolutionary explanations have approached this question. For example, some have argued that in some instances the symptoms of ADHD are best viewed from the perspective of our ancestral environments that were unsafe, impoverished, and time critical. In such an environment there would be advantages to maintaining a response-ready versus a problem-solving attitude (Jensen et al., 1997; Urcelay & Dalley, 2012). Being distractible is perhaps better attuned to survival when every change in the environment could mean a threat or an opportunity. Acting on impulse may have left few opportunities for questioning later, but it has undeniable survival value in dangerous environments. Other potential advantages for ADHD-like symptoms include: alertness to novel stimuli; willingness to depart from local environments predisposed to high levels of prenatal and perinatal stressors, and potential positive founder effects upon discovery of novel, resource-rich environments.

Among the many attempts to explain the persistence of ADHD, Killeen, Tannock, and Sagvolden (2012) provided the most current and comprehensive review as they consider the four causes of ADHD and point to the vast interdisciplinary literature from brain structure, electrophysiology, and neuropsychology to the role of neurotransmitters and genes. Specifically, interconnections between attention-regulating subsystems in temporal, parietal, and prefrontal cortices are likely involved in many cases of ADHD (Arnsten, Berridge, & McCracken, 2009). The prefrontal cortices, in particular, play a top-down inhibitory function by regulating emotions and behaviors, sustaining attention, and by screening out distracting stimuli. In this context, it appears that cortical development lags in children with ADHD compared with their peers (Shaw et al., 2007).

Family, twin, and adoption studies also indicate that ADHD is highly heritable with heritability estimates consistently around 0.8 (Faraone & Mick, 2010). A large number of candidate genes have been and continue to be evaluated. Historically, much of the focus has been on genes involved in the synthesis and processing of biogenic amines. However, large scale GWAS have yet to identify convincingly any common genetic variants associated with increased susceptibility to ADHD (Neale et al.,

2010). It appears likely that the genetic vulnerability to ADHD is mediated by multiple generalist genes each of small effect. In considering GxE, it is clear that perinatal risk factors such as birth trauma, anoxia, and prematurity can contribute to the risk of a child developing ADHD (Barry & Gill, 2007). It will also be important to examine how adverse environments characterized by low parental responsivity, high and critical expressed emotion, under stimulation, harsh or coercive disciplinary techniques, conflictual parental relationships, and low socio-economic status, can shift early brain development and neural systems more toward ADHD-like outcomes. Moving forward, the possibility that these risk factors operate through epigenetic mechanisms is an important set of molecular mechanisms to consider (Mill & Petronis, 2008). It is also worth noting that some individuals with ADHD are more likely to engage in risky sexual behaviors that may lead to their having more children with multiple partners (Flory, Molina, Pelham, Gnagy, & Smith, 2006; Hosain, Berenson, Tennen, Bauer, & Wu, 2012). These empirical observations are also consistent with the growing literature of differential susceptibility. As noted earlier in this chapter, in some adverse environments impulsivity, risk taking, and frank antisocial behavior may be adaptive to the degree that they enhance an individual's reproductive fitness (Belsky & Pluess, 2013).

The findings of an innovative computational modeling study undertaken by Williams and Taylor (2006) are also consistent with differential susceptibility. Briefly, they attempted to simulate the potential evolutionary benefits for groups when they have in their midst a minority of individuals who were highly variable, i.e., unpredictable, in their risk-taking approaches to secure food resources within changing environments. They initially constructed five groups of ten individuals. Nine of the individuals were programmed to be very predictable. Information about the availability of local foods was shared within each of the groups. Ninety per cent of the matings were programmed to occur outside the individual's original group. In the simulation each of the offspring who had one of the five brittleness genes were randomly selected from the two parents, and in 10% of matings one of the five genes randomly mutated. Whenever the overall population exceeded 200, a group was randomly selected for elimination. Individuals started reproducing at age 10, and life span was limited to 50 years. When groups exceeded 20 individuals, they split into two groups. They then simulated the ability of two interventions to alter the reproductive fitness of the groups. These were the rate of environmental change and the relationship between an individual's predictability and rate of reproduction. They found that increased environmental variability produced a small, but definite and reversible reduction in population predictability. Given the parameters used in their simulations, they concluded that there is a class of tasks (group exploration tasks) in which unpredictable behavior by a minority of individuals optimizes results for the group. Characteristics of these tasks were risk taking, because its cost is borne mainly by the individual, and information sharing, because its benefits increase with group size. More importantly they found that a reproductive bias favoring the unpredictable individuals helped populations cope with rapid environmental change, without imposing major cost during periods of stability. In contrast, when they programmed in a reproductive bias favoring predictable individuals, they observed an opposite effect on reproductive fitness. Despite the obvious limitations of reducing ADHD to a single behavioral characteristic—unpredictability—the use of computational modeling may prove useful in evaluating other evolutionary hypotheses for ADHD and other forms of developmental psychopathology. This perspective is also consistent with the widely held view that the factors that shape human development do so in a probabilistic rather than a deterministic fashion (Belsky & Pluess, 2013).

Co-optation of Neurobiological Systems Associated With Establishing Salience and Reward

Perhaps the most compelling evolutionary explanation to be considered in this chapter relates to substance abuse and addictive disorders. Here it comes down to how our brains are built. If we rely on specific genetic pathways, neurotransmitters, and circuits to establish what is salient and rewarding in our world, then exogenous agents that affect these neurobiological systems may well have effects that are sufficiently maladaptive to be labeled a form of psychopathology.

Substance Use Disorders and Addictive Disorders

Drug abuse and addictive disorders including pathological gambling exact an enormous emotional, medical, and financial toll on societies across the globe in the form of the loss of an individual's potential to contribute to society, loss of employment, crime, and family disintegration, in addition to medical complications in the case of an overdose (Anthony, Warner, & Kessler, 1994; Le Moal, 2010; Chapter 18 and 19 Volume 3). Considered together, alcohol, tobacco, and illicit drug use are implicated in

over 12% of mortality worldwide. Their use constitutes the leading cause of preventable death (World Health Organization, 2009a, 2009b).

Addiction is a chronic, relapsing disorder that has been characterized by the impulsive and compulsive need to seek and consume the drug (craving); an inability to control intake leading to intoxication; and the emergence of a distressed emotional state, e.g., dysphoria, irritability, during periods of withdrawal when access to the drug is prevented (Koob & Volkow, 2010). Animal and human studies have identified widely distributed neural circuits that mediate each of the three stages of the addiction cycle. Remarkably, virtually all substance use disorders engage many of the same neural circuits. As reviewed by Koob and Volkow (2010), key elements of the reward and salience mesolimbic dopamine pathways are structures that once activated can lead to a cascade of neuroadaptations in the ventral striatum (i.e., a brain region that includes the nucleus accumbens core and shell and some nuclei of the olfactory tubercle) that receives projections from the ventral tegmental area and prefrontal cortex. Once addiction has been established, multiple interconnected brain regions are involved in craving including the orbitofrontal and other regions of the prefrontal cortices, as well as the insula, basolateral amygdala, and hippocampus.

Although many individuals are exposed to nicotine, alcohol, and drugs of abuse, only a subset becomes addicted. Although the genetic contribution to risk for addiction is approximately 50%, the specific genetic variants have yet to be identified (Goldman, Oroszi, & Ducci, 2005; Kendler, Myers, & Prescott, 2007). One probable explanation for this failure is that the relevant sequences do not lie within the protein coding regions of these genes but rather in the recently discovered regulatory elements which are physically associated with one another and with expressed genes. Since an individual's susceptibility to drug use and addiction is strongly influenced by the psychological and social context in which drug exposure occurs, and since these genomic regulatory elements can be modified by environmental exposures, it is not surprising that the search for key transcription factors, as well as efforts to identify the molecular events that can regulate transcription through modifications of DNA and chromatin structure in specific brain areas have become a major focus for research (Robison & Nestler, 2011; Wood & Lipovich, 2012). For example, Robison and Nestler (2011) recently reviewed some of the multiple mechanisms by which drugs of abuse can alter the expression of key transcription factors, i.e., proteins that, in response to cell signaling pathways, bind to specific sequences of DNA to increase or repress the expression of downstream genes. Their review focuses on four specific transcription factors: ΔFOSB, cyclic AMP-responsive element binding protein (CREB), nuclear factor-κB (NF-κB), and multiple myocyte-specific enhancer factor 2 (MEF2) and their roles in addiction. They also usefully reviewed the current state of knowledge concerning various epigenetic mechanisms including histone tail modifications which alter the accessibility of genes within their native chromatin structure to the molecules needed for transcription, DNA methylation which can have enduring effects on gene expression as well as non-coding microRNAs. MicroRNAs are found in all mammalian cells and serve as post-translational regulators that bind to complementary sequences on target mRNAs to repress translation, thus silencing gene expression. Like histone modifications and DNA methylation, expression of microRNAs can alter gene transcription in the absence of any change to the DNA coding sequence. It is reasonable to anticipate that as future insights on transcriptional and epigenetic mechanisms of addiction accumulate, a more complete understanding of how addictive substances modify specific neural circuits will emerge. Hopefully this in turn will contribute to the identification of new targets for the treatment of addictive disorders.

In sum, addiction and substance use disorders provide a compelling example of how our evolutionary history has left us vulnerable to certain forms of psychopathology (Nesse & Berridge, 1997). Specifically, the conserved neural circuitry involved in reward processing and salience determination in vertebrate species can be co-opted or hijacked by exogenous substances, leading to addiction and associated behavioral dysfunction and impairment.

An Evolutionary Arms Race: Infections and Autoimmunity

At first glance, the mention of infectious processes in a listing of evolutionary mechanisms might seem odd. However, our long-standing evolutionary relationship with bacterial and viral pathogens and the endless arms race between our species (theirs and ours) has probably done much to shape aspects of our genome and so our vulnerability to disease (Chapman & Hill, 2012; Dawkins, 1987; Dawkins & Krebs, 1979). In psychiatry these effects include post-infectious autoimmune disorders that have neuropsychiatric sequelae such as Sydenham's chorea (Husby, van de Rijn, Zabriskie, Abdin, & Williams, 1976; Kiessling, Marcotte, & Culpepper, 1993; Swedo et al., 1989).

PANDAS

Swedo and coworkers (1998) described a group of children with PANDAS characterized by the sudden overnight onset of OCD as well as at least two other neuropsychiatric symptoms (i.e., anxiety, emotional lability, irritability, aggression or oppositional behavior, behavioral regression, deterioration in school performance, sensory or motor abnormalities including motor or vocal tics, and somatic signs and symptoms like sleep difficulties, enuresis, and urinary frequency) in children who had been previously developing normally. Currently, the predominating theory to explain the pathophysiology behind PANDAS is molecular mimicry whereby antibodies formed to target Group A beta-hemolytic streptococci (GABHS) also targets proteins in the cells of the basal ganglia.

However, since the introduction of PANDAS as a clinical entity, it has been a source of a fair amount of controversy, partly stemming from how the original PANDAS criteria have been interpreted by subsequent teams of investigators (Singer, Gilbert, Wolf, Mink, & Kurlan, 2012; Swedo, Leckman, Rose, 2012). Despite this controversy cogent models of disease pathogenesis have been put forward in which the neurotransmitter dopamine is influencing the functional status of the immune system (Besser, Ganor, & Levite, 2005; Kipnis et al. 2004; Sarkar, Basu, Chakroborty, Dasgupta, & Basu, 2010) and that antibodies directed against GABHS can increase the amount of dopamine released and affect the functional status of dopamine receptors (Kirvan, Swedo, Heuser, & Cunningham, 2003; Kirvan, Swedo, Kurahara, & Cunningham, 2006; Murphy, Kurlan, & Leckman, 2010).

Additional clinical, translational, and basic science investigations are needed. Strikingly, animal models are again providing a proof of concept for PANDAS as a clinical entity (Birmberg et al., 2012; Yaddanapudi et al., 2010). For example, GABHS infections can trigger the production of cross-reactive antibodies that not only lead to some of the same neurologic and behavioral symptoms in the originally infected mice, but also evoke symptoms when they are passively transferred from donor to wild-type mice. Expanding these investigations to evaluate the effects of a variety of infectious agents and other immune stimulants would be useful, particularly if the animal models can be used to evaluate potential therapeutic interventions.

From an evolutionary perspective since humans are the only known natural host for GABHS, the persistence of Sydenham's chorea and PANDAS in our species is attributable to our continued vulnerability, as a species, to this pathogen that has made its permanent home in our bodies.

Other Evolutionary-Based Explanations

Several other evolutionary-based accounts of psychiatric disorders have been proposed. They include the limited power of natural selection to eliminate mutations, particularly recessive mutations, if their adverse effects on reproductive success are modest. This may be particularly germane for mild or late-onset disorders. For example, in Huntington's disease the initial symptoms do not appear until after many of the affected individuals have had offspring.

In contrast, inbreeding and consanguineous marriages which are commonplace in many cultures do have the potential to disrupt neurodevelopmental pathways and cause early onset neuropsychiatric disorders. A recent example, cited above, concerns inactivating mutations in the gene BCKDK in consanguineous families with ASD, epilepsy, and intellectual disability (Novarino et al., 2012). The heterozygote carriers of this mutation develop normally and their reproductive fitness is not otherwise affected. However, individuals can develop this syndrome when the mutation is transmitted within extended families so some descendants are homozygous for the same mutated recessive gene.

CONCLUSIONS AND CRITIQUE

The study of evolutionary principles suggests that many of the mental and neurodevelopmental disorders encountered by professionals working with infants, children, and adolescents (e.g., clinical psychologists, pediatricians, primary care clinicians, child and adolescent psychiatrists, social workers, teachers) are likely to persist despite their being associated with a reduction in reproductive fitness. In many instances their ultimate causes are built into the genetic and neurobiological mechanisms that underlie highly conserved features of our basic behavioral and cognitive repertoires. While we usually confine our discussion of these conserved features to humanoid, primate, or mammalian lineages, the fossil record is clear that some of the most defining events in our neurobiological history date back more than 500 million years with the emergence of our first chordate ancestors. Examination of the cranial endocasts of our earliest vertebrate ancestors indicate that by 480 million years ago they already had the major divisions of the central nervous system (CNS): telencephalon, diencephalon, mesencephalon, metencephalon, myelencephalon, and spinal cord as well as olfactory capsules, orbital cavities, a hypophysis, labyrinths, and the exit

foramina for the 10 cranial nerves (Miklos, 1993; Karen, 1970). Remarkably, our CNS is simply a variant on the same theme.

A second point focuses on the intrinsic population-based nature of evolution. Variation within populations is an essential ingredient for natural selection (Pujadas & Feinberg, 2012). This is true at each level of understanding from linear arrays of genes in genomes, to populations of molecules within cells, to collections of neurons, to organized behavioral repertoires, and even to collections of people in social communities. Several corollaries to this point are also apparent. First, at each level it appears that any single function can usually be carried out by more than one configuration of units or individuals. For example, many genes are pleiotropic with many functions. These functions can overlap with one another so that the loss of one gene can be made up by another (Finch & Rose, 1995). Similar arguments are possible at each of the other levels as well. Second, there is the potential for pleiotropy at more proximate levels. For example, central oxytocin pathways appear to play an important role in the initiation of a wide range of complex behaviors from pair bonding and sexual activity to uterine contractions during delivery and milk release during nursing. In the body, oxytocin is synthesized in the heart, thymus, gastrointestinal tract, as well as reproductive organs. The distribution of the oxytocin receptors in both the brain and periphery is even more far-reaching and its expression is subject to changes over the course of development. Oxytocin receptor expression is also sensitive to changes in the external environment and the internal somatic world. The net result is a vast, complex, and developmentally sensitive bio-behavioral system (Gordon, Martin, Feldman, & Leckman, 2011). Other elements include sensory inputs, the salience, reward, and threat detection pathways, the hypothalamic-pituitary-gonadal axis, and the hypothalamic-pituitary-adrenal stress response axis.

A third inescapable lesson from the study of evolutionary mechanisms is the importance of the environment (ancestral, intrauterine, and the infant's early nurturing environment) in shaping our genome and its capacity to be programmed to maximize adaptation and diversity. For each proposed mechanism some aspect of the environment, past or present, is playing or has played a crucial role. Perceived threats to survival, emotional attachments to others, the availability of drugs of abuse, the existence of reservoirs of beta-hemolytic streptococci, are just a few examples.

A fourth point concerns the self-organizing character of these bio-behavioral systems—namely, that they have the capacity to modify and reorganize in response to new environmental perturbations and to settle into one or a few modes of organization (Thelen & Smith, 1995). Behaviorally this is seen throughout the animal kingdom as we tend to settle into familiar habits. Indeed, one way of conceptualizing some forms of psychopathology is to consider them to be a reflection of individuals getting stuck in a restricted set of otherwise normal behaviors. Examples include the washing and cleaning rituals of some forms of OCD or the motor stereotypes seen in individuals with ASD. The basis for this fractal property of evolution (the ability of populations to self-organize regardless of the temporal or spatial scaling) remains speculative, but it would seem to be a requirement for evolution to have occurred in the first place.

A fifth conclusion concerns the incomplete nature of evolutionary explanations. They may provide a plausible explanation of why certain vulnerabilities persist within human populations, but they do not account for why a particular individual is affected. Here the study of individual differences and of particular developmental histories is required. Special attention should be directed at events occurring early as they can constrain the later development of the CNS (Edelman & Tonini, 1995). Models of pathogenesis of early-onset disorders must embrace both developmental and evolutionary perspectives.

Finally, we must acknowledge that although some of these evolutionary accounts have a certain degree of face validity (co-optation of conserved neurobiological systems, evolutionary arms races) many of the evolutionary accounts discussed above are speculative and largely untestable. Given the historical nature of the proposed accounts, the fragmentary fossil record, and the limits of paleobiology to document brain evolution, we must admit that the actual course of these events remains inexplicable. While computational models may be useful in establishing the plausibility of some of these mechanisms, many of these accounts may be justly characterized as just so stories that provide explanations that cannot be disproved. We must be content then with (1) their heuristic value to raise questions concerning data already available to us, (2) their ability to provide a framework for the integration of new knowledge from a broad range of scientific disciplines, and (3) their value to clinicians.

Future Prospects

The conceptual framework underlying emerging models of brain evolution and development provides a powerful framework for understanding aspects of disease

pathogenesis in developmental psychopathology. This framework is consistent with the pioneering efforts of investigators such as Baldwin (1902), Bowlby (1969, 1973), Darwin (1872), Ekman (1982), and Waddington (1977) among others who have applied evolutionary and developmental principles to the study of normal variation or psychopathology. Although progress has been slow, due in part to the scope and complexity of the emerging scientific knowledge base, incremental progress can be anticipated that should enrich and refine our emerging models of disease pathogenesis. Future progress is likely to follow in the wake of powerful and promising technologies in genomics, epigenomics, neurodevelopment, neuroimmunology, longitudinal neuroimaging, computational modeling, and information processing, as well as taking greater advantage of population-based registries.

Despite the relative failure of most GWAS it is clear that many rare genetic variants acting alone or together can be lethal for the normal emergence of species-typical behavioral patterns (as may occur in some forms of ASD). Despite many disappointments, it is reasonable to expect the eventual identification of multiple alleles of major and minor effect that act in concert (co-action) that contribute to a number of heritable disorders including some forms of intellectual disability, dyslexia, ASD, schizophrenia, Tourette's syndrome, and antisocial behavior (Bentley et al., 2013).

Future translational work with animal models should focus on the role that genes and/or environmental factors play in the development of circuits that regulate specific physiological and behavioral outcomes. This emphasis on circuit formation, as a fundamental unit for understanding behavior, is distinct from current approaches of modeling psychiatric illnesses in animals (Kaffman & Krystal, 2012). The work over the past several decades of Capecchi and his team at the University of Utah on the role of homeobox genes on development provides a clear illustration of this point. Homeobox genes are a class of regulatory genes that act primarily as transcription factors in the promoter regions of the genome. They are also known as master control genes because of the key role they play in the control of embryonic development along the longitudinal axis of the developing embryo from head to toe in all multicellular animals from fruit flies to humans. Capecchi and his team have for some time been pursuing the systematic analysis of the mouse homeobox genes by monitoring the animals' somatic and behavioral phenotypes after a specific homeobox gene was knocked out. In 2002, Capecchi and his team knocked out the Hoxb8 gene. Remarkably, although this gene is anatomically expressed no higher than the lumbar region of the developing embryonic spinal cord, all of the Hoxb8 (–/–) mice displayed excessive grooming behaviors leading to hair removal and skin lesions (Greer & Capecchi, 2002). Why did this behavioral phenotype emerge? Eight years later, they provided the answer. The Hoxb8 cell lineage is associated with the bone marrow-derived microglia that migrates into the brain during embryonic development from the yolk sac (Chen et al., 2010). The conclusion is clear: a behavioral disorder, with some resemblance to trichotillomania, is associated with mutant microglia in the brain. The role of microglia in normal brain development and circuit formation has also become increasingly clear given their active surveillance of synaptic activity and their capacity to prune presynaptic inputs based on their level of neural activity (Schafer et al., 2012).

This brings us to another conclusion, namely, that we still have a great deal to learn about the role of the immune system and its role interconnecting the brain and body as well as its interface with other bio-behavioral systems. Based upon our limited knowledge, one can safely predict that additional stories will emerge that will strengthen the link between psychoneuroimmunology and stress response, maternal bonding, and sexual behaviors, as well as salience and reward pathways. Recently, data also suggest that the immune system will play a role in modulating feeding behavior and energy homeostasis, and perhaps even in the multi-directional microbiome-gut-brain network (Poutahidis et al., 2013). All of which point to the importance of the central role the immune system plays at the dynamic interface of physical and mental health (see Leckman, 2014).

Although animal model systems may permit the testing of the effectiveness of novel pharmaceutical agents as well as a deeper understanding of how the expression of these particular alleles constrains the developing nervous system (Andersen & Navalta, 2011), species differences and ethical constraints place a natural limit on the testability of evolutionary and developmental explanations of human psychopathology. The recent finding for the various ENCODE studies concerning the many differences in noncoding regulatory regions of the human genome compared with other species reinforce the view that animal models will always be incomplete.

Our ability to genotype accurately individual patients with regard to known vulnerability alleles as well as regulatory regions of the human genome may lead to more accurate clinical predictions of course, outcome, and treatment response. Similarly, the results of neuropsychological, neuroimaging, and other biological studies may become more interpretable by classifying patients according to their respective genotypes (Bansal et al., 2012).

For developmental neurobiologists the ongoing studies comparing genomes across species as well as comparing spatiotemporal differences of gene expression should provide a clearer understanding of the transcriptional foundations of human brain development (Johnson et al., 2009; Ward & Kellis, 2012). Future studies of human postmortem brain material that include recently discovered regulatory elements in the human genome should also allow investigators to generate expression trajectories of the interactive genes present in large-scale networks.

Future progress may also depend on the refinement of psychopathological phenotypes and endophenotypes. Psychopathological states vary in their complexity and are often best seen as multidimensional composites. The Research Domain Criteria project launched by NIMH in 2009 seeks to implement this strategy by defining basic dimensions of functioning (such as the fear circuits or working memory) to be studied across multiple units of analysis, from genes to neural circuits to behaviors, cutting across disorders as traditionally defined (Cuthbert & Insel, 2010).

Finally, there is the need to continue to examine the factors and mechanisms that promote and weaken resilience particularly among individuals experiencing significant adversity (Cicchetti & Toth, 2009). Resilience is an evolutionarily conserved trait that supports reproductive fitness. Consequently gaining a deeper understanding of the factors that contribute to resilience is an important area of continuing research in the area of developmental psychopathology. Given the multi-finality in developmental processes and the diversity of ways in which individuals respond to and interact with vulnerability and protective factors at each ecological level, continuing longitudinal efforts are needed to understand the complex matrix of the individual's biological and psychological organization and its response to adversity over the course of development (Cicchetti, 2013). Thus far, it is clear that an individual's resilience resides in a broad range of genomic, epigenomic, neural, neuroendocrine, and behavioral mechanisms, but more work is needed (Grigorenko & Cicchetti, 2012; Karatoreos & McEwen, 2013; Chapter 8, this volume). From an evolutionary perspective, although certain genetic variants may confer an increased vulnerability in the face of adversity, such as maltreatment, it is equally probable that other variants at the same locus may serve a protective function against environmental insults (Belsky, Jonassaint, Pluess, Stanton, Brummett, & Williams, 2009; Cicchetti & Blender, 2006). There is also evidence, in the case of maltreated children, while some genetic variants had a negligible effect for the maltreated group in predicting resilience, the same genotype contributed to higher resilient functioning in non-maltreated children (Cicchetti & Rogosch, 2012).

Clinical Implications

The present conceptualization of neurodevelopment and the factors that selectively influence its course has important implications for the prevention, treatment, and care of individuals with various forms of developmental psychopathology. The identification of risk factors, both environmental and genetic, is likely to lead to screening procedures and preventive interventions such as public health programs aimed at reducing lead exposure in children. This conceptualization emphasizes the environment as a crucial factor in designing treatment interventions. Identifying features in the home and educational environments that will allow children to build on their strengths and improve their adaptive capacities should continue to be a major priority for research (Leckman, 2013). Advances in our understanding of those components of the environment that are most crucial for resilience and sustaining successful adaptations will doubtless refine interventions designed to prevent and treat various forms of psychopathology (Panter-Brick & Leckman, 2013; Rutter, 2013).

Finally, aspects of this approach may permit a deeper empathetic understanding of individuals with early onset disorders. For example, if some forms of OCD bear some relationship to the mental states associated with highly conserved behavioral repertoires typically encountered in expectant parents (intrusive worries about some misfortune befalling the fetus or infant), it should be easier for clinicians to have a deeper emotional empathy for the anguish a patient is experiencing if they can relate the patient's symptoms to emotional experiences in their own lives as parents and members of extended families (Kim et al., 2013; Leckman & Mayes, 1998; Leckman et al., 1999).

Although these models can appear to be reductionistic approaches that neglect the inner worlds of children, some of the emerging models of mental development (Edelman & Tononi, 1995; Fricchione, 2011) are fully compatible with the rich, dynamic complexity of intrapsychic states that we encounter in ourselves, in the consulting room, in our families, and throughout our social ecological systems.

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CHAPTER 5

Animal Models of Developmental Psychopathology

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INTRODUCTION

Early life adversity is a well-documented risk factor for developmental psychopathology. While there is no substitute for directly studying human populations with early experience-related high risk for developmental psychopathology (e.g., maltreated children, children adopted from orphanages; Ehlert, 2013; Neigh, Gillespie, & Nemeroff, 2009; Teicher, Tomoda, & Andersen, 2006), animal studies offer a unique opportunity to understand the basic neurobiological and developmental underpinnings of these disorders at a level not possible in humans (Kaufman, Plotsky, Nemeroff, & Charney, 2000). This includes understanding the underlying cellular and molecular mechanisms involved and critical sensitive periods. A better understanding of the neurobiological mechanisms underlying increased risk for developmental psychopathology has led not only to more targeted research and clinical questions in human studies, but also to the inception of effective interventions and preventative therapies. If we can determine what is changing, when, and how, and the specific subsequent alterations in behavior, we would be able to design treatments aimed at specific processes and developmental time points. An important, but often overlooked, step in this process is to have a strong understanding of the normative patterns of neurobehavioral development not only in children, but also in the animal models being used (Machado & Bachevalier, 2003), which requires models and experiences with ecological validity. Understanding each species' typical experiences and developmental trajectories provides the critical context in which to place outcomes associated with disruptions of neurobehavioral systems early in life, such as those that occur in response to early life adversity. Thus, the goal of this chapter is not only to describe animal models of developmental psychopathology, but to also present what is known about species-typical development of biological systems thought to play an especially strong role in developmental psychopathology and how these developmental processes compare to those in humans.

Clinical studies have identified a series of irregularities in structure and function of specific neural circuits

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related to developmental psychopathology (De Bellis, 2005; De Bellis, Baum, et al., 1999; De Bellis, Keshavan, et al., 1999; Drevets, Gadde, & Krishnan 2011; Teicher, Andersen, Polcari, Anderson, Navalta, & Kim, 2003; Tottenham & Sheridan, 2009), and thus the focus of much animal research has targeted how these regions mature. They include the prefrontal cortex (PFC), particularly the ventromedial PFC (vmPFC: medial and orbital areas), and subcortical limbic structures that communicate with it, including the amygdala and hippocampus (Bale et al., 2010; Pryce et al., 2005; Sanchez, Ladd, & Plotsky, 2001; Veenema, 2009). These corticolimbic circuits play very important roles in emotion regulation and control of the stress response, including the activity of the neuroendocrine hypothalamic-pituitary-adrenal (HPA) axis (Herman, Ostrander, Mueller, & Figueiredo, 2005; Herman et al., 2003; Ulrich-Lai & Herman, 2009). Exposure to elevated levels of circulating stress hormones due to repeated activations of the HPA axis is thought to be one of the primary biological mediators of the increased risk for developmental psychopathology associated with early life adversity (Doom & Gunnar, 2013). Our knowledge of the developing HPA axis is still growing, but thanks in great part to animal models we are beginning to understand how perturbations of this system contribute to increased risk for developmental psychopathology. Other mechanisms involved, including inflammation, changes in gut microbiota and epigenetics will also be reviewed in this chapter, but we will focus on the HPA axis in the next section.

HPA Axis: Development and Regulation in Humans and Animal Models

It is important to have an understanding of normative developmental patterns in both humans and animal models to be able to accurately translate research between species. Thus, we begin this section with a brief description of normative development of the HPA axis in humans and some commonly used animal models. Typically developing human newborns are able to activate the HPA axis in response to stressors, but do not exhibit a mature circadian cortisol rhythm. However, they do show two peaks of cortisol about 12 hours apart that are independent of the time of day (Gunnar, 1992). Some studies have reported an adult-like circadian cortisol rhythm emerging as early as 2 weeks of age while others were unable detect a mature rhythm until 3 months of age (Price, Close, & Fielding, 1983; Santiago, Jorge, & Moreira, 1996). At about 3 months of age, there is also a decrease in the cortisol response to physical examinations, an effect that continues throughout the first year of life (Gunnar, 1992) and is paralleled by decreases in basal cortisol (Tollenaar, Jansen, Beijers, Riksen-Walraven, & de Weerth, 2010). This period of apparent stress insensitivity is thought to mirror the stress hyporesponsive period (SHRP) described in rodents and may be dependent on the quality of the caregiving provided (Gunnar & Quevedo, 2007).

In rodents, the SHRP is characterized by a quiescent HPA axis, evidenced by both an inability to mount a cortisol response to stressors that are effective in activating the axis at other ages, and by failure to suppress circulating cortisol levels in response to challenge with the synthetic glucocorticoid (GC) dexamethasone, suggesting insensitivity to the inhibitory effects of high levels of GCs observed in adults (Sapolsky & Meaney, 1986; Vazquez, 1998). Given the broad effects of GCs on homeostasis and gene expression, the purpose of this hyporesponsive period is thought to be to maintain the low level of GCs necessary for normative brain growth and development (Sapolsky & Meaney, 1986). There is strong evidence that maternal presence plays a major role maintaining these low GC levels during the SHRP and that the mother regulates the development of the pup HPA axis and fear systems, as well as their transition out of the SHRP. During the first couple weeks of life rat pups will not mount a corticosterone response to a stressor in the presence of the dam, but when removed from her they are able to show stress-induced elevations in corticosterone (Moriceau & Sullivan, 2006; Stanton, Gutierrez, & Levine, 1988; Stanton, Wallstrom, & Levine, 1987). More recent research into this phenomenon has shown that a sensitive period for attachment learning in rodents coincides with the low corticosterone levels associated with the SHRP, at the same time that fear learning is turned off (Sullivan & Holman, 2010). Interestingly, the transition from this early sensitive period when attachment (approach) learning is turned on but fear (avoidance) learning is turned off to the next developmental period when the pup starts exploring and fear is turned on seems mediated by the presence of higher levels of corticosterone acting on the amygdala, as shown by elegant manipulations of the corticosterone system during this time by Sullivan and colleagues (Moriceau, Roth, Okotoghaide, & Sullivan, 2004; Moriceau & Sullivan, 2004; Sullivan & Holman, 2010). Thus, in the early period, when maternal presence is paired with an aversive stimulus (i.e., foot shock) attachment and proximity seeking behavior (i.e., odor preference) is induced in pups due to the suppression of corticosterone release and subsequent suppression of amygdala activation by the dam, while in her absence elevated corticosterone activates the amygdala resulting in fear and avoidance behavior (Moriceau & Sullivan, 2006). Similarly, in nonhuman primates and humans there is also evidence that the period of relative stress hyporesponsivity described earlier is dependent on the quality of parental care, and may extend through childhood (Gunnar & Fisher, 2006;

McCormack, Newman, Higley, Maestripieri, & Sanchez, 2009), which is consistent with the hypothesis that GC levels need to be tightly regulated during brain development to support typical maturational processes. This is also supported by alterations in the stress response and brains of humans exposed to early life stress (Gunnar & Quevedo, 2008; Loman & Gunnar, 2010; Tarullo & Gunnar, 2006).

The role of salient social interactions, such as caregiving in infancy and peer relationships during adolescence, in regulating a developing human's response to stressors has been demonstrated in many studies. In infants, sensitive and responsive parenting is able to decrease levels of cortisol elicited in response to a mild stressor (Albers, Riksen-Walraven, Sweep, & de Weerth, 2008). The developmental trajectory of this ability of caregiving to buffer the stress response is exemplified by a child's response to inoculations over the first year and a half of life. In the presence of a parent 2, 4, and 6 month old infants show increases in cortisol; however, as early as 12 months old and to at least 18 months, this increase is no longer detectable when the parent is present (Jansen, Beijers, Riksen-Walraven, & de Weerth, 2010). The neurobiological mechanisms that underlie this ability have yet to be completely elucidated, but emerging evidence suggests some likely candidates (Hostinar, Sullivan, & Gunnar, 2014). The hormone oxytocin, induced by caregivers and with some anxiolytic and antistress properties (Cardoso, Ellenbogen, Orlando, Bacon, & Joober, 2013), is one possible route. Another may be through recruitment of brain regions linked to safety signal learning, including the vmPFC, as suggested by a recent report where viewing of one's mother's face resulted in changes in functional connectivity between the amygdala and the vmPFC that was accompanied by an increased ability to regulate affect in children, but that did not work in adolescence (Gee et al., 2014). Exactly how these safety learning mechanisms change over time is unknown, although recent evidence suggests that the caregiver's ability to modulate offspring's stress response may decrease in adolescence (Hostinar, Johnson, & Gunnar, 2014). Other changes in stress physiology taking place during adolescence include an increase in basal HPA activity, with increased stress reactivity also being reported in some studies (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009). Sex differences in HPA axis function are not apparent in childhood but begin to be reliably measured around adolescence, with girls having higher cortisol levels than boys (Gunnar et al., 2009; Reynolds et al., 2013).

The development of the HPA axis in nonhuman primates follows a similar pattern as that described for humans, making them ideal model organisms when attempting to model complex sequelae related to stress physiology. The presence of a basal HPA diurnal rhythm has been reported in infant rhesus monkeys, but it still appears to be immature at 5 months of age (which is the equivalent to 18–24 months in humans), with high cortisol levels early in the morning but only a slight decline from morning to afternoon, followed by a steep decline from afternoon to bedtime—around sunset for animals housed outdoors (Raper, Bachevalier, Wallen, & Sanchez, 2013). By the juvenile stage (starting around 12 months, equivalent to 4 years in humans) cortisol sharply declines between morning and afternoon, and between afternoon and night, demonstrating an adult-like diurnal pattern of cortisol secretion (Barrett, Noble, Hanson, Pine, Winslow, & Nelson, 2009; Raper et al., 2014; Sanchez et al., 2005). Although there is no solid evidence of a true SHRP in rhesus monkeys, socially familiar cues, specifically the presence of a nurturing mother, do buffer the HPA axis stress responses in infant macaques (McCormack, Newman, Higley, Maestripieri, & Sanchez, 2009; Sanchez, 2006). Thus, as described for humans, nonhuman primate mothers also function as external regulators of infant HPA axis activity, serving as strong social buffers that prevent stress-induced activations to potential threats. In contrast, highly rejecting, abusive, and low protecting rhesus mothers fail to buffer their infants' HPA axis stress responses (McCormack, Newman, Higley, Maestripieri, & Sanchez, 2009). This highlights the importance of early social experiences, in particular the role of nurturing caregiving, on the development of the HPA axis across different mammalian species, as well as the utility of animal models to study the role of adverse caregiving on the etiology of early life stress-induced developmental psychopathology.

The mammalian HPA axis is regulated by different neural pathways that transmit specific information about exteroceptive (psychological, environmental) and interoceptive threats (hemorrhage, infection, pain) to the hypothalamic paraventricular nucleus (PVN) (Herman et al., 2003; Herman et al., 2005; Ulrich-Lai & Herman, 2009). Psychological/emotional stressors are processed by brain regions that include corticolimbic structures such as the vmPFC, amygdala, and hippocampus, which convey information about threatening stimuli to the PVN via indirect projections, and undergo massive prenatal and postnatal developmental changes in mammals, making them particularly vulnerable to adverse early social experiences (Andersen, 2003). These brain regions, as well as their connectivity, have a protracted development. Recent research has focused on the development of vmPFC-amygdala circuits and its relevance for the development of the HPA axis and emotional regulation. One successful approach to disentangle the complex interplay of interconnected structures that develop together within

a brain circuit is to lesion one of the regions and observe what happens to the other parts of the circuit during development using animal models. For example, although in adult nonhuman primates the amygdala plays a stimulatory role on the HPA axis, so that lesions of the amygdala result in blunted HPA axis reactivity (Kalin, Shelton, & Davidson, 2004; Machado & Bachevalier, 2008), without effects on basal HPA axis activity (Kalin et al., 2004; Machado & Bachevalier, 2008; Norman & Spies, 1981; Sapolsky, Zola-Morgan, & Squire, 1991), recent studies by our group showed that when the amygdala is lesioned during the neonatal period (around 2 weeks of age) alterations in both HPA axis reactivity and basal function result, with lesions being associated with heightened—instead of blunted-basal and stress-induced HPA axis reactivity during infancy and the juvenile period (Raper, Bachevalier, et al., 2013; Raper, Wallen, Sanchez, et al., 2013; Raper, Wilson, Sanchez, Machado, & Bachevalier, 2013; Raper et al., 2014). These findings suggest that the amygdala may have a paradoxical inhibitory influence on HPA axis activity in primates during development, switching later on to have a stimulatory role on cortisol release. Both adult and neonatal lesions of these limbic circuits result in similar alterations in emotional reactivity though (Kalin et al., 2004; Machado & Bachevalier, 2008; Machado, Emery, Capitanio, Mason, Mendoza, & Amaral, 2008; Machado, Kazama, & Bachevalier, 2009; Raper, Wallen, et al., 2013; Raper, Wilson, et al., 2013), which combined with the differential effects of lesion timing on the HPA axis highlights the need for further carefully thought out experiments to pinpoint the underlying neural mechanisms.

The previous findings in nonhuman primates support emerging evidence of developmental switches in the role the amygdala plays in the regulation of stress and fear responses in humans, where amygdala functional coupling with PFC seems to switch from positive (i.e., when the amygdala is active so is the PFC) during early childhood to a more adult-like negative coupling during the adolescent transition (Gee, Humphreys, et al., 2013). This developmental switch from positive to negative coupling between PFC and amygdala could have a potentially important functional role, as it has been associated with stronger emotional regulation (Gee, Gabard-Durnam, et al., 2013). The findings from our studies using neonatal amygdala lesions in infant rhesus monkeys are consistent with this evidence, supporting an intriguing role of developmental switches in the amygdala's role in emotional and stress regulation.

Altogether, this evidence highlights the need to challenge the assumption that developing systems will be affected in the same ways as their mature counterparts. Thus, while the study of developmental psychopathology in humans is somewhat limited to observing the correlational relationships between environmental influences, alterations in brain structure and function during development, and the emergence of psychopathology, animal models, both rodent and nonhuman primate, allow for very precise and ingenious manipulations of the developing organism's environment, as well as the organism itself (e.g., neuroendocrine stress systems, brain circuits), providing invaluable information regarding possible biological, neurodevelopmental, molecular and system level mechanisms.

RODENT MODELS OF DEVELOPMENTAL PSYCHOPATHOLOGY

Rodent models include mostly mice and rats, and are some of the most commonly used model organisms in biomedical research. They allow for precise manipulations of neural systems and a level of experimental control not possible in humans and even in nonhuman primate studies. A full description of the natural history and ecology of rodents used in biomedical research is beyond the scope of this chapter, but has been reviewed for mice elsewhere (see Fox, Barthold, Davisson, Newcomer, Quimby, & Smith, 2006), although not for other species (e.g., rats). One notable difference between the early environment in rodents commonly used for research and that of a human infant is that rodents are altricial, born at a much earlier developmental stage than primates (equivalent to the end of the second trimester) and in litters, so that pups are not only exposed to their mothers, but also to their siblings. This allows for valuable within- and between-litter comparisons not possible in humans (except perhaps in the case of twin studies), but may also represent conceptual challenges when trying to understand the underlying mechanisms of developmental changes. Although there are obvious differences between rodents and humans, there are also certainly commonalities in neurodevelopmental patterns and physiology that make them strong animal models.

Prenatal and Postnatal Development: Critical Periods

Extensive research has been conducted on the plasticity of the prenatal and postnatal periods in the rat and mouse. Nearly 6,000 peer reviewed research papers have been indexed in the U.S. National Library of Medicine and it is beyond the limits of this chapter to recount all of the findings here. Many of the models and early findings of manipulations during the prenatal period and postnatal period are thoroughly detailed elsewhere (Marco, Macri, & Laviola, 2011; Molet, Maras, Avishai-Eliner, & Baram, 2014; Sanchez et al., 2001). Here we will briefly define the major models of prenatal and postnatal stress used in

the field to study mechanisms leading to developmental psychopathology and highlight the systems that have been reported to be affected. Finally, we will summarize some of the recent work examining the potential reversibility of early stress effects and explore the evidence that suggests that these early life stressors create an inherent susceptibility to insults later in life.

Common Models of Prenatal Stress

Although a wide range of stressors are employed with rodents including both psychological and physical stressors, those applied prenatally need to be moderate enough so that to they do not cause reabsorption of the pregnancy. Because of this concern, most stressors applied prenatally in the literature are of a psychological nature and typically do not include massive physical challenges such as temperature manipulations or forced physical activity like swimming. Several of the widely used paradigms are summarized herein, but there is a great deal of variability among research groups and the descriptions in this chapter are not exhaustive, as our focus is mainly in postnatal experiences.

Repeated Restraint

Repeated restraint has been commonly used as a model of prenatal stress. Restraint is generally facilitated through the use of plastic restraining devices sold for use in collection of unanaesthetized blood samples. These devices have sufficient numbers of holes to allow for heat exchange and guard against hyperthermia and are designed to confine the rodent such that it cannot make head to tail turns but the chest wall is in no way compressed so that breathing is unencumbered. Restraint devices are available in a variety of sizes such that larger sized restrainers can be used as pregnancies progress and the rat's abdominal circumference increases. The most common paradigm for prenatal restraint stress involves exposing the pregnant dam to restraint three times a day for 30–60 minutes under bright lights during the final week of gestation (days 14–21) (Bowman, MacLusky, Sarmiento, Frankfurt, Gordon, & Luine, 2004; Herrenkohl & Whitney, 1976; Kinsley & Bridges, 1988; Szuran, Pliska, Pokorny, & Welzl, 2000; Weller, Glaubman, Yehuda, Caspy, & Ben-Uria, 1988). Also reported in the literature are variations on this model in which the dam is exposed for a longer duration of restraint (2 hours) once a day for the final week of gestation (Wiggins & Gottesfeld, 1986). Although much less frequently reported, some research groups have also used this paradigm during early gestational periods (days 7–10 postconception; Glavin, 1984) or even throughout the duration of the pregnancy (Rojo, Marin, & Menendez-Patterson, 1985). An extensive number of publications exist which demonstrate that the application of repeated restraint stress alters both the offspring behaviors with relevance to psychopathology and related neurotransmitter systems. But, the main issue is the ecological validity and translational value for human prenatal conditions of this stress model.

Despite that caveat, repeated restraint stress of the dam results in intriguing alterations of multiple neural systems and behaviors relevant to psychopathology and neuropsychiatric disorders. As with many perturbations during development, the results are not necessarily uniformly negative or positive, reminding us that most of these developmental changes are a result of adaptations to the early environment. In one report of repeated prenatal restraint, although the offspring developed the previously described phenotypes of increased anxiety-like and depressive-like behaviors, they also demonstrated a resistance to chemically induced seizures (Marrocco et al., 2012). These findings highlight the adaptability of the developing brain, which in this instance were attributed to alterations in glutamatergic signaling (Marrocco et al., 2012). Prenatal restraint stress also alters attentional processing in offspring, renders the pups more susceptible to additional stress challenges after parturition (Burton, Lovic, & Fleming, 2006), and leads to modifications in responsiveness to psychostimulant drugs such as cocaine (Kippin, Szumlinski, Kapasova, Rezner, & See, 2008). As one might expect, prenatal restraint stress also causes robust alterations in the HPA axis both in terms of output of corticosterone and signaling within the hypothalamus and pituitary. More recently abundant evidence has emerged that supports the claim that the effects of prenatal restraint stress are not uniform and vary depending on the sex of the offspring (Garcia-Caceres, Diz-Chaves, et al., 2010; Garcia-Caceres, Lagunas, et al., 2010; Louvart, Maccari, & Darnaudery, 2005; Louvart, Maccari, Lesage, Leonhardt, Dickes-Coopman, & Darnaudery, 2006; Louvart, Maccari, Vaiva, & Darnaudery, 2009) and genetic factors such as gene polymorphisms (C. Kinsley & Svare, 1987; Lovic et al., 2013; Schroeder, Sultany, & Weller, 2013; van den Hove et al., 2011).

Noise

Noise stress is an easily delivered and potent inescapable stressor, sometimes delivered in combination with other stressors, as will be discussed in the next section. One common model of noise stress is exposure to 85- to 90-decibel

noise for 1 hour daily during the last week of gestation (Kim et al., 2006; Sobrian, Vaughn, Ashe, Markovic, Djuric, & Jankovic, 1997). In some cases, noise (880 Hz; 77 decibels) is applied to the pregnant dam for 15 minutes per day during midgestation (days 10–18) and the rat is also exposed to forced swim for 15 minutes per day (Nishio, Kasuga, Ushijima, & Harada, 2001). Given that forced swim is a very physically demanding stressor, this is not frequently used in gestational stress studies, but some groups have had success, meaning that the pregnancy is not compromised. A very common combination with noise stress is the addition of intense light, based on the ecology of most rodent species used in research, which are nocturnal animals, and therefore photophobic. This model has been published extensively (Fride & Weinstock, 1989; Kay, Tarcic, Poltyrev, & Weinstock, 1998; Weinstock, Matlina, Maor, Rosen, & McEwen, 1992). Noise stress has been reported to impact both somatic and cognitive outcomes in the offspring (Kay et al., 1998; Nishio, Tokumo, & Hirai, 2006; Sobrian et al., 1997), but overall less research has been conducted with these noise models than with either prenatal restraint stress or the combination of stressors used in the chronic mild stress paradigm described in the next section.

Chronic Mild Stress

Chronic mild stress (CMS), also referred to as chronic variable stress (CVS), is the pseudorandom exposure to multiple mild stressors over a series of days. Frequently the battery of stressors includes: restraint, noise, bright light, light cycle disruptions, dirty bedding, wet bedding, cage tilt, and crowding. There is a high degree of variability among research groups and there is no standard set of individual stressors in the CMS battery that is universally applied. The general principle of CMS is that these stressors represent daily hassles or unpredictable mild stressors that will trigger a stress response but are unlikely to result in habituation or severe physical detriment. CMS was first reported by Willner (Willner, Towell, Sampson, Sophokleous, & Muscat, 1987) and variations of CMS during gestation have been reported in the literature over the past decade with the first report appearing in 1998 (Secoli & Teixeira, 1998). The precise effects of CMS/CVS on offspring outcome are highly dependent on the timing of the gestational stress exposure (Mueller & Bale, 2006) and some effects of prenatal CMS/CVS may be mediated by influences on maternal behavior (Bourke, Capello, et al., 2013). CMS during gestation also increases startle responses, a metric associated with anxiety, in male (Hougaard, Mandrup, Kjaer, Bogh, Rosenberg, & Wegener, 2011) and female offspring (Kjaer, Wegener, Rosenberg, & Hougaard, 2010). In some cases the cognitive deficits in offspring exposed to prenatal stress can be improved with antidepressant exposure (Abdul Aziz, Kendall, & Pardon, 2012). Although prenatal CMS/CVS has been demonstrated to also alter neuronal dendritic spine density in cortical regions of the adult offspring, there is less evidence that this manipulation modifies amphetamine responses (Muhammad & Kolb, 2011). The high variability in behavioral and neurological effects of CMS/CVS during pregnancy are likely due to the wide variety of stressors used to compose the CMS/CVS paradigm among laboratories and the range of gestational days to which the paradigm is applied. When considering CMS/CVS, or any prenatal stressor, it is important to consider the neural processes involved in the neuropsychiatric disorder of interest and design the paradigm to best target the development of these systems.

Diet and Immune Challenge as Models of Prenatal Stress

In addition to the classic prenatal challenges of psychological and physical stress, more recently it has been established that both dietary challenges and immune challenges during gestation can result in neural and behavioral manifestations that are reminiscent of psychopathology. The additional strength of these models is that they have more ecological validity and translational relevance for human pregnancy. High fat diet during gestation has been shown to further impair the changes in both dopamine signaling and the HPA axis response that normally result from prenatal stress exposure (Naef, Gratton, & Walker, 2013; Vucetic, Kimmel, Totoki, Hollenbeck, & Reyes, 2010). Further, high fat diet leads to delayed physical and neural development, increased aggression, and depressive-like behaviors in the offspring (Giriko et al., 2013). A different model using protein restriction during pregnancy also results in neural and behavioral deficits. Offspring of protein-restricted dams during pregnancy demonstrate deficits in memory, elevations in depressive-like behavior, and deficits in neurogenesis (Godoy et al., 2013) when assessed in adulthood. Given the profound energetic demands of development during gestation and the survival needs that drive adaptation to the environment, diet is a robust signal for the developing organism that garners lasting changes in neurobiology and behavior and some of these may contribute to the development of psychopathology depending on the adult environment.

In terms of immune challenges during pregnancy, several rodent models have been used to examine the consequences of pathogens on later offspring development. For example, prenatal exposure to lipopolysaccharide

(LPS) results in depressive-like behaviors and reduced neurogenesis in the offspring (Lin & Wang, 2014). In an alternate model of maternal immune activation using the immunogenic agent Poly I:C, the pregnant dams' physiologic response to the challenge predicted behavioral changes in the offspring. Thus, dams that gained weight after the immune challenge gave birth to offspring with normal behavioral responses to amphetamine challenge, locomotor activity, and prepulse inhibition, while those that lost weight postimmune challenge had offspring with abnormal behavioral responses in these metrics (Missault et al., 2014). These findings suggest that the developmental alterations resulting by these (and other) early insults are complex and highly dependent on many maternal physiological factors, including her metabolic state. Not only that, but there is strong evidence that an important mechanism mediating the impact of psychological prenatal stress on offspring development involves immune activation. As shown by Bronson and Bale (Bronson & Bale, 2014), prenatal stress results in placenta inflammation, which mediates behavioral alterations in the adult offspring, in particular locomotor hyperactivity—which reflects brain dopaminergic dysregulation—and that were prevented by maternal treatment with nonsteroidal anti-inflammatory drugs during gestation. This literature linking maternal stress with proinflammatory states and the variety of prenatal immune challenge protocols being used in rodent models have been recently compared and contrasted (Meyer, 2014). Given the growing recognition that immune activation during pregnancy contributes to the etiology of psychopathology in the offspring, including the recent evidence that stress-induced activation of proinflammatory pathways in the placenta and stress-induced changes in maternal vaginal microbiome (Bronson & Bale, 2014; Howerton & Bale, 2012) mediate prenatal stress programming effects on offspring behavioral development, rodent models of gestational immune stress are proving critical to understand this early programming and to test treatment options for human patient populations.

Rodent Models of Postnatal Stress

Multiple postnatal stress paradigms have been used in the literature and most capitalize either directly or indirectly on manipulation of the powerful dam-pup relationship. One of the reasons behind the broad use of these models is based on the remarkable developmental changes in HPA axis regulation during the early postnatal period, which includes the thoroughly characterized transition to the HPA axis hyporesponsive period, as well as the critical role of the dam as an external regulator of pup behavior and physiology. This maternal regulatory role is not only evident for the pup neuroendocrine stress responses, but for the development and regulation of fear responses (Rincon-Cortes & Sullivan, 2014; Sanchez et al., 2001). The most well-known mechanisms mediating the effects of maternal care on offspring neurobehavioral development have been reviewed elsewhere (Howell & Sanchez, 2011; Sanchez et al., 2001) and are not the focus of this chapter. They include (1) feeding regulation of the pup's heart rate through milk actions on gatrointestinal receptors, (2) tactile stimulation via licking, grooming, nursing and retrieving, which stimulates sensory pathways that modulate the activity and development of limbic emotional circuits involving amygdala function, and also (3) epigenetic modifications such as DNA methylation changes in many genes, including GR, estrogen receptor, neurotrophic factors (e.g., brain derived neurotrophic factor: BDNF) and other brain proteins that regulate synaptic development (e.g., protocadherins), which altogether cause long-term genomic programming effects that seem part of extensive and coordinated biological responses to adapt to the environment, and that can be transmitted to future generations through epigenetic modifications in the germ line. While multiple postnatal stress paradigms exist in the literature, the two most commonly used with strong implications for behavior and neurobiology relevant to developmental psychopathology are reviewed next.

Maternal Separation

Maternal separation is a long-standing postnatal stress manipulation that has appeared in a variety of forms. The first apparent report of maternal separation was in 1969 by La Barba and colleagues (La Barba, Martini, & White, 1969) and the paradigm consisted of separation from the dam for 21 hours/day for 18 consecutive days beginning 24 hours after birth. Each separation period lasted for 6 hours with a 1 hour feeding period in which the dam was returned to the pups. This rather extreme paradigm has been replaced by a relatively standard model of 180 minutes of daily separation (maternal separation; MS) on postnatal days 2–14 that was originally described by Plotsky and Meaney (Plotsky & Meaney, 1993). This model has a much higher ecological validity than the previous longer separations as it is based on the fact that rat mothers in the wild leave the litter in the nest for short periods of time to forage, but when food sources are scarce, that time can increase to 2–3 hours (Fleming, 1986). As previously reviewed (Molet et al., 2014; Sanchez et al., 2001), this separation paradigm has robust and long lasting effects

on both behavioral and neurobiological endpoints with implications for developmental psychopathology, including increased anxiety/fear, stress reactivity and anhedonia. The effects of maternal separation have been shown to be mediated not really by separation-induced stress activation in the pups, but mostly by alterations in the dam's maternal behavior following reunion after these prolonged separations, which becomes disorganized and harsh (Huot, Gonzalez, Ladd, Thrivikraman, & Plotsky, 2004).

Maternal Abuse of Pups Induced by Impoverished Environment

A recent rodent model of adverse caregiving induces abusive and neglectful maternal behaviors by reducing the bedding of the cage where the rat dam lives with her litter. This simple manipulation triggers drastic alterations in the mother's behavior, which becomes very disorganized, and includes trampling the pups and carrying them around in a very rough manner. This impoverished environment model developed by Baram and colleagues (Avishai-Eliner, Gilles, Eghbal-Ahmadi, Bar-El, & Baram, 2001; Brunson et al., 2005; Gilles, Schultz, & Baram, 1996; Ivy et al., 2008), directly affects maternal behavior by manipulating the nesting environment and without separating the pups from her, leading to dysfunctional nurturing as well as physically abusive behaviors in the dam (Ivy, Brunson, Sandman, & Baram, 2008 Rice, Sandman, Lenjavi, & Baram, 2008; Roth & Sullivan, 2005). This paradigm induces cognitive and emotional alterations in the offspring (Baram et al., 2012), including the emergence of a behavioral phenotype later in life that includes depressive-like behavior as well as disrupted HPA-axis and amygdala function (Rincon-Cortes & Sullivan, 2014). Some of these behavioral and emotional alterations seem, at least in part, mediated by reduced BDNF expression in the PFC via epigenetic modifications (DNA methylation changes) in the BDNF gene (Roth, Lubin, Funk & Sweatt, 2009). Altogether this body of literature underscores the critical role of competent and nurturing parental behavior for proper neurobehavioral development of the offspring across mammalian species and points to some of the underlying biological and molecular mechanism involved.

Plasticity and Susceptibility of Adverse Early Life Experiences

The high degree of plasticity early in life in terms of both brain and behavior can work either for or against the ultimate adaptive development of an organism. Thus, if the immature animal grows in a generally positive environment, with a nurturing mother and environmental enrichment, following early life adversity some effects of the stressor exposure can be mitigated. However, if an additional challenge is experienced, commonly referred to as a double-hit, then the outcome for the organism could be highly maladaptive and lead to overt somatic or behavioral deficits and potentially psychopathology. Models of either reversal of early insults by enrichment or further insult have begun to be applied in the laboratory setting with rodent models. Thus, alterations in synaptic proteins that are created by maternal separation have been reported to be reversible through exercise exposure, a type of enrichment, in early adulthood (Dimatelis et al., 2013). In addition, housing of maternally separated rat offspring in enriched environments postweaning was sufficient to prevent the manifestation of anxiety-like behaviors that were evident in maternally separated offspring that were not afforded the benefit of postweaning enrichment (Vivinetto, Suarez, & Rivarola, 2013). Similarly, both the HPA axis over-activation and deficits in play behavior that are induced by prenatal stress can be reversed by housing in an enriched environment during adolescence (Morley-Fletcher, Rea, Maccari, & Laviola, 2003). Conversely, exposure to LPS followed by repeated restraint in early development creates a more profound anxiety-like phenotype than either manipulation in isolation (Walker et al., 2009). Prenatal immune challenge also creates a susceptibility to restraint stress applied in the juvenile period such that mice exposed to both challenges develop deficits in prepulse inhibition and dopaminergic signaling. This susceptibility can be prevented by treatment with alphalipoic acid during the juvenile period (Deslauriers, Racine, Sarret, & Grignon, 2014), which is an antioxidant essential for aerobic metabolism. This suggests that factors in the diet can palliate the deleterious impact of stress. Thus, dietary modifications during stressor exposure during pregnancy (such as fish and coconut oil) can improve the behavioral phenotype of the offspring (Borsonelo, Suchecki, Calil, & Galduroz, 2011). However, there are also negative diet by stress interactions such that rats who have been exposed to stress prenatally are more susceptible to the negative effects of a high fat and high sugar diet in adulthood (Paternain, de la Garza, Batlle, Milagro, Martinez, & Campion, 2013).

Puberty: The Perfect Storm

Major depressive disorder (MDD) can have devastating consequences; it can be particularly detrimental if it develops during adolescence because it interrupts the

development of social skills and causes potentially life-long alterations in physiology and behavior. The incidence of depression in the child and adolescent population is rapidly increasing in prevalence with an estimated rate of 8% near the beginning of adolescence and 25% by the end of adolescence (Kessler, Avenevoli, & Ries Merikangas, 2001). Furthermore, an adolescent episode of an anxiety or depressive disorder is associated with a two- to threefold increased risk for adult affective disorders (Pine, Cohen, Gurley, Brook, & Ma, 1998). Subthreshold depression during adolescence produces an increased risk of adult depression and suicidal behaviors similar to that of individuals who meet the criteria for major depression during adolescence (Fergusson, Horwood, Ridder, & Beautrais, 2005; Leuner, Mendolia-Loffredo, Kozorovitskiy, Samburg, Gould, & Shors, 2004). Finally, treatment plans for adolescents suffering from MDD are based largely on adult studies, and are not as efficacious in adolescents as they are in adults. The mechanisms of these differences are not understood but may be linked to the rapid physiological changes that occur during puberty and the concomitant demands on energy availability.

Although ketones are a significant fuel source prenatally, glucose is the quintessential cerebral fuel source for the majority of the life span (Clarke & Sokoloff, 1994). In the resting state, the adult brain uses approximately 20% of whole-body glucose for brain metabolism (Cremer, 1982). While the cerebral demand for glucose is clearly substantial in the adult, the requirement is heightened during development. In fact, the demand for brain glucose is 3–4 times higher in children and adolescents, with as much as 80% of whole-body glucose utilization being demanded by the brain (Cremer, 1982). This substantial allocation of energetic resources is particularly remarkable in light of the substantial peripheral demands during childhood and adolescence for overall growth and maturation of the reproductive organs. The introduction of additional energetic demands during this life phase, in the form of stress, can be energetically costly and cause developmental delays (Laugero & Moberg, 2000).

In addition to the demands of growth, there are dramatic and dynamic changes in sex steroids during puberty, and sex differences in physiology and behavior become more robust at this life phase. The precise timing of growth demands, sex steroid changes, and stress appear to result in a situation where intersectionality is important. Studies suggest that the timing of puberty influences the impact of stressful life events in humans (Ge, Conger, & Elder, 2001) and similar findings have been reported for rodents. Exposure during development appears to be fundamentally different than exposure in adulthood. Exposure to a single stressor episode postweaning in rats, close to the time of the onset of puberty, increases anxiety-like behavior following a single stressor in adulthood, to a greater degree than exposure to two stressors in adulthood (Avital & Richter-Levin, 2005). Exposure to chronic variable stress during puberty enhances the acoustic startle response both at the end of puberty and in adulthood (Maslova, Bulygina, & Popova, 2002), and short-term exposure (3 days) to a psychogenic stressor (predator odor and elevated platform) during puberty produces sustained changes in fear-related behavior (Toledo-Rodriguez & Sandi, 2007). Finally, chronic stress exposure during adolescence results in sustained depressive-like and anxiety-like behaviors that are still evident in adult female rats but not male rats further suggesting that the hormonal milieu interacts with other demands of puberty to cause variable outcomes (Bourke & Neigh, 2011).

Defining Adolescence in the Rodent

As in humans, adolescence in rodents is difficult to precisely define and definitions can vary depending on the endpoint in question. Adolescence is loosely defined as PND 22–59 with less certainty placed on the ends of the time zone as the pubertal process is subject to environmental influence. Factors to consider when defining adolescence are social changes, sex steroid changes, and neurogenesis changes. In regard to social behavior, it is commonly accepted that infancy and early childhood in the rodent ends at weaning (PND 21) and adulthood begins at PND 60 (Beckman & Feuston, 2003; Marty, Chapin, Parks, & Thorsrud, 2003). This milestone is marked by development of social and motor behaviors which allow the rat/mouse to be independent of the mother including food seeking, reaching, play fighting, and maturation of sensory systems (Whishaw & Kolb, 2005).

When using sex steroids to define adolescence, the peripubertal period is generally divided into three phases governed by the maturation of the sex organs: (1) early puberty (PND 22–35), which ends prior to the beginning of sexual organ maturation (i.e., vaginal opening in the female and balanopreputial separation in the male); (2) midpuberty (PND 35–49), which ends with the completion of sex organ maturation and the origination of sexual behavior; and (3) late puberty/early adult (PND 49–60), characterized by additional neurodevelopmental changes and cognitive behavioral changes (McCormick & Mathews, 2007; Spear, 2000).

In regard to the third criteria, neurogenesis, while it is well described that neurogenesis occurs in humans

(Eriksson, Perfilieva, Bjork-Eriksson, Alborn, Nordborg, Peterson, & Gage, 1998), developmental changes in neurogenesis have been best characterized in rodent species. Androgens and estrogens are known to influence neurogenesis (Galea, 2008; Galea, Spritzer, Barker, & Pawluski, 2006; Li & Shen, 2005; Tanapat, Galea, & Gould, 1998) and more than twice the number of newly dividing cells in the brain are described during puberty as opposed to in adulthood (Cameron & McKay, 2001). Although many of the newly divided cells die in both the adolescent and adult brain, new cells can be retained if the animal is exposed to learning around the time of the birth of the new cells (Leuner et al., 2004). This process was first described in adults (Leuner et al., 2004), but has also been identified in adolescents (Curlik, Difeo, & Shors, 2014). Given the greater number of cells that are born in the adolescent brain, this may predispose the adolescent brain to be more likely to retain new information than the adult brain. In the context of psychopathology, this is a potentially interesting mechanism to explain why adolescent individuals exposed to the exact same traumatic event as adults are more likely to develop posttraumatic stress disorder (PTSD). An illustration of this phenomenon is the Ehime Maru sea accident in which 78% of adolescent survivors developed PTSD and only 12% of adults developed PTSD (Maeda, Kato, & Maruoka, 2009).

Common Rodent Models of Stress During Puberty

Because of the limitations associated with conducting experiments in human subjects, animal models are invaluable in understanding the pathologic consequences of stress. Although rats cannot be queried to determine their affective state and are unlikely to experience depression in the sense that humans do, it is possible to study similar behavioral patterns and neurochemical phenomena in rodents. The neurobiology of rats is very well characterized and careful behavioral assessment can identify patterns of behavior that parallel depressive/anxiety-like behaviors in humans (Whishaw & Kolb, 2005). A multitude of preclinical studies have demonstrated that early life stressful experiences, such as maternal deprivation, exert both acute and long-term effects on neuroendocrine, cognitive, and behavioral systems (Gutman & Nemeroff, 2002; Weinstock, 2007). Consistent with the clinical literature, early life stress-induced changes in affective-like behavior and the HPA axis are more prevalent in female rats than male rats (Weinstock, 2007). Laboratory animals exposed to stressful conditions during development manifest adverse short and long-term cognitive dysfunction and abnormal behavior associated with alterations of the normal physiology and genetic regulation of the stress response (Gutman & Nemeroff, 2003; Ladd, Huot, Thrivikraman, Nemeroff, Meaney, & Plotsky, 2000). Although prenatal and postnatal stress have been studied for several decades, studies of stress during puberty are more recent. Many of the stressors employed during adolescence function off of principles of isolation and aggression. Social isolation in mice is profoundly detrimental and causes prolonged changes in aggressive behavior and neurogenesis (Ibi et al., 2008). Social stress exposure during puberty alters the formation of agonistic behaviors in both male and female golden hamsters (Taravosh-Lahn & Delville, 2004; Wommack, Taravosh-Lahn, David, & Delville, 2003). Finally, social stress during puberty can alter subsequent stress responses (McCormick & Mathews, 2007), behavior (Barnum, Pace, Hu, Neigh, & Tansey, 2012; Bourke et al., 2013; Bourke & Neigh, 2011; McCormick, Smith, & Mathews, 2008), neuroanatomy (Weathington & Cooke, 2012; Weathington, Hamki, & Cooke, 2014), and increase substance abuse behaviors in animals (Ferris & Brewer, 1996; Ferris, Messenger, & Sullivan, 2005; McCormick, Robarts, Gleason, & Kelsey, 2004). Here we will describe several of the most commonly published models of adolescent stress currently used in rodents, as well as the most relevant findings in each model.

Social Isolation

Isolation can be a powerful stressor in social animals regardless of the species. Although individual housing has profound health and behavioral effects on adult rodents, the positive influences of social housing have been mostly reported in the context of recovery from brain injury and peripheral wound healing (DeVries, Craft, Glasper, Neigh, & Alexander, 2007). However, in the context of development, social isolation has strong effects even in the absence of an additional physical challenge such as an injury. For example, a history of isolation housing starting in early puberty (postnatal day (PND 22) significantly increases the vulnerability to cocaine self-administration in adulthood. These data suggest that social isolation during puberty alters the development of reward brain circuits, predisposing the organism to greater drug abuse potential later in life.

The specific effects of timing of social isolation during puberty is another current research question. An interesting approach to these social isolation stress paradigms involves starting the isolation towards the end of early puberty (PND 30) and to regroup the rats following the isolation. One such approach confines the isolation to

just 5 days after PND30, returning the rats to group housing at PND 35. Although a very succinct period of isolation, this manipulation results in striking behavioral alterations in the forced swim test and elevated plus maze suggesting elevated anxiety- and depressive-like behaviors, as well as reductions in synaptic neuroplasticity (Leussis & Andersen, 2008). Furthermore, the reductions in synaptic plasticity are still evident when assessed weeks later, in adulthood (Leussis, Lawson, Stone, & Andersen, 2008). Extending the time of isolation to PND 30–50 results in further alterations in the HPA axis both at the level of output (corticosterone) and in terms of central neuronal changes (Weintraub, Singaravelu, & Bhatnagar, 2010). In addition, this prolonged separation paradigm results in sex-specific alterations in behavior and brain endpoints such that both males and females exhibit alterations following the separation, but the patterns are distinct (Weintraub et al., 2010). If the window of isolation is extended even further, PND 30–60, alterations in social learning are also observed. Thus, when tested for social recognition with a conspecific, mice that were group-housed their entire life performed better than mice housed alone from PND 30–60, independently of whether or not the isolated mice were returned to social groups for several weeks before they were tested (PND 80) (Kercmar, Budefeld, Grgurevic, Tobet, & Majdic, 2011). Altogether, this body of recent research highlights the strong long-term impact that even brief periods of social isolation during adolescence have on brain and behavioral development, emphasizing the important role of social relationships during this developmental period for humans.

Restraint Stress

Although the ecological and ethological validity of this model is questionable, restraint stress has been one of the most commonly used stressors used in rodent research. Plastic restraints commonly used for collection of blood samples are commercially available, and placement in a restrainer will generate a robust HPA axis response (Neigh, Bowers, Pyter, Gatien, & Nelson, 2004). Restraint is sometimes applied as a single acute stressor to challenge the HPA axis and examine the physiology of the activated state and in other cases is used as a repeated chronic stressor with multiple daily exposures. The range of days used in chronic restraint stress paradigms vary widely and can occur anywhere from days to multiple months. Repeated restraint was one of the first stressors applied in the context of adolescence and there is a wealth of data regarding the response of the adolescent rat to both acute and chronic restraint. Acute restraint increases anxiety-like behavior in the elevated plus maze as compared to adult rats exposed to the same restraint paradigm (Slawecki, 2005). Five days of repeated restraint (90 minutes/day) cause increased social anxiety in adolescent rats and the HPA axis response to restraint did not habituate as efficiently in adolescent as it did in adult rats (Doremus-Fitzwater, Varlinskaya, & Spear, 2009). Similar divergences in effects of repeated restraint on HPA axis function between adolescents and adults have also been reported by other research groups (Lui et al., 2012). Ten days of restraint (1 hour/day) from PND 25–35 caused increased basal corticosterone and increased cocaine-induced locomotion (Lepsch, Gonzalo, Magro, Delucia, Scavone, & Planeta, 2005). Restraint during adolescence has also been demonstrated to alter ethanol-induced behaviors differentially from similar exposure in adulthood (Acevedo, Pautassi, Spear, & Spear, 2013; Varlinskaya, Truxell, & Spear, 2013; Willey & Spear, 2013). Neural function and morphology are also impacted by chronic restraint stress during adolescence with reports of reduced neurogenesis in females, but not males, (Barha, Brummelte, Lieblich, & Galea, 2011), enhanced hypothalamic glutamatergic transmission in males (Kusek, Tokarski, & Hess, 2013), evidence of lower synaptic transmission in the prelimbic cortex (Negron-Oyarzo, Perez, Terreros, Munoz, & Dagnino-Subiabre, 2014), and alterations in conditioned fear behaviors (Zhang & Rosenkranz, 2013).

While restraint is a frequently used stress paradigm during adolescence, this approach has some limitations. For restraint to serve as an effective stressor, the rodents generally have to be individually housed. While this does not discount the value of restraint as a stressor, it is important that investigators acknowledge that they are using a combination of restraint and the more chronic stressor of isolation, which has strong developmental effects on brain, behavior, and physiology. This fact has strong implications for the interpretation of findings, particularly for translation to humans. Another concern is that rodents have the ability to habituate to restraint stress (Gray, Bingham, & Viau, 2010), which may create a situation in which the investigator is actually documenting the effects of habituation to a repeated stressor as opposed to the effects of chronic stress. Again, this does not necessarily invalidate the use of restraint as a chronic stressor, but it is essential to understand and differentiate which phenomenon is being studied to adequately and accurately interpret the experimental findings. Finally, repeated restraint has been criticized due to its lack of ethological relevance (Figueiredo, Bodie, Tauchi, Dolgas, & Herman, 2003) as this is not a stressor that a rodent would likely encounter

repeatedly in its natural environment and therefore the resulting physiological and behavioral processes may be contrived. Given these concerns and limitations of restraint as a model of chronic adolescent stress, additional stress paradigms have been recently generated that use more ethologically relevant stimuli or combine restraint with additional stressors.

Social Instability Stress

An adolescent stress approach that combines social isolation with instability is the social instability stress model. In this model, the rodent is isolated for one hour and then returned to a social group containing unfamiliar conspecifics. Social instability stress applied for 16 days during puberty (PND 30–45) has many behavioral, cognitive, emotional, and neural consequences. For example, it increases the risk for addiction, as shown by alterations in the locomotor effects of nicotine, with more pronounced neural correlates in male than female rats (McCormick & Ibrahim, 2007). In contrast, females appear to be more sensitive to deficits in spatial memory, which are paralleled by reduced hippocampal cell proliferation following social instability stress. Assessment of memory in an object spatial location task demonstrated that although female rats exposed to social instability had similar spatial memory to control rats shortly after the social stress paradigm in adolescence, their memory was impaired in adulthood (McCormick, Nixon, Thomas, Lowie, & Dyck, 2010). Some similar behavioral effects were also found in males exposed to social instability stress during adolescence, with memory appearing to be intact at the end of adolescence but a deficit in spatial memory evident in adulthood (McCormick, Thomas, Sheridan, Nixon, Flynn, & Mathews, 2012). Although social instability stress resulted in fewer newly generated cells in the hippocampus of females, the study design did not allow for the assessment of causation or determination of whether fewer cells were born or fewer cells survived (McCormick et al., 2010). The effects of social instability stress also extend to fear conditioning, with adolescent males (Morrissey, Mathews, & McCormick, 2011) and females (McCormick, Merrick, Secen, & Helmreich, 2007) exposed to this social stress during adolescence showing deficits in fear conditioning that could not be replicated when adult animals of either sex were exposed to the same chronic stressor. Collectively, these data highlight the plasticity of the brain and behavior in adolescent animals in response to exposure to complex social stressors and demonstrate the potential for these effects to be both delayed in onset, adolescence-specific, and enduring.

Social Defeat Stress

Social defeat is a robust and ethologically relevant stressor that has been applied to adult male rodents for over three decades (Van de Poll, De Jonge, Van Oyen, & Van Pelt, 1982). More recently, this stress paradigm has begun to be applied to adolescent rodents. Although there is a broad range of precise experimental designs, the protocols typically involve using large adult male Long Evans rats as an aggressor against an adolescent rat (either male or female). The adult aggressor is frequently housed with a female rat to increase territorial behavior. The female is removed from the cage prior to the defeat episode. A partially obstructive barrier that divides the cage in half but allows exchange of olfactory and visual cues is placed in the center of the home cage of the aggressor and then the adolescent experimental rat is placed on the opposite side of the barrier. After a short period of acclimation (generally 5–10 minutes, depending on the specific laboratory protocol), the barrier is removed and the adult and adolescent are allowed to freely interact. There is a large degree of laboratory specific variation for how long the interaction lasts, but after a predetermined period of time or a specific number of pins, the rats are separated by the barrier and remain in visual and olfactory contact for an additional exposure period (30 minutes to 24 hours depending on the lab).

Social defeat stress is a powerful stressor with high ecological and ethological validity with demonstrated wide range of effects in both male and female adolescents following exposure. Males exposed to social defeat for the entirety of puberty develop depressive-like behavior in the forced swim test and anhedonic behavior, and these effects are only partially reversible by either fluoxetine or a CRF antagonist (Bourke, Glasper, & Neigh, 2014). The demonstration of depressive-like and anxiety-like behavior following chronic adolescent social defeat has been replicated by multiple research groups with varying defeat parameters and in both rats and mice (Bourke et al., 2014; Huang et al., 2013; Iniguez et al., 2014; Vidal, Buwalda, & Koolhaas, 2011; Weathington, Arnold, & Cooke, 2012). The impact of chronic social defeat stress also impacts neural function and structure (Coppens et al., 2011; Watt et al., 2014; Weathington et al., 2012). Further, these changes in neural endpoints appear to have implications for drug abuse (Burke, Forster, Novick, Roberts, & Watt, 2013; Burke, Watt, & Forster, 2011; Novick, Forster, Tejani-Butt, & Watt, 2011), nicotine use (Zou, Funk, Shram, & Le, 2014), and alcohol consumption (Rodriguez-Arias et al., 2014). Finally, consistent with the effects of the previously discussed adolescent stress exposures, exposure to adolescent social defeat

causes impairments in spatial memory (Novick, Miiller, Forster, & Watt, 2013). Altogether, these recent findings support the validity of this model as an emerging model of social stress during adolescence, which some research groups argue could potentially serve to model bullying and physical abuse during human adolescence.

Chronic Mixed Modality Stress

Some stress paradigms in the literature use a combination of multiple types of stressor exposures to avoid habituation to a specific stress stimulus or situation. A classic example of this strategy is the use of the chronic unpredictable stress model which consists of pseudo-random exposures to multiple types of stressors including restraint, isolation, extended light cycle exposure, damp bedding, cage tilt, cage crowding, and other rodent-specific stress manipulations. A less variable model that has been more recently used with adolescent rats is the chronic mixed modality stress model. This model combines isolation housing, social defeat, and restraint exposures. The isolation component of the stressor begins at PND 35 and then social defeat and restraint exposures occur over 12 days in midpuberty (PND 37–48) with a single exposure a day. This paradigm causes robust and long-lasting depressive-like and anxiety-like behaviors in females and increased body mass (Bourke & Neigh, 2011), and exaggerated inflammatory responses in males (Pyter, Kelly, Harrell, & Neigh, 2013). The combination of these individual stressors provides a context-rich stress paradigm that may have more pervasive effects than any one stressor given repeatedly. However, this is a newer stress paradigm and it has not yet been determined whether it also has implications for drug addiction-related behaviors, physiology or learning and memory.

Predatory Stress

In the wild, rats and mice have multiple predators and exposure to a predator or cues signaling the presence of a predator can be used to elicit a robust stress response. For both rats and mice, cat or cat-related signals and fox-related signals are frequently employed as predatory stressors, and they are now being applied during adolescence. For instance, in a study comparing adolescent and adult rat exposure to cat odor, adolescent rats were exposed to cat odor on PND 38–42 and adult rats were exposed on PND 60–64. Three weeks later, all adolescent and adult rats were assessed and the findings indicated that the adolescent rats were more impacted in terms of HPA axis response, anxiety-like behavior, and social behavior, than adult rats exposed to the predatory stress paradigm (Wright, Muir, & Perrot, 2012). In a separate study, adolescent rats were subjected to 12 alternate days of cat fur exposure from PND 33 to 57. During exposure, adolescent rats demonstrated defensive huddling (all rats in the cage congregating away from cat fur) and reduced weight gain over the days of exposure. However, when the long-term effects of this experience were examined in adulthood, the rats exposed to cat fur actually showed reduced passive coping in the forced swim test (commonly interpreted as reduced depressive-like behaviors, although the actual functional meaning of these behaviors are a matter of debate in the field) and increased social behaviors, perhaps suggesting resilience (Kendig, Bowen, Kemp, & McGregor, 2011). It is important to note that these rats were not housed in isolation and the social housing may have provided social buffering from the repeated stress, again highlighting the powerful effect of positive social relationships during adolescence.

An additional predatory stress model that is specific to mice, is the use of a rat as the predator. In this paradigm, a mouse is placed in a four inch plastic activity ball and then the ball is placed in the home cage of a pair of adult male Long Evans rats. The rats typically engage in physical interactions with the activity ball with the mouse housed inside. In this paradigm the mouse is exposed to the smell and sight of the rat as well as the unpredictable physical movement of the rats manipulating the activity ball. Although no physical injury is experienced, this predatory stress paradigm initiated during adolescence has been shown to increase anxiety-like and depressive-like behaviors as well as measures of inflammation (Barnum et al., 2012). The pro-inflammatory phenotype induced by this intense stressor exposure is even more potent than a chronic mild stress paradigm (Barnum et al., 2012; Burgado et al., 2014). However, the robust effects of these stressful exposure may not be specific of adolescence because effects of the same stressor have also been demonstrated when the predatory stress is applied in adulthood (Burgado et al., 2014).

Brain Injury during Adolescence as a Model of Psychopathology

Sports-related traumatic brain injury (TBI) is a significant public health concern in the US and the incidence has risen with estimates as high as 3.8 million cases in the US each year (Langlois, Rutland-Brown, & Wald, 2006). The number of child and adolescent emergency room visits for sports-related TBI have more than doubled in the past decade (Mitka, 2010) and the majority of this increase is attributable to adolescent sports-related TBI (Graves, Whitehill, Stream, Vavilala, & Rivara, 2013). TBI is associated with a myriad of somatic

and psychological pathologies (Losiniecki & Shutter, 2010) and the long-term consequences of adolescent TBI are often overlooked (Graves et al., 2013; Ives, Alderman, & Stred, 2007). Further complicating the effects of adolescent TBI is the immature nature of the central nervous system. One example is the HPA axis, which undergoes substantial changes during adolescence, making this developmental stage a time of particular HPA axis susceptibility such that modifications to the HPA axis have profound and prolonged effects that are distinct from similar insults during adulthood or even early childhood (Avital & Richter-Levin, 2005; Bourke & Neigh, 2011; Greco, Hovda, & Prins, 2013, 2014; Maslova et al., 2002; McCormick & Mathews, 2007; McCormick et al., 2008; Pyter, Kelly, Harrell, & Neigh, 2013; Toledo-Rodriguez & Sandi, 2007). Adolescents are also susceptible to second-impact syndrome. Second-impact syndrome is rare in adults, but in adolescents, a second impact before complete resolution of the original injury, can lead to serious neurologic injury and death due to prolonged neuroinflammation and edema (Bruce, Alavi, Bilaniuk, Dolinskas, Obrist, & Uzzell, 1981; Cantu, 1995; McCrory & Berkovic, 1998). Even in the absence of a secondary injury, the prolonged neuroinflammation following TBI in an adolescent can cause profound changes, including possible dysregulation of the HPA axis. This is significant as the consequences of a dysregulated HPA axis response have been well documented in paving the way for a myriad of diseases including neurodegeneration and may underlie the progression of TBI-associated pathologies (Barnum et al., 2012; Bourke, Harrell, & Neigh, 2012; Bourke, Raees, Malviya, Bradburn, Binder, & Neigh, 2013; DeVries et al., 2007; McEwen, 1998, 2000, 2001, 2008; McEwen & Seeman, 1999; Neigh et al., 2009; Neigh & Nemeroff, 2006). Because of the clinical relevance of studies of TBI and evidence of developmental TBI involvement in the development of psychopathology, researchers have begun to focus on laboratory animal models of adolescent TBI, and potential treatments. This is a relatively new area of research with most studies focused on somatic outcomes. To date, research in adolescent rats has demonstrated implications of either single or repeated concussive injury on pituitary function (Greco et al., 2013, 2014) and sexual dysfunction (Greco et al., 2014). Much more work has been completed in adults with demonstrations of TBI-induced anxiety-like and depressive-like behaviors (Jones, Cardamone, Williams, Salzberg, Myers, & O'Brien, 2008; Pandey, Yadav, Mahesh, & Rajkumar, 2009; Rodgers et al., 2014) and deficits in learning and memory (Gorman, Shook, & Becker, 1993; Shear, Galani, Hoffman, & Stein, 2002; Sweet, Eakin, Munyon, & Miller, 2014). Given the general susceptibility of the adolescent brain to injury and the high incidence of TBI in adolescents, it will be important to extend these studies of TBI to its impact on adolescent neurobehavioral development.

NONHUMAN PRIMATE MODELS OF DEVELOPMENTAL PSYCHOPATHOLOGY

Nonhuman primates are more closely related to humans phylogenetically than rodents while still allowing for experimental manipulations not possible in studies investigating humans directly, making them crucial when studying the neural mechanisms of developmental psychopathology (Gibbs et al., 2007). Rhesus monkeys are a nonhuman primate species commonly used to study the neurobehavioral effects of early experience due to several advantages. In the wild they live in large troops made up of several multi-generational female-headed families and a few immigrant adult males, resulting in a complex social environment. They also have well-developed brains that closely resemble humans' in respect to organization and neurochemistry (Barbas, 2000; Croxson et al., 2005; Reep, 1984; Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012), particularly regarding the PFC, which is very different in primates versus rodents (Öngür & Price, 2000; Preuss, 1995; Preuss & Goldman-Rakic, 1991a, 1991b). Stress physiology, including the regulation and development of the HPA axis, as well as the distributions of glucocorticoid receptors (GR) and corticotropin releasing factor (CRF) receptors are comparable in rhesus monkey and human brains, particularly regarding their high expression in PFC (Pryce, 2008; Sanchez, Young, Plotsky, & Insel, 1999, 2000; Seckl, Dickson, Yates, & Fink, 1991), suggesting that some effects of early life adversity on the developing brain induced by elevations in stress hormones and neuropeptides (e.g., GCs and CRH) could be similar in both species. Neuromaturational processes also occur with similar temporal and anatomical patterns in humans and monkeys, although over a condensed period of time in monkeys (approximately 1:4 years, monkey to human age) (Diamond, 1991; Gibson, 1991; Huttenlocher & Dabholkar, 1997). To provide a translational framework on which to place the findings from nonhuman primate studies presented in the following sections we will first present a brief overview of normative nonhuman primate brain development as it relates to human brain development.

Primate Brain Development: Sensitive Periods

Early adversity is thought to be so detrimental because it occurs at a time of rapid developmental changes in the brain, creating windows of vulnerability in which adverse experience can be encoded (Andersen, 2003; Knudsen, 2004; Rice & Barone, 2000). In both developing monkey and human brains cellular processes (e.g., synapse formation, pruning, and dendritic changes) are revealed by gross region specific decreases in gray matter (GM) and increases in white matter (WM) due to pruning of synaptic connections and myelination of axons (Lenroot & Giedd, 2006; Malkova, Heuer, & Saunders, 2006). Although early reports in humans of GM volume changes with age suggested linear decreases (Reiss, Abrams, Singer, Ross, & Denckla, 1996), more recent studies of GM volumes describe a region-specific inverted U shape during development (that is, an initial developmental increase that, after reaching a postnatal peak, follows a developmental decrease), with frontal and parietal GM peaking at 12 years of age, temporal GM peaking at 16 years, and occipital GM continuing to increase through 20 years (Giedd, 2004; Giedd, et al., 1999). These developmental patterns suggest region-specific sensitive periods, with some lasting for several years as a result of protracted developmental trajectories (Andersen, 2003). More detailed analyses of longitudinal data suggest that cortical maturation (i.e., GM loss) occurs in low-order regions (e.g., regions that process visual or somatosensory stimuli) prior to the association cortices that integrate this sensory input such as portions of the temporal and frontal cortices (Gogtay et al., 2004). Cortical development also seems to follow the maxim "ontogeny recapitulates phylogeny," with phylogenetically older regions such as the piriform and entorhinal cortex maturing before evolutionarily newer regions such as the inferior temporal cortex and PFC (Giedd, 2004; Gogtay et al., 2004; Shaw et al., 2008). These data suggest the specific brain regions undergo increased developmental changes early in life, and those with protracted developmental trajectories, including regions such as the PFC, may be particularly vulnerable to environmental insult, and thus may contribute to developmental psychopathology.

In monkeys the elimination of axons occurs both prenatally and postnatally in a region specific manner that coincides with the emergence of related behavioral and cognitive functions, with some regions such as the corpus callosum (CC) not reaching adult axon numbers until postnatal day 60 (LaMantia & Rakic, 1990). In both monkeys and humans myelination begins in some regions prenatally (e.g., motor cortex) but it takes place postnatally in most other cortical regions and continues in association areas, namely temporal, prefrontal and parietal regions, into early adulthood (Gibson, 1991). Thus, cerebellar, temporal and prefrontal tract myelination occurs massively during childhood, with the cerebellum achieving adult levels of myelin between 3 and 6 months of age in monkeys and 1 to 2 years in humans, while WM of commissural and association tracts only reach adult levels of myelination at 3.5 years in monkeys (equivalent of 14 years in humans, peripuberty) and around 20 years in humans (Gibson, 1991). This suggests that commissural and association tracts, which are important for integrating information between brain regions, such as the uncinate fasciculus (UF), a WM tract connecting PFC with temporal regions and the last WM tract to myelinate in humans (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008), are particularly sensitive to critical aspects of maternal care as well as early adverse experiences because of their protracted development. This, combined with the important role the UF plays in emotion and stress regulation (Kim et al., 2011) via prefrontal–amygdala connectivity (i.e., prefrontal top-down control on amygdala reactivity to threat) suggest that adverse early experience-related alterations in the development of these networks are a likely neurobiological mechanism contributing to developmental psychopathology.

Much of what we know about the rapid structural development that occurs early in life in the amygdala comes from studies of rhesus monkeys. The amygdala is composed of several heterogeneous nuclei that differ in cellular composition, connectivity, and function, which is why it is often referred to as the amygdaloid complex. Development of the amygdala in rhesus monkeys follows nuclei-specific patterns. The medial nucleus (which is involved in sensory processing) is near adult size at birth, while the lateral and basal nuclei, which are involved in emotional processing and learning, increase in volume from birth through 3 months of age (Chareyron, Lavenex, Amaral, & Lavenex, 2012). The volume of the central nucleus (which has direct connections to the autonomic nervous system, and is involved in modulating the stress response through these connections) is about half of adult size at birth and continues to increase beyond one year of age, during the juvenile period (Chareyron et al., 2012). These nuclei specific patterns are reflected in a postnatal increase in total amygdala volume, which occurs at the highest rates during the first 4 months of life (Payne, Machado, Bliwise, & Bachevalier, 2010). Thus different amygdala nuclei, and the specific functions and behaviors that they support,

may be vulnerable at specific times during development. Numbers of oligodendrocytes in the amygdala increase in parallel with the increase in amygdala volume after 3 months of age, while neuronal size, astrocyte number, and neuron number do not change (Chareyron et al., 2012). This suggests that the increase in amygdala volume is not only due to neuronal changes, but also in the glia that produce the myelin in WM, and that these cells may also be vulnerable to early life adversity. This also suggests that WM in amygdala circuits supporting specific behaviors may be affected by early life stress. For example, in monkeys, amygdala afferents from portions of temporal cortex that relay visual information mature at week 3 when an animal first begins to respond appropriately to social cues, while efferents from these same temporal regions to orbital PFC do not become mature until 2 months when curiosity and frustration become apparent (Machado & Bachevalier, 2003). Thus, early adverse experiences in primates, particularly alterations in proper maternal care, occurring during the first few weeks of life may interrupt the ability to process social information, while adversity occurring during the second month of life might affect detection of stimuli salience and, therefore, exploratory behaviors. The complexity of the interplay of timing of these adverse experiences and neurodevelopment is one challenge the field of developmental psychopathology faces, and one in which nonhuman primate models may be especially informative given the similarities in neurobehavioral development highlighted earlier.

Although there is still much to be learned about normative neurobehavioral development, we are beginning to appreciate the importance of first understanding how these brain circuits and processes develop under species typical conditions when trying to disentangle the many factors that contribute to developmental psychopathology. During normative development drastic changes occur at the cellular, molecular, structural, functional, and systems levels in brain networks that have been consistently linked with developmental psychopathological symptomatology. It is this rapid maturation early in life that is thought to make these regions sensitive to environmental influence (Andersen, 2003). Therefore, several nonhuman primate models of early adversity and social stress have been used to study these effects, and to determine the underlying mechanisms of these experiences on the brain and behavior (Kalin & Shelton, 2003; Machado & Bachevalier, 2003a; Nelson & Winslow, 2008; Parker & Maestripieri, 2011; Sanchez, 2006; Sanchez et al., 2001; Stevens, Leckman, Coplan, & Suomi, 2009), which will be reviewed in the next sections.

Social Deprivation and Nursery Rearing

Arguably the most salient experience for a newborn primate is the relationship with its primary caregiver. Thus disruption of species typical early interaction with the primary caregiver, either through experimental manipulations or as sometimes occurs in nature, can serve as potent paradigms for studying the neurobiological underpinnings of developmental psychopathology. Studies of the effect of this type of early life stress (ELS) began in the 1960's with Dr. Harry Harlow's seminal work using experimental manipulations of the early rearing environment to model ELS including rearing in partial social isolation. Removing the vast majority of social interactions typically experienced by young primates resulted in severe behavioral and social deficits including stereotypies, self-injurious behavior, inability to read social cues or develop normal social relationships (including maternal behavior), and hyperaggressiveness (Suomi, Harlow, & Kimball, 1971). Rearing in complete social isolation led to similar outcomes, but with increased severity of developmental outcomes, and also included increased fear and anxiety (Seay & Gottfried, 1975). Alterations in the HPA axis have also been reported in this model (for review, see Sanchez et al., 2001), and recently several studies have reported evidence supporting possible genetic mechanisms mediating individual vulnerability to the severity of outcomes (i.e., gene-by-environment interactions that highlight strong effects of the serotonin transporter and monoamine oxidase A gene polymorphisms) as well as ELS-induced epigenetic alterations (Barr et al., 2003, 2004; Newman et al., 2005; Provençal et al., 2012). One recent study looked at whether levels of cortisol accumulated in hair (a measure of chronic glucocorticoid exposure) were related to anxious behavior and early experience in the form of peer-rearing. This study found that animals reared in the nursery were more anxious and had higher levels of accumulated cortisol (Dettmer, Novak, Suomi, & Meyer, 2012). These manipulations of the early social environment have been invaluable in understanding the importance of social stimuli on socioemotional and physiological development, but these are all somewhat artificial paradigms with limited ecological and ethological validity (except for extreme cases of social deprivation in children, such as orphanage rearing), which are complemented by other early adversity models discussed in the following sections.

Experimental Alterations in Maternal Care

Maternal separation has also been used to model developmental psychopathology in both New and Old World

nonhuman primates, including rhesus monkeys, squirrel monkeys (*Samiri sciureus*), and common marmosets (*Callithrix jacchus*). In rhesus monkeys, separation from the mother is a potent stressor for infant monkeys that leads to increased activity, vocalizations, and HPA axis activations (Bayart, Hayashi, Faull, Barchas, & Levine, 1990; Harlow, Harlow, & Suomi, 1971). Maternal separation has been related to decreased left dorsolateral PFC activation, as well as increased right dorsolateral and right ventral temporal/occipital lobe activation, effects related to concurrent elevations in plasma cortisol concentrations (Rilling, Winslow, O'Brien, Gutman, Hoffman, & Kilts, 2001). Repeated maternal separation in infancy has been related to alterations in stress responsivity including increased cortisol reactivity in females and flattened diurnal cortisol rhythms, as well as increased acoustic startle responses (i.e., reflecting increased anxiety) later in life (Sanchez et al., 2005). These effects are predicted by both exposure to chronically elevated levels of stress hormones and impaired maternal care following mother–infant reunion after the separation (Sanchez et al., 2001). Cameron and colleagues have gone one step further and looked at the long-term effects of complete maternal deprivation on infant behavior as a function of when the mother and infant are separated. The primary findings of these studies are consistent with those reported in children. That is, rhesus infants separated from their mothers at earlier ages (beginning at 1 week of life) showed the most detrimental effects (O'Connor & Cameron, 2006). These effects included social disturbances and alterations in fear behaviors that appeared to depend on the timing of separation. For example, animals that were separated at 1 week of age did not seek comfort when anxious, while those separated later at 1 month of age did seek comfort but were hypervigilant to social cues (O'Connor & Cameron, 2006). These adverse early experiences were also related to alterations in both PFC and amygdala (O'Connor & Cameron, 2006).

Marmosets are useful model organisms when studying the effects of alterations in early caregiving for a few reasons: (1) they are small, making them logistically easier to work with; (2) they are biparental; and (3) they typically give birth to twins, allowing for twin experimental designs to tease apart genetic versus experiential effects. Studies using marmosets have demonstrated the importance of considering parental factors when studying the effects of adverse early experience (Dettling, Schnell, Maier, Feldon, & Pryce, 2007). For example, in a model using parental-infant separation consisting of daily separations between days 2 and 28 (Dettling, Feldon, & Pryce, 2002a, 2002b), the adolescent animals that experienced parental separation showed decreases in GR mRNA, hippocampal growth-associated protein-43 (GAP-43) mRNA, serotonin 1A receptor (5-HT_{1A}R) mRNA and binding ([^{3}H]WAY100635), and increased vesicular GABA transporter mRNA in the hippocampus (Arabadzisz et al., 2010; Law et al., 2008). They also showed decreased levels of the dendrite-enriched protein spinophilin in the subgenual anterior cingulate cortex (Law, Pei, Feldon, Pryce, & Harrison, 2009). Increases in both urinary norepinephrine and dopamine, along with increased systolic blood pressure have also been reported (Pryce, Dettling, Spengler, Spaete, & Feldon, 2004; Pryce, Dettling, Spengler, Schnell, & Feldon, 2004), and these physiological alterations may be related to alterations in both the physiological and behavioral responses to stress reported (Dettling et al., 2002a, 2002b). Cognitive effects of this adverse early experience include increased sensitivity to perceived loss of control, reduction in reward motivation, impairments in behavioral inhibition, and impairments in reversal learning (Pryce, Dettling, Spengler, Spaete, et al., 2004; Pryce, Dettling, Spengler, Schnell, et al., 2004). All of the aforementioned studies corroborate the importance of parental care in neurobehavioral development, and support the involvement of several systems in the etiology of development psychopathology including the HPA axis, the PFC, and subcortical brain regions such as the amygdala and hippocampus.

The aforementioned nonhuman primate models have certainly demonstrated the critical role of the early social environment (including the mother and the father, in biparental species like humans) on primate neurobehavioral development, but they are based on artificial experimental manipulations (maternal deprivation since birth, repeated mother infant separations), which these species may not otherwise experience in the wild (e.g., in contrast to rats, rhesus monkey mothers don't leave their infants behind to forage), making it difficult to interpret their developmental consequences, as well as determining the generalizability and ethological relevance of the biological mechanisms involved for the human experience. Thus, we now discuss the complementary information provided by more naturalistic nonhuman primate models with stronger ecological and ethological validity.

Variable Foraging Demand

The variable foraging demand model contrasts the previously described models in that it was specifically developed as an ethologically valid model of early life adversity that exploits species typical behavior (i.e., foraging for food).

This model was first developed by Leonard Rosenblum and colleagues and consists of variable, and most importantly, unpredictable, availability of food (i.e., periods of intense foraging alternated with periods of free access to food), and has been used to study disruption of the early social environment in bonnet macaques (*Macaca radiata*) (Rosenblum & Paully, 1984). It is important to point out that even under conditions where the mother had to spend more time foraging enough food was available to maintain her and her infant's health. Thus, this manipulation does not involve malnutrition, but alters maternal behavior by reducing the amount of time spent responding to infant solicitations for care (Rosenblum & Paully, 1984). These alterations in mother–infant interactions resulted in several behavioral alterations in the infants including increased clinging to the mother, reductions in exploratory and play behavior, as well as behavioral disturbances such as despair-like behaviors involving self-clasping (Andrews & Rosenblum, 1994; Rosenblum & Paully, 1984). At 2.5 years of age animals raised under high foraging conditions showed decreases in affiliative behaviors and reductions in reactivity in response to a mildly threatening stimulus (Andrews & Rosenblum, 1994; Rosenblum, Forger, Noland, Trost, & Coplan, 2001). Long-term behavioral alterations in the infant also include social incompetence, increased fearfulness, increased social subordination, and both behavioral and physiological hyperresponsiveness to stressful stimuli (Andrews & Rosenblum, 1994; Coplan et al., 1996).

This environmentally induced change in mother–infant interactions does not only result in the behavioral alterations described already, but also alters neurobiological development. For example, behavioral and hormonal responses to neurochemical manipulation using the alpha2-adrenergic agonist clonidine, the alpha2-antagonist yohimbine, and the mixed serotonin 2C/1B receptor agonist m-chlorophenylpiperazine were reported in infants raised under the high foraging demand condition as compared to those raised under low foraging demand (Rosenblum, Coplan, Friedman, Bassoff, Gorman, & Andrews, 1994; Smith, Coplan, Trost, Scharf, & Rosenblum, 1997). The high foraging demand animals also had elevated levels of CRF and somatostatin, as well as monoamine metabolites including the serotonin metabolite 5-hydroxyindoleacetic acid (5HIAA), the dopamine metabolite homovanillic acid (HVA), but reduced levels of cortisol compared with those raised under low foraging demand (Coplan et al., 1996, 1998, 2001). The increase in CSF CRF in high foraging demand offspring was due to higher levels found in those carrying the short allele of the serotonin transporter polymorphism, paralleling findings in maternally separated animals (Coplan, et al., 2011). In vivo imaging studies of these animals in adulthood have reported reductions in corpus callosum area, hippocampal and temporal gyrus volumes, the neuronal viability marker N-acetylaspartate in the anterior cingulate and medial temporal lobe (reflecting signs of neuropathology in these brain regions), as well as reductions in tract microstructural integrity of the anterior limb of the internal capsule (Coplan et al., 2010; Jackowski et al., 2011; Mathew et al., 2003). Just as the previously described models that involved more invasive manipulations of maternal care, this more ecologically and ethologically valid model points to the involvement of similar brain regions in the alterations associated with changes in mother–infant interactions. They also provide evidence that specific neurochemical systems and brain regions not traditionally thought to play an active role in developmental psychopathology, such as white matter tracts, may also contribute to the etiology of developmental psychopathology.

Social Subordination

Nonhuman primates live in highly structured societies that provide unique opportunities to model human socioeconomic status (SES), particularly during development (Hackman, Farah, & Meaney, 2010). Rhesus monkeys, for example, live in societies organized by a strict dominance hierarchy that functions to maintain group stability (Bernstein, 1976; Bernstein, Gordon, & Rose, 1974). This is true of other nonhuman primate species as well, such as cynomolgus macaques (*Macaca fascicularis*), another species of Old World monkey often used when studying the effects of social subordination (Shively, Laber-Laird, & Anton, 1997; Shively, Register, Friedman, Morgan, Thompson, & Lanier, 2005). An animal's place within the hierarchy determines its access to resources, such as food and mates (Sade, 1967). These matrilineal hierarchies are maintained through contact and noncontact aggression and threats of aggression from dominant to subordinate animals (Bernstein, 1976; Bernstein & Gordon, 1974; Bernstein et al., 1974). The defining feature of social subordination is the presentation of submissive behaviors from subordinate animals in response to agonistic interactions with dominant animals (Bernstein, 1976; Bernstein & Gordon, 1974; Bernstein et al., 1974). These agonistic encounters are unpredictable, and often unprovoked, increasing uncertainty and stress in subordinates (Silk, 2002). This presumably reduces a subordinate animal's sense of control over the social and physical environment. Infant rhesus monkeys acquire the relative rank of their

mothers within their social group (Sade, 1967), a process thought to be attributable to latent observational learning as well as harassment from higher ranking females (Holekamp & Smale, 1991). Thus, infants of low ranking mothers are subject to the pressures of their rank beginning very early in development. While we know social subordination affects pubertal timing (Wilson, Bounar, Godfrey, Michopoulos, Higgins, & Sanchez, 2013; Wilson, Gordon, & Collins, 1986; Zehr, Van Meter, & Wallen, 2005), an effect that is associated with increased emotional reactivity in these animals (Wilson et al., 2013), the subordinate phenotype is less well understood in developing monkeys. It is important to recognize that this form of social stress is experienced throughout the life of the animal, and not just during early life, which is a main difference between this and other animal models used to study the underlying neurobiological mechanisms of stress-related developmental psychopathology, apart from the different adverse experience in comparison to animal models of disrupted maternal care. Consequences of this unpredictable, continual harassment in adult females include stress-related phenotypes, such as HPA dysregulation, evidenced by hypercortisolemia and impaired GC negative feedback (Jarrell, Hoffman, Kaplan, Berga, Kinkead, & Wilson, 2008; Kaplan et al., 2010; Michopoulos, Higgins, Toufexis, & Wilson, 2012; Shively et al., 1997). Subordinate animals receive higher rates of aggression and lower rates of affiliation (Michopoulos et al., 2012). It is interesting then to note that these two behaviors were the best predictors of increased cortisol in subordinates found in a meta-analysis of several primate species (Abbott et al., 2003). Thus, social subordination in rhesus monkeys is a well-established nonhuman primate model of chronic psychosocial stressor exposure, with high ethological validity. This model has been used to study the adverse effects of chronic social stress on a broad range of adult behavioral, neuroendocrine, neuromodulatory, immune and health outcomes (Gust et al., 1991; Kaplan, Adams, Clarkson, Manuck, Shively, & Williams, 1996; Kaplan et al., 2010; Michopoulos, Berga, Kaplan, & Wilson, 2009; Morgan et al., 2002; Paiardini et al., 2009; Tung et al., 2012); however many of these studies were performed on experimentally derived groups, meaning that animals from a single rank were taken and used to form new groups under well-controlled conditions, or animals were raised in nurseries beginning in infancy. While this approach can answer many valuable questions about the effects of chronic psychosocial stress on adult animals, it is not an ideal design when trying to answer questions relating to the effects of ecologically valid and species-specific adverse early experiences. Given the success of this model in studying effects of chronic social stress in adults, though, recent investigations are just now beginning to focus on the effects of this chronic stressor during development. For example, a recent study by our group examined the effects of social status on WM microstructure development during the juvenile period and found increased microstructural integrity in prepubertal subordinate animals in frontal (motor and sensorimotor regions) and prefrontal WM (Howell. Godfrey, et al., 2014). In this study animals with higher fractional anisotropy (increased cortical WM structural integrity) in cortical regions involved in emotional and sensory processing were observed to be also more submissive in their home social groups and more emotionally reactive (fearful) during a standardized emotional reactivity task (the Human Intruder Paradigm) (Kalin & Shelton, 1989), suggesting that increased integrity in these cortical WM regions is related to increases in socially adaptive behavior (i.e., exhibiting submissive behavior and more emotional reactivity if you are a subordinate) (Howell, Godfrey, et al., 2014). Future studies will need to address genetic versus experiential contributions to these outcomes.

Infant Maltreatment

Child maltreatment is not a uniquely human phenomenon, but has also been reported in both wild and captive populations of nonhuman primate species, including macaques, baboons, and marmosets (Brent, Koban, & Ramirez, 2002; Carroll & Maestripieri, 1998; Johnson, Kamilaris, Calogero, Gold, & Chrousos, 1996; Maestripieri, 1998; Maestripieri & Carroll, 1998; Maestripieri, Wallen, & Carroll, 1997; Troisi & D'Amato, 1984; Troisi, D'Amato, Fuccillo, & Scucchi, 1982). In macaque species infant maltreatment is an adverse early experience that includes two comorbid types of behavior in the mother that both result in overt signs of infant distress (vocalizations, tantrums, etc.): (1) physical abuse in which the mother exhibits aberrant violent behaviors towards the infant that cause pain and distress (drags, crushes, sits on, or roughly grooms the infant) and typically occur during the first 2–3 months of life, and (2) high rates of infant rejection early in life, which consists of pushing the infant away when it solicits contact with the mother (Maestripieri, 1998; Maestripieri & Carroll, 2000; McCormack, Sanchez, Bardi, & Maestripieri, 2006). Infant physical abuse has been more widely studied and characterized in the literature. It occurs within specific families, and by cross-fostering females born to control mothers to abusive mothers and observing their behavior with their own infants, Maestripieri and colleagues were able to

show that this type of infant maltreatment is experientially passed from generation to generation (Maestripieri, 2005; Maestripieri & Carroll, 1998; Maestripieri, Megna, & Jovanovic, 2000). Abusive mothers will often abuse successive infants, and primiparous mothers show higher rates of both abuse and neglect (Maestripieri & Carroll, 1998). Using sophisticated statistical methods Maestripieri and colleagues showed that physical abuse was not triggered by infant signals, such as crying, although abusive mothers were less likely to respond positively to their infants' cries (Maestripieri, Jovanovic, & Gouzoules, 2000), possibly leading to alterations in vocal emotional communication later in life (Jovanovic & Maestripieri, 2010).

Studies using this animal model have identified several alterations in the HPA axis associated with this adverse early experience, including increases in both basal and stress levels of cortisol, as well as blunted ACTH responses to a CRF pharmacological challenge that reflects down regulation of CRF receptors in the pituitary (Koch, McCormack, Sanchez, & Maestripieri, 2014; McCormack et al., 2003; Sanchez, 2006; Sanchez, McCormack, Grand, Fulks, Graff, & Maestripieri, 2010). Altogether these findings suggest that maltreatment is a stressful experience that results in elevated activity of the HPA axis, including a likely hypothalamic CRF overproduction that causes pituitary downregulation of its receptors. Socioemotional alterations include increased emotional reactivity, comparable to those seen in maltreated children (Howell, Grand, et al., 2014; McCormack et al., 2006; Sanchez & Pollak, 2009). Infant rejection was associated with decreases in brain serotonin and dopamine metabolite levels, and rejection and low serotonin function were, in turn, associated with increased activity of proinflammatory pathways (Maestripieri, Higley, Lindell, Newman, McCormack, & Sanchez, 2006; Maestripieri, McCormack, Lindell, Higley, & Sanchez, 2006; Sanchez et al., 2007), an interesting finding given that other studies have found modulation of some maltreatment related outcomes by serotonin transporter gene polymorphisms. For example, abused infants carrying a short (risk) allele showed increased vulnerability to exhibit increased anxiety and alterations in the HPA axis than abused infants with the long allele (McCormack et al., 2009). Delays in social development including delayed independence from the mother and less exploration and play have also been reported in this model (Maestripieri & Carroll, 1998; Maestripieri, Jovanovic, et al., 2000). The increased emotional reactivity caused by infant maltreatment persists throughout the juvenile and adolescent periods (Howell, Grand, et al., 2014). Recent neuroimaging studies have reported a positive correlation between amygdala volume and abuse rates received by the animals during infancy, as well as negative correlations between infant basal cortisol (collected at 1 month of age, when abuse rates were highest) and juvenile WM integrity in tracts important for behavioral and emotional regulation (Howell, Grand, et al., 2014; Howell et al., 2013). These findings parallel long-term consequences found in maltreated humans, supporting the construct validity of this model to gain understanding of the mechanisms underlying the poor developmental outcomes associated with this adverse early experience in humans.

Stress Inoculation Model: the Important Issue of Timing of Early Adverse Experiences for Resilience Versus Vulnerability to Psychopathology

In contrast to the evidence presented in this chapter that early adverse experiences (prenatal and postnatal stress, immune/inflammatory challenges, and disruptions in the mother–infant bond) are strong risk factors for developmental psychopathology, there is an interesting body of literature showing evidence that moderate stress at specific times of development actually has the opposite effect. That is they increase resilience when the individual faces challenges later in life. Most of the evidence for this phenomenon in nonhuman primates comes from studies in squirrel monkeys showing that manageable mild stress exposure at specific developmental times (weaning) may actually be protective, allowing the animal to better adapt to environmental challenges (Lyons & Parker, 2007; Lyons, Parker, & Schatzberg, 2010; Parker, Buckmaster, Schatzberg, & Lyons, 2004). This phenomenon has been termed *stress inoculation* and has been most extensively studied by exposing young squirrel monkeys during weaning (around 16 weeks of age, when they are no longer as dependent on maternal care) to mild intermittent stress consisting of separation from the mother and social group for 1 hour, once a week for ten weeks. Although rodent studies suggest that the quality of maternal care upon reunion following a prolonged (3 hours) mother-pup separation is altered and constitutes the critical factor in the increased risk for developmental psychopathology in the offspring, the stress resilience observed in the stress inoculation model does not seem to be caused by changes in maternal care (Parker, Buckmaster, Sundlass, Schatzberg, & Lyons, 2006). Although seemingly contradictory to everything presented so far, both the resilience outcomes and the lack of maternal mediation on the effects could be explained by the fact that these infants are in a later developmental stage (weaning), and are less dependent on maternal care. These studies have shown several

positive behavioral outcomes related to stress inoculation including increased exploratory behavior in adolescence and enhancements in inhibitory control of behavior lasting into early adulthood (Parker, Buckmaster, Justus, Schatzberg, & Lyons, 2005; Parker, Buckmaster, Lindley, Schatzberg, & Lyons, 2012). The HPA stress response also seems to be better calibrated to handle challenges, as evidenced by reductions in basal levels of stress hormones and the ability to mount a comparable neuroendocrine response to a moderate stressor as compared to animals that had not been inoculated (Parker et al., 2005; Parker et al., 2012). Neurobiological effects of this early experience include alterations in PFC morphology and GC receptor distributions in regions related to alterations in reward related-learning, but without accompanying effects on the hippocampus (Lyons, Afarian, Schatzberg, Sawyer-Glover, & Moseley, 2002; Lyons & Schatzberg, 2003; Patel, Katz, Karssen, & Lyons, 2008). These studies highlight how important the timing of the experience is in determining risk and resilience for developmental psychopathology (Parker & Maestripieri, 2011).

CONCLUSIONS

Animal models, both rodent and nonhuman primate, are indispensable when trying to determine the underlying biological mechanisms of developmental psychopathology. These models have led to significant progress in our understanding of not only maladaptation and dysfunction as it relates to developmental psychopathology, but by utilizing more ethologically valid models they have also begun to provide the normative developmental and ecological context necessary to draw meaningful conclusions. Animal models also allow us to compare and contrast findings to gain an even deeper understanding of the specific role of the early environment and caregiving in neurobehavioral development. Despite the many evolutionary, developmental, neurobiological, behavioral, and ecological differences between rodents, nonhuman primates, and humans, some striking cross-species parallelisms have emerged in studies of developmental psychopathology. These include developmental alterations of PFC and limbic regions like the amygdala and hippocampus in the etiology of developmental psychopathology, as well as the complex interplay between these regions as they change across development resulting in specific sensitive periods and windows of vulnerability. Shifting research paradigms to use more naturalistic and ethologically valid animal models has highlighted the unique role of competent and sensitive early caregiving in mammalian neurodevelopment. These paradigm shifts have also provided compelling evidence that there is a strong evolutionary, adaptive purpose for the developmental changes triggered by early life adversity, which are advantageous as they prepare the offspring to live in a harsh and challenging environment, but also result in significant and costly poor developmental outcomes. Animal models will remain invaluable as the field of developmental psychopathology moves towards understanding even more complex mechanisms involving epigenetic modifications and transgenerational transmission of experience-sensitive behaviors.

Translational Implications

The goal of translational research using animal models of developmental psychopathology is to understand the biological mechanisms, predictors, developmental processes, and critical periods by which early adversity gets under the skin, resulting in life long alterations. More recently the field has moved towards understanding resilience factors and developing interventions to positively impact human populations with developmental psychopathology. But, as in all translational animal research, it is difficult to definitively quantify its impact. We are just beginning to understand the neurobiological underpinnings of dysfunctions that cut across species and suggest highly conserved phenomena, which is the first step in designing effective treatments and preventative therapies. The work presented here has identified key biological mechanisms (not only the classical stress hormones, but inflammatory processes, epigenetic modifications and alterations in gut and vaginal microbiomes), brain regions and early experiences that are now being targeted to not only treat children at risk, but to ideally prevent symptoms from developing altogether (see Gunnar & Fisher 2006 for review).

As highlighted in the previous examples from animal research, and from the expansive body of human literature that has been built over the past century, the primary caregiver is especially important in shaping the development of the neurobehavioral repertoire of a child. Thus, one striking translational consequence of animal research since the seminal studies by Harlow (1958) and other work in animals that led to attachment theory (Ainsworth, 1969, 1979; Bowlby, 1958) is to encourage and emphasize warm and sensitive caregiving in our society, as especially critical early in life. This has led to the development of interventions and therapies that significantly improve child outcomes, such as educating the primary caregiver on how to properly and attentively care for their child.

One such intervention developed by Dozier and colleagues stemmed directly from some of the animal work finding alterations in the HPA axis in response to disruption of the caregiver–offspring relationship described already. Based on the evidence in animal models that HPA axis dysfunction is part of the etiology of developmental psychopathology, the explicit goal of this intervention was to normalize HPA axis function among children in foster care. In this intervention caregivers were shown how to provide an environment for their child that encourages development of the child's ability to regulate their emotions and behaviors, as well as teaching the caregiver how to interpret the child's difficult behaviors (Dozier, Higley, Albus, & Nutter, 2002). This intervention resulted in the normalization of cortisol levels, as well as improved behavioral outcomes (Dozier et al., 2006; Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008), constituting a beautiful example of how animal research can directly inform strategies to improve the lives of children facing early life adversity.

Another example of the direct impact of research using animal models of developmental psychopathology to improve outcomes in children early in life is the emphasis on skin-to-skin contact and tactile stimulation, or kangaroo care, often prescribed to parents of low birth weight babies and babies being treated in the neonatal intensive care unit (NICU; Jefferies 2012). This strategy was supported by rodent work that demonstrated tactile stimulation of pups, both via naturally high rates of maternal licking and grooming as well as experimental stroking of pups, was related to neurodevelopmental changes in the brain, including arousal–amygdala pathways, that were related to improved performance on several behavioral tasks (Kaffman & Meaney 2007; Richards, Mychasiuk, Kolb, & Gibb 2012). Kangaroo care has been shown to decrease infant mortality, illness, and infection, and also to improve cardiorespiratory and temperature stability, sleep organization, and neurodevelopmental outcomes (Head 2014; Jefferies 2012). This practice is a prime example of how animal research can be used to not only understand the mechanisms underlying developmental psychopathology but also to develop interventions, as described in the previous example, and even to prevent these poor outcomes.

Future Directions

Translation of findings from animal models into direct treatments and applications that can be used to positively impact affected human populations is a challenge for researchers in all health related disciplines, but it is particularly problematic for mental and behavioral health, which has been the focus of recent discussions (see Insel, 2007). In addition to these challenges, the field of developmental psychopathology has a unique challenge because the human population involved is undergoing massive normative changes in brain, behavior, physiology and social relationships on which psychopathology is superimposed. Without a clear understanding of normative development and pathology in humans and in each animal species being utilized as a model organism it is difficult to know exactly how to model human conditions and experiences. An important way to address how to model processes that translate to humans is to consider the natural history of each species, both the commonalities that suggest direct translation to humans (as exemplified by some of the animal work on maternal care highlighted earlier), and the differences that highlight possible specializations (as shown by the wonderful work explaining maternal control over the stress response in rodents during specific developmental times). This idea of ecological validity has been a recent discussion target for research using animal models (or model animals, as Dr. Thomas Insel emphasizes in a recent article (Insel, 2007), and we think it is critical for translation. Another point we want to emphasize as we reach the closing remarks of this review is that the best way to accomplish advances in the future is through interdisciplinary collaborations that allow us to understand human phenotypes and experiences to design studies with model animals that tap into similar constructs or developmental processes (see the Research Domain Criteria published by the National Institute of Mental Health; Cuthbert & Insel, 2010), also termed *reverse translation*, to then apply what we learn with animal models to guide human studies. This would allow for direct comparisons of results in human and animal studies, and through these direct comparisons a much clearer idea of underlying mechanisms and translational value of the animal model.

The question of how early experience is translated to epigenetic changes is currently being investigated in parallel in both humans and animal studies. Due to an explosion in biotechnological capabilities to study the mind-bending complexity of genetic regulation, we are beginning to appreciate how deep early experience can get under the skin, not only of the individual, but how these changes can be transmitted to future generations (Anacker, O'Donnell, & Meaney, 2014; Kundakovic & Champagne, 2014). Work showing epigenetic alterations (heritable traits not due to changes in the DNA sequence itself) related to

early experience, including variations in maternal care in rats (Champagne & Curley, 2009; Weaver et al., 2004) and nursery rearing in nonhuman primates (Dettmer & Suomi, 2014), are leading the way for in depth neurobiological studies that go beyond the immediate impact of early adversity on the individual's neural systems to expand our understanding of how that experience also causes changes at the molecular level, not only in somatic cells, but in the germ line, supporting the transgenerational transmission of phenotypes and memories. Consistent with other approaches and findings presented already, epigenetic modifications of genes and brain regions involved in the stress response have been identified in both animal models and humans (Anacker et al., 2014; McGowan et al., 2009). Using these techniques other cellular systems, including those involved in synaptogenesis, have been implicated in the brain's adaptations to early adversity, providing new targets for future research. This is still a nascent field that is opening new avenues of research into the neurodevelopmental mechanisms of early life adversity underlying developmental psychopathology.

New and fast advances are being made in other fields in addition to epigenetics which are impacting the way we understand how early experiences shape neurobehavioral development. The new emphasis on the gut-brain axis, for example, highlights the powerful role that something once thought to be static and unrelated to central nervous system functioning, the gut microbiome, plays in the control of neural processes and how early experiences can change this interaction, leading to developmental alterations in neurotransmitter function, such as the serotonin system (Cryan & Dinan, 2015). The role of the vaginal microbiota during birth, which is extremely sensitive to prenatal stress (Jašarević, Rodgers, & Bale, 2015), is to inoculate the neonate's gut with commensal microbiota shown to be important in neurobehavioral development (Borre, O'Keeffe, Clarke, Stanton, Dinan, & Cryan 2014). This is not only a growing field in the study of developmental psychopathology but is of particular relevance for the current review because much of the evidence for the role of the gut microbiota in normative neurobehavioral development comes from studies of animal models (i.e., germ-free animals raised without any microbiota; Clarke, O'Mahony, Dinan, & Cryan, 2014). These animals show alterations in the behavioral and physiological stress responses, as well as alterations in socioemotional behavior (Clarke, et al. 2014). Based on this evidence, physicians are now inoculating babies delivered via cesarean section with their mother's vaginal microbiota (De Jesus-Laboy et al., 2014). By incorporating measures of the gut and vaginal microbiome and other related physiological systems, and molecular techniques including epigenetic methods, we are now expanding our understanding of the complex etiology of developmental psychopathology to the systems biology level.

These are very exciting times of change, both technological and conceptual, that are opening opportunities to advance our understanding and potential for intervention and prevention of developmental psychopathology. We are able now more than ever to study the etiology of developmental psychopathology using multiple levels of analysis, all the way from the molecular to the behavioral level. Animal models have been instrumental in identifying some of the systems and underlying neurodevelopmental mechanisms involved in the brain's responses to early life adversity, but there is still much more for us to learn from them. The future of developmental psychopathology animal research is taking shape, and brings much hope for the development of efficacious treatments and preventative therapies. By combining knowledge gained in animal models and human studies with the ever-expanding frontiers of science and engineering, such as nanotechnology, the brain–machine interface, and biofeedback research (revolutionary technological and conceptual advances in the way we can manipulate the brain to treat behavioral and mental disorders), there is great potential for alleviating the burden of early life adversity and developmental psychopathology.

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CHAPTER 6

The Role of Early Nutritional Deficiencies in the Development of Psychopathology

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THE ROLE OF EARLY NUTRIENT DEFICIENCIES IN THE DEVELOPMENT OF PSYCHOPATHOLOGIES

Background

The influence of early nutrition on the developing brain has been a scientific issue over the past century (Susser & Stein, 1994). However, popular culture has recognized the importance of early nutrition in children's health dating back to Roman times. The Nobel Prize–winning author Pearl S. Buck wrote about the devastating effects of starvation on young children in her 1931 classic book *The Good Earth*. In this novel, the first daughter of the main character is born at the height of a severe famine. Buck implies the significant malnutrition the child endured early in life resulted in devastating brain damage, leaving her profoundly retarded. While such a profound effect likely overstates the case, the role of undernutrition and malnutrition in developmental psychopathology has strong scientific basis. It is the goal of this chapter to review and update the evidence for this science and to highlight the importance of a developmental psychopathology perspective for studying this complex issue.

Our species comes from a long history of inadequate access to food and thus malnutrition is generally conceptualized as undernutrition. Undernutrition can be global when there is an overall lack of nutrition (as occurs in famine) or specific, as in the absence of specific nutrients in an otherwise sufficient diet. More recently, the term *malnutrition* has taken on a broader meaning more consistent with its literal roots: bad nutrition. In this conceptualization, overnutrition is also a risk to somatic and brain development and, like undernutrition, could be due to a global excess of nutrients or the presence of toxic amounts of a specific nutrient. Indeed, risk from nutrients represent a U-shaped curve, where the lowest risk and greatest efficacy are from a range of nutrient sufficiency, while deficiency or excess confer risks to developing systems such as the brain.

Specific conditions such as phenylketonuria (PKU), where there is an excess of the amino acid phenylalanine due to a genetic inability to metabolize the amino acid, illustrate the importance of nutritional factors in brain development. If not addressed, PKU can result in mental retardation (Huttenlocher, 2000; Sullivan & Chang, 1999). The build-up of this amino acid during brain development results in a toxic reaction leading to brain damage (Huttenlocher, 2000). Reports hypothesizing a nutritional origin of some forms of mental retardation first appeared in the early 1950s when researchers noted high amounts of phenylketones in the urine of some mentally retarded individuals (Huttenlocher, 2000). Subsequent investigations linked PKU to various neuropathologies including diffuse

white matter changes and reduced dendritic branching (Huttenlocher, 2000). Specific genetic disorders resulting in deficiencies of micronutrients (such as copper in Menkes disease), regional geographic deficiencies of trace elements (such as iron, iodine and selenium), the presence of inhibitors of nutrients from the diet (all divalent metals including zinc, copper and iron) and low prenatal levels of maternal nutrients (such as folate and iron) have all been linked to severe neurological abnormalities or intellectual deficits (Hibbard & Smithells, 1965; Lozoff, 1989; Pharoah, Buttfield, & Hetzel 1971; Prohaska, 2000; Shim & Harris, 2003; Yi-Ming, 1996).

The famines and food shortages throughout Europe during the Second World War created an interest in studying the changes in psychological and physiological functioning caused by general undernutrition (Keys, 1946; Pollitt, 1988). Although many of the outcomes were chronicled as alterations to adult behaviors, it is pertinent in our context because (1) children likely exhibit similar, if not greater, psychological consequences and (2) by affecting the psychological state of their caregivers, parental malnutrition may exert indirect effects on children regardless of their nutritional status (Brozek, 1990).

In a more controlled scientific approach to the general malnutrition question, Keys and colleagues (at the University of Minnesota) exposed 36 healthy adult males to 6 months of semistarvation followed by 3 months of controlled rehabilitation (Franklin, Scheile, Brozek, & Keys, 1948; Keys, 1946). Results indicated that during the period of semistarvation the participants became lethargic, apathetic, less sociable, uninterested in sexual activity, less alert (except with regard to hearing), and depressed (Franklin et al., 1948; Keys, 1946). Although the participants complained about changes in mental alertness and inability to think cogently, researchers noted no decreases on tests of memory or intellectual ability (Franklin et al., 1948; Keys, 1946). The participants in the study exhibited unusual behaviors involving food such as compulsive gum chewing and coffee/tea drinking (up to 40 packs of gum a day and 15 cups of coffee a day), souping (i.e., the practice of drinking the liquid in soup and then refilling the bowl with hot salted water and repeating the process before eating the vegetables in the soup), and unusual eating habits including novel spice concoctions, hoarding of food, and doting over every last piece of food on the plate (Franklin et al., 1948). Many of the participants greatly increased their daily consumption of water and either began smoking or substantially increased the amount they smoked (Franklin et al., 1948). Finally, participants displayed numerous physiological reactions such as decreased sensitivity to heat, increased sensitivity to cold, edema, skin discoloration, and reduced hair growth (Franklin et al., 1948).

During the controlled rehabilitation phase, participants were initially irritable and easily frustrated (Franklin et al., 1948). These effects were short-lived; however, weight gain and sexual interest did not immediately return to prestarvation levels. In fact, participants did not reach their prestarvation weight and level of physical fitness until almost a year after the conclusion of the semistarvation phase (Franklin et al., 1948).

These findings are important because they indicate in adults periods of substantial undernutrition result in demonstrable acute but reversable alterations in behavior, physiology, and mood (Franklin et al., 1948; Keys, 1946). The reversibility of these symptoms suggests, in adults, behavioral changes occur secondarily to acute changes in neurotransmitter systems, as opposed to neuronal structure, induced by the nutrient deficiency. Research in humans and animals show dietary manipulations result in rapid changes in behavior and concentration of specific neurotransmitters (Fromentin, Gietzen, & Nicolaidis, 1997; Gietzen & Magrum, 2001; Phillips, Oxtoby, Langley, Bradshaw, & Szabadi, 2000; Pierucci-Lagha et al., 2004; Riedel, 2004). The developing brain of the child is at greater risk for the effects of undernutrition and these may not be as amenable to rehabilitation, thus resulting in long-term of lifelong behavioral abnormalities. The child's brain is at greater risk for residual abnormalities (after the nutritional burden is lifted) because in contrast to the adult brain, malnutrition likely impacts neuroanatomic organization in addition to neurotransmitter systems during periods of sensitive or critical periods of regional brain development (Winick & Rosso, 1969). While neurotransmitter recovery may seem more likely to occur, disordered neuroanatomical organization in childhood is more difficult to overcome because of sensitive periods of development (Wachs et al., 2014).

To test this question of long-term risk of psychopathology following early life global malnutrition, Stein et al. (1972) used a natural experiment to investigate whether prenatal exposure to famine in the Dutch hunger winter of 1944–1945 adversely affected intellectual abilities in a sample of 19-year-old males. In September 1944 the Netherlands cooperated with allied forces in an attempt by British paratroopers to force a bridgehead over the Rhine River (Stein et al., 1972, 1975; Susser et al., 1998). The attempt failed, and in retaliation the Nazi army imposed a trade embargo on Holland. Unfortunately, when the army lifted the embargo, previous railroad strikes and a severe

winter that had frozen the shipping channels resulted in serious food shortages in much of Western Holland. At the height of the famine, daily food rations could be as low as 450 kilocalories per person, a quarter of the standard amount. The most significant period of the famine began in November 1944 and lasted until allied armies crossed the Rhine and liberated Holland in May 1945. The severity of famine was indicated by a sharply increased death rate in the affected cities (many of these deaths were attributed to starvation), substantial (up to 25%) loss in body weight, and the occurrence of physical signs associated with severe malnourishment such as osteomalacia and hunger edema (Stein et al., 1972, 1975).

This event was unique because it occurred at a specified time and place in a population which before and after famine had good nutrition, there was good reporting on food rations provided to the population, and excellent public health records allowed researchers to divide individuals into groups of varying exposures based on birth date and birth location. This natural experiment has generated numerous investigations on the effects of prenatal famine exposure on a multitude of psychological and medical variables.

Stein et al. (1972) grouped individuals into six birth cohorts based upon their intrauterine exposure to famine: (1) individuals born before the beginning of the famine; (2) individuals prenatally exposed to famine in the third trimester only; (3) individuals exposed to famine in the middle 6 months of gestation; (4) individuals conceived during the famine and exposed in the first and second trimesters; (5) individuals conceived during the famine and exposed during the third trimester only; and (6) individuals conceived and born after the famine occurred. Stein and colleagues used Raven Progressive Matrices scores gathered at age 19 during military induction testing to compare these cohorts with control cohorts born during the same time frame in similarly sized cities not affected by the famine. The researchers failed to find significant declines in average IQ or increases in the rates of mild or severe mental retardation in the four groups prenatally exposed or in the one group exposed postnatally. Because many births occurred at home, the researchers could not evaluate the influence of prenatal famine exposure on the birth weight of the entire cohort; however, a subsample of births occurring in hospitals in the famine and control cities indicated no relationship of birth weight to IQ at age 19.

These findings cast doubt on the assertion that maternal malnutrition alone results in significantly declined intellectual abilities. However, the authors emphasize that their findings should not be generalized to chronically malnourished populations where the mother is likely to be malnourished before and after parturition, the child is at high risk for postnatal nutritional deficits, or deficiencies in specific trace nutrients are common. The authors suggest their findings reveal either a high degree of protection afforded to the developing child in utero or the considerable resilience of many children in the face of prenatal insult.

Over the years, many people have speculated that nutrition acutely affects behavior (e.g., sugar increases activity levels). Although careful research has not substantiated this particular assertion, there are many clearly documented short-term effects of specific nutrients (or substances) on behavior (Beyth & Baratta, 1996; Fernstrom, 2000; Fishbein & Pease, 1994; Lieberman, 2003). These acute effects are not the topic of this paper. Rather, the discussion focuses on the effects of generalized malnutrition or specific micronutrient deficiencies on the developing brain during fetal life, infancy and childhood and how these insults may contribute to the later emergence of psychopathology.

Before beginning the discussion in detail, it is important to define several terms. First, in this chapter *early undernutrition* refers to nutrient restriction occurring prenatally (sometimes even prior to conception) or in the first few years of postnatal development (prior to age 3). Second, *undernutrition* refers to a general reduction in macronutrient intake, also known as protein energy malnutrition (PEM). Nutritional deficits can be characterized by PEM, by deficits in specific micronutrients such as iron (Fe), Zinc (Zn), or iodine (I), or by both, as is often the case. Most of the extant research concerns PEM/undernutrition, and this will be the focus of the first section of this paper; however, each of the three micronutrients is discussed in the second half of the chapter because of their high prevalence rates around the world and their profound impact on early brain and behavior development.

An unambiguous definition of what constitutes psychopathology has proven elusive (Lilienfeld & Marino, 1999; Meehl, 1979; Spitzer, Fleiss, & Endicott, 1978; Wakefield, 1993, 1999), but is not necessary here. We will use major mental disorders as listed in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition* (*DSM-5*; American Psychiatric Association, 2013) as constituting a large subset of psychopathology pertinent to this discussion. Most research relevant to this review examines schizophrenia and schizophrenia spectrum disorders, internalizing disorders (such as major depression and anxiety disorders), and externalizing problems (such as

attention-deficit/hyperactivity disorder and antisocial personality disorder).

Basic Principles

When examining the effects of nutritional deficiencies on the developing brain and the role these may play in the genesis of psychopathology, it is important to keep in mind several core principles. First, brain development occurs in overlapping but dissociable stages, and each of these stages may be uniquely vulnerable to injury (Honig, Herrman, & Shatz, 1996; Monk, Webb, & Nelson, 2001; Morgane et al., 1993; Teicher, Andersen, Polcari, Anderson, & Navalta, 2002; Wachs et al., 2014; Webb, Monk, & Nelson, 2001). These stages include neurulation, neurogenesis, proliferation, migration, differentiation, synaptogenesis, myelination, apoptosis, and synaptic pruning (Andersen, 2003; Monk et al., 2001; Webb et al., 2001). Disturbances in some of these processes are associated with neurobehavioral deficits—as in the nonverbal impairments and psychiatric symptoms seen in the leukodystrophies—or the hypothesis that aberrant synaptic connections play a role in the etiology of autism and schizophrenia (Innocenti, Ansermet, & Parnas, 2003; Keller & Persico, 2003; Percy & Rutledge, 2001; Rosebush, Garside, Levinson, & Mazurek, 1999; Van Geel, Assies, Wanders, & Barth, 1997).

Some of the initial processes of brain development (e.g., neurulation and neurogenesis) occur during a single early period whereas other later stages (e.g., myelination, apoptosis, and synaptic pruning) occur independently at different times in various brain regions (Monk et al., 2001; Webb et al., 2001). Thus, a brain structure or region will have its own time course through which development proceeds. Moreover, certain highly metabolic brain regions such as the hippocampus are more vulnerable to injury than other regions (Walsh & Emerich, 1988). Ultimately, the result of any insult to the developing brain depends on the time of onset of the insult and what developmental processes are occurring/brain structures are actively developing at that time, how innately vulnerable these processes/structures are to injury—a factor driven largely by the relationship between metabolic demand and blood supply—and the magnitude of the insult (i.e., the severity and duration of the injury). Thus, a specific nutrient deficiency can have different effects on the developing nervous system, largely dependent upon these variables. (Adams et al., 2000; Georgieff & Rao, 2001; Kretchmer, Beard, & Carlson, 1996; Morgane et al., 1993; Pollitt, 1996; Wachs et al., 2014). In this context, it is worth highlighting that the timing of rapid development of certain "major" systems spans fetal and early postnatal life. The hippocampus, which is so central to discriminative recognition memory, undergoes its most rapid differentiation between 32 weeks gestation and 18 months postnatal age. Myelination, a mediator of speed of processing throughout the nervous system, also begins in earnest around 32 weeks gestation and proliferates rapidly until approximately 3 years of age. The dopamine neurotransmitter system, which is integral to reward, motivation and attention, starts to develop in mid-gestation and is solidly regulated by 3 years of age. Each is particularly sensitive to common nutrient deficiencies of pregnancy and young children such as protein malnutrition, iron deficiency and fatty acid deficiencies. Not only is there concern about the primary functions mediated by these three systems, but also proper function of these primary areas during development is key for establishing connections to more distal areas (e.g., frontal cortex) and for the efficiency of integrated circuits in mediating complex behaviors (e.g., prepulse inhibition).

A second important principle underlying the current discussion is the concept that abnormal behavior (as in psychopathology) is the efferent expression of brain activity, and changes in neuroanatomy, neurochemistry, and neurophysiology can result in alterations in behavior (Brower & Price, 2001; Moffitt, 1993; Moffitt & Caspi, 2001; Nestor, Kimble, Berman, & Haycock, 2002; Pennington & Ozonoff, 1996; Raine, 2002). Thus, early malnutrition may lead to the expression of cognitive deficits or abnormal behavior stemming from alterations in fine neuroanatomy (delicate structures such as dendritic arbors and white matter tracks), neurochemistry (disturbances in neurotransmitter systems), or neurophysiology (the functioning of ion channels and specific receptors) (Arnold, 1999; Benes & Berretta, 2001; Bowley, Drevets, Öngür, & Price, 2002; Fuglestad et al., 2008; Konradi & Heckers, 2003; Molnar, Potkin, Bunney, & Jones, 2003). Although specific findings (e.g., white matter abnormalities or increased receptor density in a certain region) are sometimes difficult to replicate in new samples, disturbances in these three broad domains are consistently associated with various forms of psychopathology (Dwork, 1997; Flecher, 1998; Jones, 1997).

The last core principle running through this discussion is the concept that genes will likely prove to be the single most important long-term determinant of behavior; however, their expression can be modified (repressed or activated) by interaction with the environment (Bunney et al., 2003; Jacobs et al., 2002; Murphy et al., 2001; Rutter, Pickles, Murray, & Eaves, 2001; Rutter & Silberg, 2002; Slutske et al., 1997; Wachs et al., 2014). Environmental influences causing anomalous neurological development

(such as chronic and severe neglect or toxicity) can have especially salient and long-term effects (Barone, Das, Lassiter, & White, 2000; Castle et al., 1999; Schettler, 2001; Wachs et al., 2014; Weiss, 2000). Similarly, nutrition is an important environmental factor that can affect the developing brain (Fuglestad et al., 2008; Georgieff & Rao, 2001; Morgane et al., 1993; Morgane, Mokler, & Galler, 2002; Wachs et al., 2014).

This does not imply that environmental insults such as malnutrition have uniform effects on people of differing genetic characteristics. It is likely that individual differences in the capacity to maintain homeostasis in response to challenges (thereby allowing for reasonably normal development) and in—at present—poorly explicated concepts such as neurological integrity, plasticity, and resilience are genetically or experientially determined, and such factors likely modulate the effects of environmental challenges such as undernutrition (Bhutta & Anand, 2002; Engle, Castle, & Menon, 1996; Morgane et al., 1993; Nelson, 2000a; Sapolsky, 2001; Wachs et al., 2014; Walker et al., 2011).

Furthermore, it is rarely the case that undernutrition exists independently of other risk factors such as maternal stress, genetic predisposition, poverty, and dangerous living conditions (e.g., poor sanitation or in the presence of toxins such as lead) (Guesry, 1998; Pollitt, 1969; ; Pollitt et al., 1996; Schettler, 2001; Snodgrass, 1994; Stein & Susser; 1985; Tanner & Finn-Stevenson, 2002; Trope, Lopez-Villegas, Cecil, & Lenkinski, 2001). Pollitt (1969) reported that in developing countries children with the greatest nutritional deficits had the poorest living conditions (i.e., lack of running water or adequate plumbing, cramped housing, and large families). Thus, malnutrition may generally exert its effects by acting in concert (additively or synergistically) with other risk factors (Guesry, 1998; Morgane et al., 1993, 2002; Stein & Susser, 1985; Zeskind & Ramey, 1981). For example, Caspi and coworkers (2002) found that abused children with a genotype leading to higher levels of a neurotransmitter metabolizing enzyme (monoamine oxidase) displayed lower rates of antisocial behavior. The authors interpreted these findings to be evidence of a gene/environment interaction in which the genotype influenced an individual's response to a particular environmental stimulus. It is possible that analogous mechanisms or interactions could be at work in determining the outcome of early malnutrition.

Overview

The current chapter endeavors to examine the effect of early nutritional deficits on brain development and the role this may play in the emergence of psychopathology. We will begin the discussion by examining the possible link between early nutritional insults and the development of psychopathology in the context of those studies that have specifically researched this question. After this, we will step back and delve into other investigations that assess the effects of early malnutrition on broader issues such as cognitive development in humans and developmental neurobiology. These factors are important because they characterize a developmental path (resulting from early malnutrition) in which psychopathology may exist as part of the milieu or which may increase an individual's risk for the later development of mental illness. Finally, the chapter will conclude with a brief hypothetical discussion of potential causal mechanisms that may account for the relationship between early nutritional insults and the later development of psychopathology.

Studies on Psychopathology Related to Early Life Nutrition

Studies in this section are presented with regard to the spectrum of psychopathology they examine. Thus, studies investigating the effects of early malnutrition on schizophrenia or schizophrenia spectrum disorders, neurodevelopmental disorders (e.g., attention-deficit/hyperactivity disorder [ADHD], autism), externalizing disorders such as conduct problems and antisocial behavior, and internalizing disorders (e.g., depression) are discussed. Krueger and colleagues (in addition to other researchers) have proposed the broad dimensions of externalizing and internalizing to capture more accurately the structure of common mental disorders (Krueger, 2002; Krueger, Caspi, Moffitt, & Silva, 1998; Krueger, McGue, & Iacono, 2001). These dimensions are used in the current discussion for clarity and succinctness.

Despite numerous investigations into the cognitive effects of malnutrition on children, most of the research dealing with the effects of malnutrition on the development of psychopathology concerns individuals older than eighteen. This is a significant shortcoming of our knowledge in this area because many psychiatric disorders will likely prove to have developmental origins. Thus, it is probable that these conditions have perceptible manifestations during childhood and adolescence. Similarly, early malnutrition may influence the developmental course (e.g., age of onset, severity, or progression) of psychiatric disorders. Moreover, malnutrition may be expected to exert more powerful immediate effects upon the developing brain—thereby suggesting the effects of malnutrition may be more salient in individuals younger than 18.

Thus, children affected by early nutritional deficits may display additional or significantly different behavioral effects than mature adults (Keys, 1946). Furthermore, it is possible that some of the cognitive manifestations of undernutrition (discussed later) may have resulted from impairments secondary to various psychiatric symptoms such as inattention or anxiety.

Much of the information regarding the relationship between early malnutrition and later psychopathology comes from data collected on cohorts prenatally exposed to famine during the Dutch hunger winter of 1944–1945 and the later Chinese Great Leap Forward famine of 1959–1961 (Brown & Susser 2008; Brown et al., 1996; Butler, Susser, Brown, Kaufmann, & Gorman 1994; Hoek, Brown, & Susser, 1998; Lumey, Stein, & Susser, 2011; McGrath, Brown, & St Clair, 2011; Song, Wang, & Hu, 2009; St Clair et al., 2005; Susser, Hoek, & Brown, 1998; Xu et al., 2009). As discussed previously, Stein et al. (1972) found no evidence suggesting decreased intellectual abilities or increased rates of severe or mild mental retardation following prenatal famine exposure. However, years later, Susser (the son of the original investigators) and his collaborators revisited the famine data to examine if individuals with a history of prenatal famine exposure exhibited higher rates of psychopathology in adulthood (Brown, Susser, Lin, Neugebauer, & Gorman, 1995; Brown et al., 2000; Hulshoff-Pol et al., 2000; Insel et al., 2008; Neugebauer, Hoek, & Susser, 1999; Susser et al., 1996; Susser & Lin, 1992).

Several major admonitions regarding these natural experiment should be pointed out. First, the amount of food redistribution in families is not known (Stein et al., 1972). Thus, pregnant women who occasionally received greater rations might have been supplied more calories via sacrifice of other family members (Stein et al., 1972, 1975). Second, although probably not substantially significant, it is not known how much individuals supplemented their diets with other materials, which may have actually contained toxins (Stein et al., 1972, 1975). Third, except for records indicating profession of father within the Dutch sample, there is no information regarding familial background. Finally, because many of the births occurred at home, it is impossible to gather information on birth or gestational complications, which along with maternal infection and stress may play etiological roles in the emergence of behavioral deficits and psychopathological conditions (Anand & Scalzo, 2000; Brown, Cohen, Greenwald, & Susser, 2000; Brown & Susser, 2002; Brown et al., 2000; McNeil, Cantor-Graae, & Weinberger, 2000; Teicher et al., 2002). Regardless of these essentially unavoidable imperfections, the studies discussed below provide valuable insights regarding the possible role of prenatal malnutrition in the emergence of later psychiatric disorders. Moreover, the consistency of the findings from the two episodes serves to support the contention that early exposure to severe prenatal nutritional deprivation increases the risk for later development of various psychopathologies.

In an initial 1992 study of the Dutch sample, Susser and Lin found that women, but not men, exhibited an increased prevalence of schizophrenia following prenatal exposure to famine in the first trimester. However, they obtained these results through a broad inclusion criteria (that is, first trimester of gestation during periods of low food rations), and review of admission records to psychiatric hospital units from 1978 to 1989. Thus, they based exposure on a single criterion that may not have completely captured children who experienced the highest levels of exposure. Furthermore, individuals were at least 32 years old at the start of the review period. This age tends to be past the age that most males have their first psychotic episode; therefore, it is likely many men would have already made initial psychiatric contact prior to this age and were not re-hospitalized during the review period (Brown et al., 1996).

In a more extensive follow-up investigation, Susser et al. (1996) used stringent inclusion criteria to define a maximal exposure cohort. The inclusion criteria for the other cohorts were the same as in the 1992 study. However, they defined the maximal exposure cohort to include only those individuals conceived at the height of the famine. This cohort consisted of individuals born when the general population exhibited increases in adverse health effects and new births demonstrated excess congenital malformations (which according to Stein, et al. (1975) are associated with severe prenatal starvation). These criteria ensured that the researchers dealt exclusively with the maximally exposed cohort (e.g., the cohort that underwent the most significant early insult due to the famine). These restrictions led to the identification of a cohort born between October 15, 1945 and December 31, 1945 (Hoek et al., 1996, 1998; Susser et al., 1998). The authors extended the period of record review back to 1970, thereby more accurately reflecting lifetime history of psychiatric admission.

Based upon these data, the researchers found a significantly increased prevalence of schizophrenia in both males and females of the maximal exposure cohort. This cohort displayed a prevalence rate for schizophrenia nearly two times higher than that of the unexposed cohort. Further, the other exposed cohorts did not differ in prevalence rate from the unexposed cohort. Susser et al. demonstrated

these findings using a narrow and a broad diagnostic definition of schizophrenia. Individuals within the maximal exposure cohort had mothers malnourished during the periconceptional phase, and their prenatal famine exposure occurred early in pregnancy, generally entirely within the first trimester.

Using magnetic resonance imaging, Hulshoff-Pol and colleagues (2000) found increased brain abnormalities (specifically focal white matter hyperintensities) in a subgroup of individuals from the maximal exposure cohort (Hulshoff-Pol et al., 2000). They showed that individuals from this cohort diagnosed with schizophrenia evidenced reduced intracranial volume compared to non-exposed individuals with schizophrenia and non-diagnosed individuals with the same level of famine exposure. The authors speculated that the decreased intracranial volumes observed only in the famine exposed individuals with schizophrenia resulted from an interaction between genetic risk factors and early brain stunting caused by gestational malnutrition—eventually resulting in the development of schizophrenia. They concluded that exposure to famine early in gestation is associated with increased focal brain abnormalities—possibly secondary to specific micronutrient deficiencies. In some individuals, these aberrations may result in a higher risk for developing schizophrenia. The researchers urge discretion when examining their findings, stressing they obtained the results using a limited number of participants and other confounding factors could not be completely taken into account. Nevertheless, these data provide an initial glimpse into specific structural brain changes present following severe first trimester malnutrition.

Another study by the same group expanded their inquiry to determine if males conceived at the height of the hunger winter evidenced increased prevalence of schizophrenia spectrum personality disorders (SSPD)—as defined by *ICD-6* (Hoek et al., 1996). This study used methodology similar to the aforementioned study. Thus, the authors compared the maximal exposure cohort (see Susser et al., 1996, for a description of this cohort) to an unexposed cohort and a cohort with first trimester exposure but without maternal malnutrition at the time of conception. The authors obtained data regarding the diagnosis of SSPD from military induction records; thus, males only are represented. This maximal exposure group demonstrated a higher prevalence of SSPDs. This increase appeared to be unique to SSPDs because the three groups did not differ from one another in the prevalence of psychoneurosis (i.e., general anxiety). They noted that this relationship remains consistent when estimated SES is taken into account. However, the authors hasten to point out that despite the increased risk in the maximal exposure group, relatively few individuals actually met criteria for SSPD in the entire study. Furthermore, they cautioned that despite the apparent care taken in making these diagnoses, no formalized diagnostic system existed at the time of these evaluations. To some extent, this caution should be applied to both of the studies previously discussed.

Using information obtained from birth and medical records in a population-based cohort born between 1924 and 1932 in Helsinki, Finland, Wahlbeck, Forsén, Osmond, Barker, and Eriksson (2001) reported on the relationship between factors indicative of prenatal undernutrition and the later development of schizophrenia. This study found that children born to mothers with a low body mass index (BMI) prior to parturition, who were born with small placentas and were below-average length and weight at birth, had an increased risk of developing schizophrenia in adulthood. Furthermore, this study indicated that, independent of other predictors, children thin at 7 years of age had an increased risk for developing schizophrenia in later life. The data also indicated that children short at birth who remained lean during childhood had a fourfold risk of developing schizophrenia. The authors observed no differences in the risk for schizophrenia between groups of varying SES, replicating findings from other studies.

These results are consistent with the hypothesis that fetal and childhood factors (specifically undernutrition) play a role in the pathogenesis of schizophrenia. However, given the relatively low and consistent prevalence of schizophrenia within the population and the relatively high rate of early malnutrition, it may be more plausible to conjecture that early nutritional deficits act as predisposing or triggering circumstances. This study suggests malnutrition statistically increases the risk for later development of schizophrenia.

Wahlbeck and colleagues suggest, in their sample, nutritional status (based upon maternal BMI, birth length, and slenderness in childhood) is independent of SES; however, they provide no evidence to bolster this claim. Thus, it is impossible to discern (given the information available) if these measures reflect actual undernutrition, or are simply corollaries of low SES or a genetic diathesis that increases risk for schizophrenia.

Similar results were obtained in later studies using a cohort of individuals affected by the Great Leap Forward famine occurring in China between 1959 and 1961. In the initial study with this cohort, St Clair and colleagues (2005) found that in the most affected province, the adjusted risk of developing schizophrenia increased from 0.84% for

those born in 1959 to 2.15% and 1.81% for those born in the height of the famine in 1960 and 1961 respectively. A later investigation by Xu and colleagues (2009) confirmed these increases using a cohort from a different region of China. This study found that this result appeared largely driven by individuals from a rural population suggesting that the increase was observed in only the most affected areas (Xu et al., 2009).

Taken together, these studies suggest that the prevalence of schizophrenia and schizophrenia spectrum disorders increases in individuals who are exposed to severe generalized malnutrition early in gestation. The findings of Wahlbeck et al. (2001) also provide evidence that schizophrenia is (either directly or indirectly) related to suboptimal growth in utero through early childhood.

Hoek et al. (1998) speculated about potential mechanisms to explain the findings of their group. First, they noted that it was unlikely that this finding was related solely to nutritional restriction because if such a correlation existed, one would expect to find significantly higher rates of schizophrenia and schizophrenia spectrum disorders in developing countries that commonly have serious food shortages. Rather, it is more likely that the increased prevalence was related to a restriction in a specific micronutrient, stating that these types of deficiencies are frequently observed in both developed and developing areas. For example, early iron deficiency (a very common micronutrient deficiency in both developed and developing countries) causes impairments in prepulse inhibition (PPI) in rodents (Pisansky et al., 2013). PPI is considered a reliable endophenotype of schizophrenia (Swerdlow, Braff, & Geyer, 2000), suggesting that early iron deficiency is a plausible mechanism for the development of psychosis in some circumstances (Pisansky et al., 2013). These initial findings underscore the importance of additional research using animal models of specific micronutrient deficiencies occurring at circumscribed times during brain development that reflect a proposed pathophysiology of a disorder—for example, migration defects in schizophrenia secondary to folate deficiency.

This approach could be useful in elucidating the effects of micronutrient deficiencies on neuroanatomy, neurochemistry, and neurophysiology; however, it would fall short in illustrating possible behavioral correlates because there are currently no irrefutable animal models of mental disorders, especially schizophrenia. Finally, Hoek and colleagues (1998) stated, their findings could have resulted from the increased level of birth complications and morbidity associated with early birth found in the most affected famine cohort. They noted that areas less affected by the famine experienced similar increases in obstetric complications without the concomitant rise in schizophrenia spectrum disorders, making this potential confound less problematic.

Neugebauer and colleagues (1999) again used the Dutch famine data to investigate possible relationships between prenatal nutritional restriction and the subsequent development of antisocial personality disorder (ASPD). The researchers used diagnostic information regarding ASPD from Dutch military induction records. According to the authors, Dutch psychiatrists considered ASPD to include a constellation of behaviors such as aggression, history of criminal activity, disregard for the truth, impulsivity, volatile temperament, unreliability, and interpersonal difficulties. Furthermore, psychiatrists categorized individuals under the subclassifications of violent or nonviolent ASPD.

Individuals exposed to severe malnutrition in utero during the first or second trimesters had an increased risk for the emergence of later ASPD (specifically violent ASPD) compared to either unexposed individuals, individuals with only moderate levels of caloric restriction, or individuals severely malnourished in the third trimester alone. Malnutrition remained predictive, even after they included other proven or potential risk factors (e.g., low social class, low IQ, or large sibship size) for ASPD in multiple regression equations. The authors comment that the most likely explanation for this pattern of results is the lack of a particular unspecified micronutrients during this critical period of brain development. They argued that similarities in infant morbidity between cases and noncases, specificity of time and place of the findings, and the lack of third trimester effects indicate severe malnutrition (during the first and second trimester) supersedes other environmental insults. However, they also proposed a possible mechanism in which malnutrition potentiates preexisting genetic or environmental vulnerabilities.

Additional research with the Dutch cohort indicates that exposure to the famine during the first trimester of gestation is associated with an increased risk of development of an addictive disorder in adulthood (Franzek, Sprangers, Janssens, Van Duijn, & Van De Wetering, 2008). These investigators did not find any evidence of increased risk for those individuals with exposures limited to the second or third trimesters, although those individuals with first trimester exposure during the peak of the famine continued to be at increased risk despite reintroduction of adequate nutrition during the remainder of their gestation. Of note, this effect appeared to hold only in males and was not observed in females with exposures during similar times in development.

Using a cohort of low birth weight (LBW) children, Breslau, Chilcoat, Johnson, Andreski, and Lucia (2000), examined the relationship between LBW, soft neurological signs, and subsequent intellectual/behavioral functioning at ages 6 and 11. Soft neurological signs refer to a number of various subtle neurological abnormalities in sensory, motor, and integrative skills that do not significantly impact an individual's overall functioning but may still result in suboptimal abilities in these domains (Breslau et al., 2000). Importantly, soft signs are not thought to reflect focal brain damage, but rather a diffuse neurological pathology resulting from a variety of sources including genetic anomalies such as microdeletions or mosaics (Breslau et al., 2000). Furthermore, studies have linked soft neurological signs to early malnutrition and deficits in IQ and behavioral functioning (Breslau et al., 2000; Galler, Ramsey, Solimano, Kucharski, & Harrison, 1984).

Breslau et al. (2000) observed a relationship between LBW and the occurrence of soft neurological signs in which LBW children are nearly twice as likely to exhibit soft signs as normal birth weight (NBW) children. The researchers found a linear relationship between LBW and the frequency of soft signs. Thus, the lower a child's weight at birth, the more likely the child was to display soft signs. Moreover, the data indicated children evidencing soft signs consistently performed below average on tests of intellectual abilities regardless of birth weight; however, LBW children tended to score lower on the IQ test in general, thus indicating additive influences. They also found a relationship between soft signs in both LBW and NBW children and the occurrence of learning disorders (at age 11) and the occurrence of internalizing problems at six and eleven. In the LBW group, the investigators found a relationship between soft signs and the occurrence of externalizing behaviors including attention problems at age 6 but not at age 11.

Even though this study did not strictly deal with nutritional deficits, it is interesting because LBW and soft signs may be associated with undernutrition. This is particularly germane to the Breslau et al. (2000) study because many of the participants, especially those within the LBW group, lived in urban settings and came from low SES backgrounds and thus had an elevated risk for prenatal or postnatal malnutrition. Regardless of the nexus between LBW and soft neurological signs, the findings suggest LBW children may be at increased risk for reductions in IQ, learning disabilities, internalizing problems, and, when younger, externalizing difficulties including attention deficits. The reason for the apparent evaporation of differences in the externalizing domain may be increased levels of externalizing behaviors exhibited by the control groups (Moffitt, 1993), or the beneficial effects of behavioral/medical interventions.

In a follow-up to their 1986 study (to be discussed in a subsequent section of the chapter), Galler and Ramsey (1989) assessed a group of previously malnourished Barbadian children for symptoms of hyperactivity. Using parent and teacher reports, they found increased levels of hyperactivity and distractibility. These relationships remained consistent after taking into account environmental factors such as parental involvement, parental career/knowledge of the world, stability of the home environment, number of siblings, and quality of living conditions (e.g., quantity of modern conveniences and durability of dwelling construction). Furthermore, these results concur with earlier findings (Galler, Ramsey, Solimano, & Lowell, 1983), which suggested increased attention difficulties in previously malnourished children between 5 and 11 years of age. The current study revealed an increased prevalence of speech difficulties in the formerly malnourished children as noted by teacher report. However, difficulties with socialization, emotional reactivity, and immaturity previously observed in these children (Galler, Ramsey, Solimano, & Lowell, 1983) were not seen in the current investigation. According to the authors, this may have resulted from slight changes in the assessment tools (necessary to reflect the older age of the children) or interventions targeted at ameliorating some of the effects of early malnutrition. If the latter is the case, it is meaningful because it suggests some aspects of early malnutrition (e.g., social skills) may be more amenable to educational interventions than others (e.g., attention problems) (Galler & Ramsey, 1989). However, it is possible that effects such as emotional instability are more characteristic of younger children who were previously malnourished and would disappear in older children regardless of interventions (Galler & Ramsey, 1989). A shortcoming of this study is the researchers' failure to control for intellectual abilities. Thus, it is unknown if the increased attention problems observed in the experimental group are a unique aspect of undernutrition in the first year of life, or rather are a corollary of the lower intellectual skills previously reported in these children (Galler et al., 1986). In a long-term follow-up investigation, Galler and colleagues (Galler, Bryce, Waber, Zichlin, Fitzmaurice, & Eaglesfield, 2012) determined that those individuals previously malnourished continued to experience increased symptoms of attention problems in adulthood. This investigation used both self-report and computer-based assessments of attention difficulties and demonstrated that

the impact of early malnutrition was not attenuated by environmental factors in childhood and that self-report of attention concerns was not influenced by childhood intellectual abilities.

Other recent studies by this same group (Galler, Bryce, Waber, Medford, Eaglesfield, & Fitzmaurice, 2011; Galler, Bryce, Zichlin, Fitzmaurice, Eaglesfield, & Waber, 2012) found a relationship between a history of protein-energy-malnutrition in the first year of life and attenuated executive skills via parent report, peer directed aggression when the cohort was relatively young, and the development of conduct problems via self-report as the cohort aged. These investigators stated that findings indicated continuity between the reports of the youth and earlier obtained teacher reports (Galler, Bryce, Waber, et al., 2012). Results suggested a relative decrease in parent reported peer aggression as the children aged and also showed that the later emergence of conduct problems was partly mediated by other factors such as childhood IQ and home environment.

Although not as robust as the findings in schizophrenia, the studies discussed already imply that prenatal as well as postnatal malnutrition predisposes individuals for exhibiting a variety of externalizing behaviors. It is intriguing to speculate whether the brain is susceptible to insults causing externalizing behaviors for a longer period during development, or if there are distinct etiologies of externalizing disorders, potentially linked to disruptions at various stages of brain development. Nevertheless, this handful of studies provides an impetus for future investigations on the role of malnutrition and other neurobiological risk factors in the etiology of externalizing problems.

Brown and colleagues investigated the relationship between prenatal famine exposure and the later development of affective disorders (affective psychosis and neurotic depression) (Brown, Susser, Lin, Neugebauer, & Gorman, 1995). The researchers defined affective psychosis and neurotic depression in accordance with ICD-9 definitions. Thus, individuals with affective psychosis displayed disturbances in mood (either depression or mania) accompanied by mood congruent delusions, whereas individuals with a diagnosis of neurotic depression displayed disturbances in mood (including symptoms of depression or anxiety) but evidenced no psychotic symptoms. They formed the groups by matching birth date and location with psychiatric admission records from 1978–1991.

Prenatal exposure to famine in the second trimester increased the risk of developing affective psychosis in later life; however, the authors did not find increased risk of affective psychosis resulting from first or third trimester famine exposure. These results remained significant when sex was taken into account; however, there was a significant interaction between sex and second semester famine exposure. Thus, males but not females appeared to be at greater risk for developing affective psychosis after second semester famine exposure—whereas females had higher prevalence rates in general. The data indicated no increased risk of neurotic depression following prenatal famine exposure in any trimester or in either sex.

A possible reason for the disparity between the diagnostic categories may be that (when compared to neurotic depression) affective psychosis represents a more severe mood disorder with a greater risk of hospitalization. Furthermore, neurotic depression may be more likely triggered by life stressors and thus differences between groups could be submerged by random variation in the population. A limitation of this study is that females usually begin exhibiting mood symptoms in adolescence. Therefore, effects of prenatal famine exposure may be observed in females if the researchers reviewed earlier hospital admission records. Additionally, Brown and his collaborators caution, their findings may not represent increased prevalence of affective psychosis, but rather may reflect increased need for hospital admission or delayed onset of symptoms in prenatally famine-exposed males. Nevertheless, these results suggest that males are at greater risk for developing serious mood disorders following significant mid-gestational malnutrition.

In a follow-up to their 1995 study, Brown and colleagues (2000) greatly increased their sample size by obtaining new diagnostic records. The researchers focused on unipolar and bipolar depression requiring hospitalization. Exposure to famine during the second and third trimesters related to increased hospital admissions in both males and females with unipolar and bipolar depression. The authors indicated that this effect was particularly robust if exposure occurred in the third trimester only. These results extend the findings of the 1995 study, and suggest prenatal famine exposure predisposes adults to develop serious mood disorders requiring hospitalization and characterized by either depression or mania/hypomania.

Another more recent study with the Dutch cohort indicated increases in depressive symptoms in adulthood among those individuals whose mothers were exposed to famine prior to gestation (i.e., in the preconceptual period; Stein, Pierik, Verrips, Susser, & Lumey 2009). The authors also found decreases in self-reported quality of life among this cohort. Interestingly, differences in depressive scores did not appear dependent on trimester of exposure during pregnancy (Stein et al., 2009).

Thompson and colleagues examined the relationship between low birth weight and the incidence of depression in old age (Thompson, Syddall, Rodin, Osmond, & Barker, 2001). These investigators used data obtained from individuals born between 1920 and 1930 in the English county of Hertfordshire and who still lived in the area in the early 1990s. The authors assessed all of the participants for depressive symptoms using two measures (a self-report questionnaire and a semistructured interview), and simultaneously asked about confounding factors such as SES, recent loss, general illness, and coronary heart disease (CHD).

This study found a relationship between birth weight and depression in late life so that the lower a child's birth weight, the greater the risk for developing late life depression. The findings were more robust in males and remained significant when the researchers statistically controlled for other complicating factors such as illness, SES, and bereavement. When they specifically took into account the occurrence of chronic heart disease (another risk factor for late life depression) the relationship grew stronger. The researchers that indicated males with low birth weight but high weight at one year exhibited the highest risk for late life depression; conversely, males with above average birth weight and comparatively low weight at one year exhibited the lowest risk for late life depression. They conjectured that this pattern indicated poor prenatal nutrition followed by compensatory growth and good prenatal nutrition followed by a regression to the mean respectively. Because this study focused on current and not early life depression, the results should not be generalized to depression occurring outside of old age. The authors hypothesized their findings provided support for aberrant fetal programming (see the conclusion section of this paper) caused by undernutrition as the major factor contributing to the future development of depression. Conversely, Waber et al. (2011) using the Barbadian cohort demonstrated that the direct relationship between depressive symptoms and early malnutrition was significantly attenuated when intellectual abilities were used as a covariate.

In summary, severe prenatal undernutrition appears to increase the risk for developing internalizing disorders (specifically mood disorders). However, it is unclear if the role of postnatal undernutrition significantly increases the risk of depressive disorders once other contributing variables (e.g., cognitive functioning) are taken into account. It is interesting that the risk period for exposure to malnutrition in the externalizing and internalizing domains may be later than for the schizophrenia spectrum disorders. The stages of brain development affected during these periods of vulnerability concur with research on the neurological sequelae of these various psychopathologies, and support the timing of onset and duration of insult hypothesis. For example, the research presented already on schizophrenia strongly suggests malnutrition exerts its effects in early stages of CNS development, neural tube formation, or initial neuronal migration, all of which have been implicated in the etiology of schizophrenia (Arnold, 1999; LaMantia, 1999; Rioux, Nissanov, Lauber, Bilker, & Arnold, 2003; Susser, Brown, Klonowski, Allen, & Lindenbaum, 1998). The later period of vulnerability observed in externalizing and internalizing disorders suggests malnutrition disrupts later processes of brain development such as neurotransmitter formation, late stage migration, or gliogenesis. Abnormalities in these processes have been implicated in the etiology of externalizing and internalizing disorders (Bowley et al., 2002; Cotter, Pariante, & Everall, 2001; Jenihe et al., 1996). Further, some conditions (such as schizophrenia) may be associated with a relatively acute injury, whereas behavioral disturbances in the externalizing and internalizing domains may be associated with insults extending over longer periods.

The investigations undertaken with the Dutch and Chinese famine cohorts and similar samples suggest early severe malnutrition, even if relatively brief in duration, increases the risk for the later development of mental disorders. Furthermore, this effect is not a general increase in vulnerability, but rather appears to depend on the timing and duration of the nutritional insult. Because the Dutch famine studies lack confounds such as social class, deprived environments, parental education, and extended postnatal malnutrition (which frequently accompany early malnutrition) they cannot be generalized to a chronically malnourished population. However, they provide strong support for the unique contribution of severe prenatal undernutrition in the emergence of later psychopathology.

Few studies have addressed the role of postnatal or prenatal–postnatal malnutrition in the development of psychopathology, even though it is clear from the National Collaborative Perinatal Project data base from the United States that prenatal malnutrition followed by postnatal failure to thrive has profound effects on IQ at 7 years of age (Pylipow et al., 2009). The lack of data on an effect of prenatal–postnatal malnutrition on psychopathology is particularly disheartening because postnatal malnutrition is common throughout the world, and, as discussed later in the studies on cognition, it is likely postnatal malnutrition is associated with deficits that differ from those of prenatal malnutrition.

The previous discussion suggests that early malnutrition may lead to the later development of psychopathology. Moreover, the expression of a particular psychopathology

likely depends on when the insult occurred (e.g., prenatal vs. postnatal or first verses second and third trimester). Another contributing factor (discussed in greater detail in the concluding remarks section) is that malnutrition may exert its maximal affect if it occurs concurrently with another insult such as stress or toxicity. Now that a plausible link has been established, it is necessary to take a step back in order to examine what may underlie the development of these conditions. We will first examine human studies that have been designed to determine if early malnutrition results in adverse effects on cognitive/intellectual development.

It is necessary to note that human protein energy malnutrition or undernutrition rarely exists without concomitant micronutrient deficiencies (Gorman, 1995; Kretchmer et al., 1996). Whether long-term effects are due to global or specific key nutrient undernutrition (e.g., iron, zinc) remains an interesting research question.

HUMAN STUDIES OF NUTRITION AND COGNITIVE DEVELOPMENT

One of the shortcomings of research on humans is it is difficult to control all potentially relevant variables, sometimes even known confounds. This limitation is particularly vexing in epidemiological research regarding the long-term consequences of early malnutrition. For example, as previously discussed, early malnutrition rarely occurs independently of other risk factors such as poverty and environmental stress (Engle et al., 1996; Pollitt, 1969; Stein & Susser, 1985; Tanner & Finn-Stevenson, 2002; Wachs et al., 2014). Although there are statistical techniques that can help compensate for this co-morbidity, one must still be careful when making inferences regarding experimental interventions or the interplay of particular risk factors. Secondarily, many studies using a population-based design are unable to account for other known or conjectured risk factors such as genetic predisposition, parental education, maternal stress, chaotic home environment, or other complicating physical factors such as toxin exposure, infection, or birth complications (Grantham-McGregor, 2002; Pollitt, 1969; Wachs et al., 2014). These caveats are not indictments of these types of studies, because what such studies lack in elegant controls they often make up for in direct relevance. However, the limited control over potential third variables should be kept in mind when evaluating such studies.

There are numerous studies detailing the effects of early malnutrition on human cognitive development (Fuglestad et al., 2008; Georgieff & Rao, 2001; Gorman, 1995; Park et al., 2011; Pollitt, 1988; Walker et al., 2011). Many of these studies were conducted in developing countries where malnutrition (or perhaps more frequently, undernutrition) is likely chronic and may span all of development—from the periconceptional phase to adolescence and young adulthood (Grantham-McGregor, 2002; Pongcharoen et al., 2012; Walker et al., 2011). Given the growing minority and immigrant populations of developed countries such as the United States and the fact that a vast portion of children worldwide suffer from early malnutrition, a careful consideration of these studies is warranted—even for those primarily interested in industrialized populations (Pollitt, 1994). Furthermore, knowledge of successful nutritional interventions in developing countries may help to improve current U.S. government programs such as the Women, Infants and Children (WIC) program (Pollitt, 1994; Tanner & Finn-Stevenson, 2002). It is useful to review this literature in this chapter in order to provide insight into the broad behavioral effects of early malnutrition. Further, research has linked intellectual/cognitive deficits with various types of psychopathologies (Moffitt & Caspi, 2001). Although this link may not be causal, these conditions (i.e., cognitive abilities and psychopathology) may nonetheless be connected.

Studies on neurocognitive outcomes of children who suffered early malnutrition are presented in three sections: studies concerning prenatal malnutrition and effects of low birth weight (where the fetus is protected from certain environmental factors such as poverty), studies on postnatal or combined prenatal and postnatal malnutrition, and studies examining the effects of nutritional interventions with malnourished populations.

LBW children (<2500 grams) or small for gestational age (SGA) births at term gestation are usually the result of intrauterine growth retardation (IUGR), which is frequently associated with fetal PEM (Georgieff & Rao, 2012). Although nutritional deficits in SGA babies can result from poor maternal nutrition, they can also result from other gestational or fetal problems such as maternal hypertension or genetic disorders (Georgieff & Rao, 2012).

Numerous studies have examined the neurocognitive functioning of SGA children (Georgieff, Hoffman, Pereira, Bernbaum, & Hoffman-Williamson, 1985; Low et al., 1982; Pollitt, 1996; Pylipow et al., 2009; Stein et al., 1972). Strauss and Dietz (1998)—using data from the National Collaborative Perinatal Project—compared the intellectual performance and visual-motor skills of IUGR children to their same sex non-IUGR siblings and normal birth weight children (without IUGR siblings). These researchers demonstrated that IUGR infants are usually born to shorter women who weigh less than the average female. Furthermore, this study revealed that normal birth

weight siblings of IUGR children were typically smaller than other normal birth weight children—although they were not considered SGA. The authors found that, at seven years of age, formerly IUGR infants with a head circumference significantly below normal or less than their siblings' evidenced reduced intellectual capacity and visual-motor skills compared with normal birth weight children. However, the performance of IUGR children did not significantly differ from their non-IUGR siblings—although the data trended in this direction.

These findings suggest that reduced birth weight is a phenomenon considerably influenced by genetic factors—although it is possible the normal birth weight siblings were malnourished, albeit at a lesser level than their SGA siblings. Additionally, statistically correcting for genetic and environmental agents suggests IUGR alone does not substantially contribute to the reductions in cognitive abilities noted in other studies. However, these data indicate IUGR infants born with significantly decreased head circumference differ from the normal birth weight population, other IUGR children without reduced head circumference, and their siblings in terms of their intellectual and visual-motor skills at 7 years of age.

Low and colleagues (1982) failed to find a relationship between IUGR and cognitive deficits. Results of their study indicated that IUGR children remained smaller than their peers at 6 years of age; however, the data revealed no significant long-term effects of IUGR on cognitive, motor, sensory, or language abilities. The IUGR group exhibited higher rates of certain difficulties (such as increased language difficulties and a slightly higher fail rate in senior kindergarten), but these differences did not reach statistical significance.

The authors admitted that the small IUGR male sample may have limited statistical power to detect delays in language skills, and they rightly point out that all of the children in this study were full-term, preventing generalization to preterm IUGR infants. Furthermore, this study did not assess specific neurocognitive functions (e.g., attention and recognition memory) that, because of their mediation by the hippocampus, might be more susceptible to prenatal insults such as IUGR. It is also possible that intervening environmental factors (such as a quality home environment) attenuated deficits in IUGR children. Another explanation rests on the fact that the authors meticulously matched the IUGR and control groups on factors such as obstetric complications, newborn characteristics, socioeconomic variables, and status at one-year follow-up; thus, factors potentially contributing to the reduced cognitive performance of IUGR children in previous studies might have been eliminated in the present investigation. Moreover, although not expressly stated in this paper, it is probable that the children in both IUGR and control groups received adequate postnatal nutrition.

Other studies expressly examined the effects of decreased head growth and caloric restriction on cognitive skills (Georgieff et al., 1985; Harvey, Prince, Bunton, Parkinson, & Campbell, 1982). Winick and Rosso (1969) demonstrated that children dying of severe malnutrition in the first year after birth evidence reduced brain DNA content—indicative of fewer neuronal and glial cells. Reduced head growth secondary to reduced cell numbers is an important variable to consider because microcephaly (severely reduced head size) is linked to neurodevelopmental disorders such as fetal alcohol syndrome (FAS). Furthermore, some investigators have correlated small head circumference at birth with greater risk for developing psychiatric disorders such as schizophrenia (Archibald et al., 2001; Bracha, Torrey, Gottesman, Bigelow & Cunniff, 1992; Kunugi, Takei, Murray, Saito, & Nanko, 1996). While reduced head growth is not associated with development in a specific brain region, it may be an indirect indicator of general brain maturation (Pollitt, Mueller, & Leibel, 1982).

Georgieff et al. (1985) showed that small for gestational age (SGA) infants and appropriate for gestational age (AGA) infants experiencing a prolonged period of postnatal caloric deprivation (due to medical complications) exhibited reduced rates of catch-up head growth. As would be expected, SGA infants began showing this reduced growth rate after sustaining a shorter period of caloric deprivation. The reduced rates of catch-up growth in these infants resulted in smaller head circumference at one year, head growth curves that (although broadly within the normal range) continued to be less than optimal, and in the most severely affected infants below average motor development scores.

Harvey and colleagues found that children born SGA with intrauterine head growth that slowed prior to 26 weeks gestation obtained lower scores on tests of perceptual and motor skills at 5 years of age (Harvey et al., 1982). Furthermore, SGA children with normal head growth performed at the same level as controls in these and other cognitive domains. The researchers combined the two SGA groups and evaluated performance strictly in terms of birth weight, ignoring rate of head growth; they determined that (taken as a single group) SGA children did not perform significantly differently from controls. Although this study did not deal with frank undernutrition, these results are an interesting corollary to the findings of

Georgieff et al. (1985) because they indicate that early rate of head growth may have a long-term impact on certain cognitive abilities.

Again using the Dutch cohort, a recent investigation by de Groot and colleagues (2011) found no evidence for any significant decreases in intellectual functioning in adulthood when compared to sibling controls and a geographically similar population born outside of the years of famine exposure. The authors indicated that although their findings did not indicate notable declines in IQ among the famine exposed group, their results could not completely rule out a role for early gestational famine exposure in decreasing intellectual abilities. Another study using this adult cohort found evidence for decreases in selective attention among males and females exposed to famine during the early portion of gestation (de Rooij, Wouters, Yonker, Painter, & Roseboom, 2010). The authors speculated that these findings may indicate premature signs of aging in the famine exposed individuals.

Although not entirely consistent in their findings, these studies suggest that SGA infants—especially those with decelerated rates of intrauterine head growth—and children who have lower birth weights compared to siblings are at higher risk for developing subtle but detectable neurocognitive difficulties. The findings from studies of frank malnutrition with the Dutch sample are somewhat equivocal, but highlight the likely role of early malnutrition in continued cognitive difficulties into late adulthood (de Groot et al., 2011; De Rooij et al., 2010). Those with first trimester exposure appear to be the most vulnerable.

The mechanism behind these effects is unknown although some interesting speculations can be made by results of a study from Tirosh, Gaster, Berger, Cohen, & Scher (2000). These investigators showed that birth weight and head circumference of typically developing children positively and significantly correlated with activity level and mobility in infancy. Prenatal malnutrition in the absence of other risk factors has not been convincingly demonstrated to result in long-term decreases in cognitive abilities, and it remains unclear how meaningful any deficits will be as previously malnourished children age (Guesry, 1998; Pollitt, 1996; Stein et al., 1972; Stein & Susser, 1985). The relationship noted by Tirosh et al. (2000) is important because it suggests that babies born with low birth weights are less active and less able to explore their environment, thereby potentially reducing mental stimulation—which human and animal studies indicate is necessary for basic cortical organization and development (Black, 1998; Nelson, 1999). Researchers theorize environmental stimulation is also critical for the development of other more complex cognitive skills (Black, 1998; Nelson, 1999; Nelson, 2000; Wachs et al., 2014).

It is necessary to qualify these assertions. First, it is quite likely that the SGA infant is affected by the internal and external environments into which she or he is born, for example, by factors like maternal substance use, stress, or genetic constitutions; postnatal nutritional factors; and birth complications such as premature birth, hypoxia, maternal infections, etc. Therefore, the ultimate effects of SGA are likely graded on a continuum, depending upon the combination of other vulnerabilities and assets possessed by the child (Engle et al., 1996; Stein & Susser, 1985).

Second, SGA infants are a heterogeneous group, and it is plausible that different etiologies of IUGR have different effects on neurological development (Black, deRegnier, Long, Georgieff, & Nelson, 2005). Finally, evidence suggests that prenatal malnutrition (especially if endured early in pregnancy) can occur without resultant low birth weight (Heasman, Clarke, Stephenson, & Symonds, 1999; Lumey, 1998). Lumey (1998) determined that prenatal malnutrition restricted to the first trimester resulted in compensatory placental growth without subsequent reductions in birth weight at term. For this reason, normal birth weight does not necessarily assure adequate prenatal nutrition, particularly during the sensitive period in the first trimester.

Many children, despite being born appropriate for gestational age (AGA), may have sustained neurological insults due to prenatal malnutrition. These children as well as SGA children may be more vulnerable to further nutritional deprivation or other environmental insults (Berkman, Lescano, Gilman, Lopez, & Black, 2002; Galler & Ramsey, 1987, 1989; Galler, Ramsey, & Forde, 1986; Ivanovic et al., 2000, 2002; Liu, Raine, Venables, Dalais, & Mednick, 2003). It is therefore difficult to dissociate the precise effects of prenatal malnutrition because the populations typically studied may not represent all prenatally malnourished individuals.

In a series of papers, Galler and colleagues (Galler & Ramsey, 1987, 1989; Galler, Ramsey, Solimano, & Lowell, 1983; Galler, Ramsey, Solimano, Lowell, & Mason, 1983; Galler et al., 1986) described the consequences of moderate to severe malnutrition sustained by Barbadian children in the first year of life. Galler et al. (1986) showed that (despite apparently so-called successful nutritional rehabilitation) previously malnourished children continued to exhibit lower performance on tests of intellectual abilities up to 8 to 14 years postmalnutrition. In this study, researchers administered to participants the Wechsler Intelligence Scale for Children–Revised (WISC-R), (Galler et al.,

1986), and the participants' mother completed a questionnaire assessing living circumstances, education, family relationships, and caregiver contact, among other factors. Consistent with previous evaluations (Galler, Ramsey, Solimano, Lowell, & Mason, 1983), results indicated that previously undernourished children had lower overall intellectual abilities and performed below controls (matched on birth weight, medical illnesses other than malnutrition, age, sex, and handedness) on the verbal and performance subscales of the WISC-R. The researchers observed no sex differences or sex-nutrition interactions, except (regardless of early nutritional status) females outperformed males on the Freedom from Distractibility index.

The study reported a significant correlation between scores on the WISC-R and environmental factors (e.g., poverty and maternal employment) (Galler et al., 1986). However, early malnutrition remained significant when the authors statistically adjusted for these influences. Conversely, environmental factors remained significant when the authors statistically adjusted for early nutritional status. The significant influence of environmental factors on test performance at these older ages is interesting because this was not found in previous investigations with this cohort (Galler, Ramsey, Solimano, Lowell, & Mason, 1983). The authors concluded that a history of malnutrition continues to play a role in intellectual deficits at least into adolescence. However, as a child matures, the effects of an early nutritional insult may be overcome or attenuated by other environmental factors. Thus, the findings suggest that appropriate interventions may be effective in combating some of the intellectual impairments incurred after early malnutrition.

Using this same cohort, Galler and Ramsey (1987) found that previously malnourished children younger than 14 displayed deficient performance on Piaget's tests of conservation. These differences were not entirely accounted for by IQ—suggesting these tasks assess slightly different cognitive domains. Contrasting to the persisting differences on measures of IQ, previously malnourished children performed equivalent to controls by age 14. This pattern is similar to that observed in the Galler et al. (1986) study in that it suggests that effects of an early nutritional insult, initially very salient, grow less robust with time. However, in a recent study, Galler and colleagues (Galler, Bryce, Waber, Zichlin, Fitzmaurice, & Eaglesfield, 2012) determined that at a 40-year follow-up, children who experienced PEM early in life demonstrated decreased earnings and reduced socioeconomic status in adulthood. The investigators acknowledged that the relationship became less robust once cognitive abilities were included in the model although the affect persisted (Galler, Bryce, Waber, Zichlin, Fitzmaurice, & Eaglesfield, 2012). this suggests early malnutrition can have long-lasting detrimental effects despite adequate provision of nutrition thereafter.

Another series of papers by Ivanovic and collaborators (2000, 2002) investigated the effects of severe early malnutrition on scholastic achievement, IQ, and brain morphology in Chilean high-school graduates. Formerly undernourished and never undernourished high-school graduates of low SES participated in this study. Researchers found that individuals with a history of early malnutrition obtained lower full-scale IQs (as assessed by the Wechsler Adult Intelligence Scale [WAIS]), lower scores on a scholastic aptitude test containing verbal and numerical items, and reduced brain volume on magnetic resonance imaging (MRI). The IQ results remained consistent across verbal and nonverbal domains in both sexes, whereas the brain volumetric difference—though significant in both sexes—emerged much more strikingly in males.

In a subsequent study with a similar population, Ivanovic et al. (2002) evaluated two groups of young adults with mean IQs of about 125 and 91, respectively. Both groups included individuals of high and low SES. They assessed participants with the same battery as in the 2000 study—adding intellectual testing of both parents. The researchers verified the occurrence of malnutrition in the first year of life by reviewing hospital records.

Results indicated that, regardless of SES, children with higher IQs had greater brain volumes, higher maternal IQ, better prenatal nutrition as indexed by birth weight, no evidence of postnatal nutritional deficits, and higher scholastic achievement. Maternal IQ, brain volume, and postnatal nutrition significantly related to young adult IQ. Early malnutrition rarely occurred within the high SES, low IQ group; however, this group evidenced lower maternal IQ when compared to the high SES, high IQ group. Conversely, 64% of individuals with low SES and low IQ had a history of early malnutrition, and this group, in general, had maternal IQs lower than the other three groups. Additionally, the researchers showed individuals within the low IQ group had similar maternal IQ, scholastic achievement, and brain volume. This led the authors to conjecture that these findings are typical correlates of low IQ.

Liu et al. (2003) assessed the effect of malnutrition at age 3 upon cognitive skills at age 3 and again at age 11 while attempting to statistically control for various psychosocial risk factors (e.g., living circumstances, parental education, age of mother at time of birth, presence of mental illness in the mother, and number of children living in the home).

Study participants included children living in the island of Mauritius and enrolled in the Mauritius Child Health Project—a prospective longitudinal study of children's physical and psychological health. At three years, children were assessed for several indicators of malnutrition: angular stomatitis, kwashiorkor, sparse fine hair, and anemia. These indicators are associated with deficiencies in vitamin A and B_2; protein, zinc, and copper; protein energy, zinc, and iron; and iron, respectively. The researchers considered a child malnourished if he or she displayed one or more of these four indicators. Assessments at age 3 included subtests from the Boehm Test of Basic Concepts—Preschool Version. Assessments at age 11 included: subtests from the WISC, Trails A & B (tests of executive functions), and a test of basic reading skills.

Results indicated that children malnourished at 3 years displayed overall intellectual and verbal cognitive deficits and continued exhibiting these deficits at age 11. Moreover, at age 11 these children exhibited deficits in nonverbal abilities, scholastic skills, reading abilities, and executive functioning. They found that even though malnourished children tended to have lower parental education and higher scores on measures of social stress, the effects of malnutrition remained significant when these factors were statistically adjusted for in the analysis. Additionally, this study reported a dose–response (i.e. monotonic) relationship between indicators of malnutrition and cognitive skills, as assessed by the WISC. Thus, children with three of four indicators of malnutrition at age 3 had IQs approximately 15 points below the mean, children with two indicators had IQs nine points below the mean, and children with one indicator had IQs only three points below the mean.

Anemia at age 3 years was the most significant indicator relating to lower cognitive performance at ages 3 and 11. The researchers acknowledged that they did not obtain nutritional information at age 11. Hence, it is possible these results could be explained by current or chronic malnutrition. Furthermore, the authors did not examine birth records. Therefore, factors such as birth weight or prenatal complications may have influenced the results. Nonetheless, this is a strong experimental design supporting the hypothesis that postnatal malnutrition has repercussions for later cognitive functioning. It also suggests trace nutrients such as iron are particularly important in the manifestations of malnutrition.

The unique impact of postnatal malnutrition and its relationship with other risk factors on cognitive development remains unknown. In general, the studies presented earlier suggest postnatal malnutrition is associated with discernable decreases in intellectual abilities (Berkman et al., 2002; Galler & Ramsey, 1987; Galler et al., 1986; Liu et al., 2003). Even though this assertion appears supported by the extant data, cautions similar to those detailed in the section regarding prenatal malnutrition still apply. For example, many of the studies did not directly assess potential confounding factors commonly associated with early malnutrition such as parental IQ, biological risks (birth complications, childhood diseases, or environmental toxins), and social variables (e.g., a chronically neglectful or understimulating environment; Berkman et al., 2002; Guesry, 1998; Liu et al., 2003; Pollitt 1969, Stein & Susser, 1985). Nevertheless, a majority of the studies reviewed indirectly assessed important variables and controlled for these variables in the subsequent analyses (Berkman et al., 2002; Galler et al., 1986; Galler & Ramsey, 1987; Liu et al., 2003) allowing us to be fairly confident in the assertion that postnatal malnutrition exerts deleterious effects on the developing brain. Indeed, the effect seems to have a particular sensitive period in the first postnatal year. Growth velocity prior to 1 year of age (but not afterward) predicts IQ at 9 years of age (Pongcharoen et al., 2012).

The studies leave open the question of amelioration of the effects of early malnutrition on the developing brain. Several studies addressing this point are now considered.

Studies that examine amelioration of early malnutrition investigate either strictly nutritional or combined environmental/nutritional interventions (Joos, Pollitt, Mueller, & Albright 1983; Lien, Meyer, & Winick, 1977; Pollitt, 1996; Raine et al., 2001; Raine, Mellingen, Liu, Venables, & Mednick, 2003; Winick, Meyer, & Harris, 1975; Zeskind & Ramey, 1981). The individuals in these studies are usually assumed to suffer from postnatal malnutrition although many of the investigations did not explicitly rule out the possibility of prenatal nutritional restriction.

Pollitt and his collaborators (1993) described a nutritional intervention in four rural Guatemalan villages (Pollitt, Gorman, Engle, Martorell, & Rivera, 1993). Beginning at various times during development (e.g., before conception, during gestation, throughout lactation, and into childhood), this project provided pregnant mothers and their children with either a high-protein, high-calorie drink known as Atole or a low-protein, low-calorie drink known as Fresco. The researchers fortified both beverages with trace minerals. Individuals in two villages received the Atole drink and individuals in the others received Fresco.

Children of low SES whose mothers received Atole during gestation and until at least age 2 outperformed their peers on tests of information processing, mental

ability, academic skills, and progressed further in school than children receiving Fresco. Low SES children with shorter and later (beginning at or after age 2) periods of exposure to Atole also benefited (scoring higher on tests of numerical and reading abilities and progressing further in school than their peers), although these findings were less striking. These results are interesting because they argue for a stable, long-term improvement in intellectual, academic, and cognitive skills resulting from prenatal through postnatal nutritional supplementation in undernourished populations. Moreover, they imply that supplementation has the greatest impact and benefit on low SES individuals, perhaps because it delivers help to the children who, without it, would have fared worst. They also illustrate the differential vulnerability (or plasticity) of the brain depending on the timing of the insult and intervention.

Using data from the Mauritius health project, Raine et al. (2001) investigated the effects of an enriched educational environment on orienting and physiological arousal (measured by electroencephalography). In this study, experimenters matched children based upon psychophysiological characteristics at age 3 and randomly assigned participants to an enriched preschool or to a standard preschool educational experience on the island of Mauritius. The enriched preschool employed various types of enriching experiences including well-balanced meals, education about nutrition and hygiene to parents and children, encouragement of imaginative play, interactive conversational skills, socialization, exercise, and regular field trips. Furthermore, parental involvement was highly encouraged, timeout discipline was used instead of corporal punishment, and the children's health was carefully monitored. The enriched experiences lasted for two years, at which time the children began grade school in typical classrooms.

Results indicated the enriched preschool experience related to increases in orienting and physiological arousal at age 11. The authors speculated that these findings provided evidence of improved information processing or accelerated neurological maturation in children enrolled in the enriched preschool. They acknowledged that, given the multi-factorial nature of the enriched experience, it was impossible to surmise which component or components explained these results although research suggests both nutritional and educational enrichment have unique effects on cognitive development (Grantham-McGregor, Powell, Walker, & Himes, 1991; Grantham-McGregor et al., 2014; Wachs et al., 2014). The results may be partially explained by long-term changes in parental or child behavior caused by the early preschool experience. For example, the parental education and increased parental involvement encouraged by the preschool may have been built upon and maintained after the child began grade school. Thus, the findings may represent the consequence of being raised in a more stable, lower stress home environment and not by neurological alterations directly induced by the preschool experience. Regardless, these findings suggest that long-term alterations in physiological parameters—considered to reflect neuronal processing (Williams et al., 2000)—secondary to environmental enrichment and nutritional supplementation (Grantham-McGregor et al., 2014). These results are fascinating because reduced orienting and arousal responses are associated with various types of psychopathology (Banaschewski et al., 2003; Perry, Felger, & Braff, 1998; Schnur et al., 1999).

The studies illustrate the potential benefits of nutritional supplementation and combined nutritional/environmental enrichment in chronically undernourished populations. However, undernourished children are frequently born with other genetic and environmental risks (Guesry, 1998; Pollitt 1969; Stein & Susser, 1985). This begs the question: can comprehensive environmental enrichment rescue a child with multiple risk factors including malnutrition (Grantham-McGregor et al., 2014)?

Winick et al. (1975) and Lien et al. (1977) addressed this question by investigating the intellectual performance of Korean children who suffered early malnutrition (prior to the age of 2), but were subsequently adopted into homes in the United States. Winick and colleagues (1975) showed that even the most severely malnourished children (below the third percentile for height and weight at or before age 2) made significant advances in their physical and intellectual development after adoption. Specifically, in middle childhood the previously malnourished children attained heights and weights above the standard for Korean children (although they continued to be smaller than American children). Furthermore, these children achieved IQ scores within the average range (mean of 102) and demonstrated academic performance comparable to their American peers.

The researchers suggested that these scores were substantially greater (in excess of 40 points) than would be expected if these children remained in restricted environments. Importantly, this study showed a significant difference between the IQs of previously malnourished adopted children and those of adopted children with no history of malnutrition (mean IQ of the latter group was approximately 112). Winick and colleagues conjectured these differences were partially genetic (the parents of undernourished children being more likely to have lower

intellectual abilities), or a consequence of the nutritional deficits (i.e., the previously malnourished children had not been able to benefit as much from the adopted environment). Unfortunately, it is difficult to disentangle these possibilities without an assessment of parental IQ or a sibling design in which the other sibling was not malnourished.

Lien et al. (1977) examined the roles of malnutrition on the cognitive development, growth, and academic achievement in Korean children adopted later in childhood (between 2 and 5 years of age). The researchers again found that severely, moderately, and nonmalnourished adopted children attained weight and height above standards for Korean children but below those of American children. However, they found that severely malnourished children attained IQ scores significantly lower than American children and their nonmalnourished adopted peers. Results also indicated that severely malnourished late adoptees had academic achievement scores below their American classmates and their late adopted peers.

The effect of nutritional deficits on academic performance remained significant when age of adoption and age of placement with the adoption agency were taken into account. (This analysis was not completed on the IQ information because of the relatively small number of cases with this information provided.) Interestingly, the authors found a significant effect for age of adoption on academic performance, but no evidence relating academic performance to duration of malnutrition or for an interaction between any of these factors. Secondary factors (e.g., behavioral or emotional concerns) may explain both later age of adoption and below average performance on IQ and academic tests, but more would have to be known about a child's preadoptive history to completely discount this confound.

These two studies provide evidence for improved cognitive and scholastic performance following severe malnutrition in adopted children removed from pathological environments. However, the results of the second study suggest there is a critical period in which environmental enrichment will be maximally beneficial and after which recovery is either slowed or attenuated.

We have seen that environmental enrichment (of varying degrees and types) is able to ameliorate some of the detrimental effects of malnutrition on cognitive skills; however, a subsequent question asks, would enrichment contribute to a reduction in psychiatric correlates of malnutrition? This is especially interesting because, based upon the discrepant findings of Stein et al. (1972) and Susser et al. (1996) with regard to the effect of prenatal famine exposure on cognitive deficits and schizophrenia, it appears likely that psychopathological conditions may be more sensitive to diffuse neurological disruptions than cognitive abilities, which themselves appear more sensitive than current measures of neuropathology.

In a follow-up to their 2001 study, Raine et al. (2003) address the previous question. This study reported that children who experienced the enriched preschool environment exhibited significantly fewer conduct problems and schizotypal personality traits at age 17, and reduced self-reported levels of criminal offending at age 23. Court records of criminal offenses trended toward fewer offenses in the enriched group, but this did not reach conventional levels of statistical significance. Furthermore, the data showed significant interactions between environmental enrichment and early nutritional status. Thus, individuals with poorer nutritional status assessed at 3 years of age (see Liu et al., 2001) prior to the enriched preschool intervention demonstrated significant benefits from the program. Specifically, in addition to the results presented before, the undernourished group evidenced reduced interpersonal deficits at age 23 when compared to undernourished nonenriched controls. Subsequent analyses to account for psychosocial risk factors (see Liu et al., 2001) and physiological factors at age 3 revealed no moderating effects or changes in the results.

The authors argue that their findings indicate long-term behavioral benefits of enriched environmental experiences, and a particularly striking long-term improvement in functioning of previously malnourished children. They acknowledge the aspects of the enriched preschool experience contributing the most to the observed differences cannot be identified. However, they contend that the improved nutrition offered by the preschool likely played a role, especially with regard to the children who had previous nutritional deficits. This hypothesis is consistent with the findings of other research studies indicating a unique effect of nutritional supplementation on cognitive development (Grantham-McGregor, 2014; Grantham-McGregor et al., 1991).

Research indicates that environmental enrichment moderates the effects of malnutrition, albeit through direct supplementation or combined nutritional and educational enrichment. Some questions remain as to how permanent and significant these effects are, but certain data indicate if undertaken early in development and for a sufficient duration the beneficial effects of environmental enrichment can become stable and long lasting (Lien et al., 1977; Pollitt, 1996; Raine et al., 2001; Winick et al., 1975). However, it would be naïve to assume that all

insults, regardless of severity or genetic diathesis, can be completely alleviated by high quality schools, nutritional supplementation, and supportive parenting (Lien et al., 1977; Pollitt, 1996). No matter the interventions employed, one cannot help but suspect that some conditions remain resistant to complete amelioration. At the same time, the inherent adaptability and plasticity of the nervous system, both in children and adults, attests to the fact that some improvement in many conditions is possible, given proper stimulation (Huntley & Jones, 2002; Nelson, 1999). For example, the studies described by Pollitt (1996) suggest that in malnourished, low SES populations, nutritional supplementation alone can have a long-term ameliorative impact on cognitive functioning. Furthermore, the reports by Lien et al. (1977), Winick et al. (1975), and Zeskind and Ramey (1981) give hope that even individuals with risk factors across multiple domains can profit from quality environmental circumstances. Essentially, plasticity exists; however, recovery from early insults such as malnutrition is likely to be incomplete.

In summary, the studies discussed in this section indicate early malnutrition has discernable effects upon cognitive skills throughout all periods of brain development (gestational and postnatal). However, research also suggests that there is potential for catch-up brain growth and improved intellectual and behavioral development if nutritional needs are restored. Additionally, other studies suggest that educational and environmental manipulations may also contribute to improved outcomes following early malnutrition. It is possible that some of the manifestations of malnutrition reported in this section (e.g., reductions in intellectual and certain cognitive abilities) may have resulted from impairments secondary to various psychiatric symptoms such as inattention or anxiety. However, with the exception of the Galler and Ramsey (1989) study these two factors appear to have not been measured concurrently. At this point, the discussion will again move down another level and focus on findings which shed light upon the effects of early malnutrition on the structure and function of the developing and mature brain.

NEUROBIOLOGY OF NUTRITIONAL EFFECTS: EVIDENCE FROM BENCH SCIENCE

Early Life Macronutrient Undernutrition

Many studies link early undernutrition to disturbances in neurotransmitter development and function and to neuroanatomic abnormalities including fine structures (e.g., dendritic spines) and specific regions such as the hippocampus (Almeida, Tonkiss, & Galler, 1996b; Hernandez-Rodriguez & Manjarrez-Gutierrez, 2001; Morgane et al., 1993; Morgane et al., 2002; Wauben & Wainwright, 1999; Wiggins, Fuller, & Enna, 1984). These are important factors to consider because changes in brain morphology and physiology caused by malnutrition may be similar to the biological alterations observed in various psychopathologies (Brown et al., 1996).

Neurotransmitters and their receptors are important determinants of brain development before they become a critical part of the information processing activities of neurons (Benes, Bolte-Taylor, & Cunningham, 2000; Berger-Sweeney, 1998; Bonhoeffer & Yuste, 2002; Fernandez-Ruiz, Berrendero, Hernandez, Romero, & Ramos, 1999; Franciosi, 2001; Heine, 1999; Ma et al., 2000; Nguyen et al., 2001; Retz, Kornhuber, & Riederer, 1996; Van Kesteren & Spencer, 2003; Whitford, Dijkhuizen, Polleux, & Ghosh, 2002). Thus, if early malnutrition disturbs the balance of neurochemical systems, it could result in structural or behavioral alterations (Alvarez et al., 2002; Wauben & Wainwright, 1999; Wiggins et al., 1984).

Disruption of neurotransmitter systems due to early malnutrition could directly or indirectly affect brain development (Wauben & Wainwright, 1999). That is, a neurotransmitter may directly induce a developmental process (e.g., GABA in promoting proliferation of neuronal progenitors, acetylcholine's involvement in apoptosis, serotonin's role in synaptogenesis, and glutamates regulation of dendritic spine formation; Nguyen et al., 2001). Therefore, if early malnutrition greatly reduces or augments neurotransmitter concentration, normal processes may not occur, or may occur in an abnormal fashion (Wauben & Wainwright, 1999). Alternatively, a neurotransmitter may be responsible for modulating other neurotransmitters, growth factors, or signaling molecules (e.g., cytosolic calcium levels, immediate early gene expression, or the mitogen-activated protein kinase cascade), which in turn regulate other developmental processes (Wauben & Wainwright, 1999). All of these downstream events could be disrupted by abnormal neurotransmitter concentrations resulting from malnutrition (Evrard, Marret, & Gressens 1997; Wauben & Wainwright, 1999).

The amino acids tryptophan and tyrosine are precursors of the neurotransmitters serotonin and dopamine, respectively (Benes et al., 2000; Wauben & Wainwright, 1999). The blood brain barrier contains transporters for these amino acids, which are not directly synthesized in the brain (Wauben & Wainwright, 1999). Therefore, adequate dietary intake is essential in order to maintain proper central nervous system (CNS) concentrations

of these compounds. Serotonin is involved in neuronal proliferation, differentiation, glia formation, and synaptogenesis (Gaspar, Cases, & Maroteaux, 2003; Morgane et al., 1993; Okado, Narita, & Narita, 2001; Wauben & Wainwright, 1999).

Hernandez-Rodriguez & Manjarrez-Gutierrez (2001) found increased tryptophan uptake across the blood brain barrier and serotonin synthesis within the brain of gestationally malnourished rats. They observed these differences through weaning, and the increased serotonin synthesis continued after nutritional rehabilitation and normalization of tryptophan uptake. Based upon these animal studies and human research suggesting analogous patterns of plasma tryptophan ratios, these researchers postulated similar outcomes are likely in human infants suffering from prenatal malnutrition (see Hernandez-Rodriguez & Manjarrez-Gutierrez, 2001, for review).

Manjarrez et al. (2003) conjectured the increased concentration of serotonin observed in undernourished animals results in a desensitization of the serotonergic system secondary to chronic overactivation (Manjarrez, Manuel, Mercado, & Hernandez, 2003). Prenatally malnourished adult and adolescent rats also displayed decreased serotonin uptake sites, decreased serotonin fiber density, and enhanced serotonin release following hippocampal stimulation (Blatt, Chen, Rosene, Volicer, & Galler, 1994; Chen, Tonkiss, Galler, & Volicer, 1992; Mokler, Galler, & Morgane, 2003). In addition, prenatally and postnatally malnourished animals exhibit deficits in adaptation of the serotonergic system in response to chronic stress (Almeida et al., 1996; Mokler et al., 2003). Other studies indicate that a history of PEM decreases extracellular dopamine in the medial prefrontal cortex of adult rats and alters both dopamine and serotonin release in the cortex and hippocampus (Mokler, Torres, Galler, & Morgane, 2007). Together, these results suggest that prenatal malnutrition can lead to long-lasting or even permanent alterations of the serotonergic system—potentially contributing to the later development of psychopathology (Benes et al., 2000; Fishbein & Pease, 1994; Hernandez-Rodriguez & Manjarrez-Gutierrez, 2001; Manjarrez et al., 2003).

Pre/postnatally undernourished animals also demonstrate reduced reactivity to pharmacological manipulations of the catecholaminergic system (Almeida et al., 1996; Chen, Turiak, Galler, & Volicer, 1997; Soto-Moyano et al., 1999). For example, early malnourished animals showed an attenuated response to dopamine agonists that induced stereotyped motor behaviors, reduced sensitivity to catatonic symptoms caused by dopamine antagonists, and a developmental delay in the induction of hypoactivity after administration of an adrenergic agonist (clonidine) (Almeida et al., 1996; Bredberg & Paalzow, 1990; Goodlett, Valentino, Resnick, & Morgane, 1985). Other studies show decreased concentrations of dopamine and epinephrine receptors in specific brain regions of animals exposed to early undernutrition (Almeida et al., 1996; Wiggins et al., 1984).

Almeida and colleagues (1996) conjecture these modifications are an adaptive response to initially high levels of catecholamines during brain development in undernourished animals. However, findings of increased sensitivity to the hypothermic effects of apomorphine (a dopamine agonist) but decreased sensitivity to the hypothermic effects of clonidine suggest a more complex picture in which pre/postnatal malnutrition has a differential impact on various subtypes of catecholaminergic receptors and on receptors within certain brain regions (Almeida et al., 1996; Brioni & Orsingher, 1987). For example, using a mild (8%) protein depleted diet, Soto-Moyanoa and collaborators found increased norepinephrine release and neuronal density only within the occipital cortex of prenatally malnourished rats (Soto-Moyanoa et al., 1999). Again, early malnutrition appears to cause alterations within the catecholaminergic system regardless of the precise dietary manipulation.

Prenatally malnourished animals exhibit reduced sensitivity to the effects of benzodiazepines (BZs) (Almeida et al., 1996; Masur & Ribeiro, 1981; Tonkiss et al., 2000; Tonkiss, Trzcinska, Shultz, Vincitore, & Galler, 2000). This class of drugs potentiates the actions of the inhibitory neurotransmitter GABA (Almeida et al., 1996). Researchers observed long-term changes in sensitivity to BZs, similar to those found in the serotonergic system, during malnutrition and following nutritional rehabilitation (Almeida et al., 1996; Tonkiss et al., 2000).

Tonkiss and coworkers (2000) studied spatial learning in prenatally malnourished rats following administration of the GABAergic agonist chlordiazepoxide (CDP) at 30 and 90 days after birth. They found prenatally malnourished animals responded less than control animals to a high dose of CDP at both 30 and 90 days of age, but at 90 days the previously malnourished animals displayed greater sensitivity to a lower dose of CDP when compared with well-nourished controls. A possible reason for these differential responses may be that the drug exerts certain effects (e.g., anxiolytic versus amnesic) at high and low doses respectively. The researchers concluded that differences between the GABAergic system of malnourished and well-nourished animals resulted in differential responses to

CDP depending on age of administration and particular dosage of the drug.

Researchers have linked early malnutrition to reduced levels of GABA transmitter and increased binding of GABA and BZs to the GABA receptor complex within the CNS of rodents (Almeida et al., 1996). It is probable the alterations in GABA binding and concentration underlie the attenuated responses to BZs, and result from permanent changes in this neurotransmitter system directly caused by early malnutrition (Almeida et al., 1996; Chang, Galler, & Luebke, 2003). Again, changes in this system appear consistent across dietary manipulations, ages, and strains of animals used; therefore, they likely represent actual effects of early malnutrition and are not simply a byproduct of a specific experimental design (Almeida et al., 1996). Changes in the developing GABA system are significant because GABA is a very active transmitter in early cortical development (Ben-Ari, 2002; Davies et al., 1998).

Early malnutrition is associated with lower sensitivity to drugs acting on the opiate system; however, studies showing specific receptor changes have not been completed (Almeida et al., 1996). Similarly, studies indicate reduced cholinergic function within the early malnourished rats (Almeida et al., 1996). Specifically, differences in muscarinic receptor density, binding, and developmental course within different brain regions are seen in previously malnourished rats (Almeida et al., 1996). However, too few studies have been completed to draw firm conclusions regarding the effect of early malnutrition on the cholinergic system with relevance to possible behavioral effects (Almeida et al., 1996).

Tonkiss, Almeida, & Galler (1998) used an operant procedure to show that prenatally undernourished female rats displayed sensitivity to the blockade of glutamate receptors with an N-methyl-D-aspartate (NMDA) antagonist (MK-801). The NMDA receptor is a type of glutamate receptor highly concentrated in the hippocampus and is thought to play a critical role in learning and memory (Cui et al., 2004; Nakazawa et al., 2003; Roesler et al., 2003). Tonkiss and coworkers trained rats to a stable level of performance on a differential reinforcement of low-rates (DRL) task. On this particular DRL schedule, animals did not receive a reward unless they separated their responses by at least 18 seconds. After attaining a stable performance, the researchers administered MK-801 at various doses. Results indicated the performance of prenatally malnourished female, but not male, rats was disrupted after MK-801 administration. This experiment is interesting because it is one of the few studies to examine sex differences in generalized prenatal malnutrition. Although speculative, the increased sensitivity to NMDA blockade in prenatally malnourished females may be the result of loss or dysfunction of NMDA receptors in the hippocampus of these animals (Salinas, personal communication). This explanation is consistent with histological findings in other neurotransmitter systems showing decreased concentrations of various receptor types following nutritional insults (Almeida et al., 1996; Wiggins et al., 1984).

Alternatively, Fiacco and colleagues (Fiacco, Rosene, Galler, & Blatt, 2003) reported that prenatally malnourished rats displayed persistent increases in the concentration of kainate receptors (another type of glutamate receptor) within the CA3 subregion of the hippocampus—a region implicated in recognition memory (Fiacco et al., 2003; Lee & Kesner, 2003). These differences persisted through 220 days of age, but they did not emerge until 30 days after birth. Furthermore, Palmer, Printz, Butler, Dulawa, and Printz (2004) found evidence of increased NMDA receptor binding in the striatum of prenatally protein malnourished animals, but they observed no differences in NMDA receptor binding in the hippocampus or dopamine receptor binding in the striatum. These studies suggest that changes in the glutamate system occur in rats secondary to prenatal malnutrition; however, more studies need to be completed to specify the precise nature of these changes across brain regions, age, sex, and subtypes of glutamate receptors.

The aforementioned research indicates that early malnutrition appears to perturb an animal's responsiveness to pharmacological manipulation of various neurotransmitter systems (Almeida et al., 1996). Many studies show decreased receptor density for several types of neurotransmitters (dopamine, epinephrine, serotonin, acetylcholine, and GABA (Almeida et al., 1996). Researchers postulate that this represents an aspect of homeostatic functioning in early malnutrition in that down-regulation of receptors occurs in response to higher-than-normal levels of neurotransmitter during development (Almeida et al., 1996; Manjarrez et al., 2003). In addition, malnourished animals show decreased adaptations of the serotonergic and opioid systems in response to stress—possibly indicating permanently altered system dynamics (Almeida et al., 1996; Mokler et al., 2003). Essentially, malnutrition may exert its effects upon neurochemistry not solely by affecting a single neurotransmitter system, but rather by perturbing the intricate balance between systems in the developing brain.

The changes in neurotransmitter systems described here appear to alter how an animal reacts and interacts with its environment. Therefore, if similar biochemical changes

occur in the developing human brain, one could speculate these perturbations will also result in modifications of behavior (Almeida et al., 1996). These behavioral changes may represent interesting correlates of certain forms of psychopathology (Almeida et al., 1996). For example, Almeida et al. (1996) reported on a study that found, when compared to well-nourished controls, postnatally malnourished animals exhibited an anxiolytic reaction similar to that of panic disorder patients after chronic administration of either a tricyclic antidepressant or a monoamine oxidase inhibitor. Furthermore, numerous studies have linked dysfunction of neurotransmitter systems to the expression of various forms of psychopathology (Fishbein & Pease, 1994; Kaufman, Plotsky, & Nemeroff, 2000; Konradi & Heckers, 2003). In addition to effects on the organization of developing neurotransmitter systems, malnutrition affects structures within the brain such as the hippocampal formation. This brain region is particularly susceptible to a wide range of early insults and is implicated in various types of psychopathology (Arango, Kirkpatrick, & Koenig, 2001; De Bellis et al., 2000; Harry and Lefebvre-d'Hellencourt, 2003; Heckers et al., 1998; Kimura, Reynolds, & Brien, 2000; Korte, 2001; Laakso et al., 2000, 2001; Walsh & Emerich, 1988).

Early malnutrition results in decreased serotonergic innervation to the hippocampus due to decreased projections from the median raphe nucleus (Morgane et al., 2002). However, as noted previously, early malnutrition results in increased serotonin release within the hippocampal formation proper. The authors propose the disruption in input and local neurotransmitter concentration within the hippocampus leads to increased GABAergic activity in select inner neurons (Chang et al., 2003; Mokler et al., 2003; Morgane et al., 2002). Subsequently, this results in more inhibition of certain hippocampal regions, thereby potentially affecting information outflow and integration (Morgane et al., 2002).

Malnutrition results in deficits in long-term potentiation (LTP; Jordan & Clark, 1983), which is considered a candidate mechanism for learning and memory processes (Bliss & Collingridge, 1993; Kandel & Schwartz, 1982; Martin & Morris, 2002). Early PEM also effects LTP within the entorhinal cortex and decreases release of brain derived neurotrophic factor within the CA1 region of the hippocampus (Hernández et al. 2008). Other studies suggest perturbations of hippocampal inhibitory mechanisms produce asynchronous activity of neuronal networks—potentially leading to decreased hippocampal plasticity (Morgane et al., 1993). Jordan and collaborators suggested that malnutrition induces changes at the level of hippocampal synapses (Jordan, Howel, McNaughton, & Heatli.e., 1982). A recent study by Matos and colleagues (2011) found that a history of early malnutrition in a rodent model resulted in impaired cell proliferation in the dentate gyrus of the hippocampus. Early malnutrition appears to disturb hippocampal function through a variety of mechanisms (Morgane et al., 2002).

Early PEM is associated with a reduction in dendritic spine density and with abnormal spine morphology in the hippocampus, cerebral cortex, and cerebellum (Benítez-Bribiesca, De la Rosa-Alvarez, & Mansilla-Olivares, 1999; Fiala, Spacek, & Harris, 2002). A dendritic spine is a plastic structure frequently found in the cortex and is thought to play an important role in stimulus encoding and information processing (Bonhoeffer & Yuste, 2002; Coss & Perkel, 1985; Fiala et al., 2002; Segal, 2001; Whitford et al., 2002). Malnutrition may result in anomalies of spine number and shape of pyramidal cells within cortical layers three and five and CA3 region of the hippocampus and of granule neurons within the dentate gyrus (Fiala et al., 2002). Cerebellar granule cells, Purkinje cell spines, and giant spines are reduced in early malnutrition (Fiala et al., 2002). These findings are important because research indicates dendritic spine abnormalities exist in conditions such as mental retardation (Fiala et al., 2002).

The previous discussion supports the assertion that early malnutrition can result in distinct changes in brain neurochemistry and delicate morphology (Almeida et al., 1996; Fiala et al., 2002). However, the process of brain development is likely significantly protected (through various homeostatic and placental mechanisms) from many harmful environmental influences. This being said, the developing organism can only compensate so much before long-term changes in the chemical composition or structural organization of the developing brain result. The precise nature and extent of these changes may vary between individuals, although some general patterns (e.g., elevation of neurotransmitter concentrations and pathological dendritic spine formation) likely exist.

Although specific pathological mechanisms explaining behavioral changes are unclear, developmental alterations of neurochemistry, neurophysiology, and brain morphology resulting from early malnutrition implicate candidate mechanisms that could account for behavioral deficits. Research indicates that chronic changes in various neurotransmitter systems can affect levels of growth factors, gene expression, functioning of other transmitter systems, and the ability to acquire certain types of learning (Dudman et al., 2003; Kesslak, Chuang, & Berchtold, 2003; O'Donnell, Stemmelin, Nitta, Brouillette, & Quirion,

2003; Paule et al., 2003). Researchers have identified all of these factors as necessary components of typical central nervous system development (Acampora, Gulisano, & Simeone, 1999; Bar & Goffinet, 1999; Black, 1998; Cirulli, Berry, & Alleva, 2003; Cowan, 1998; Lyons et al., 1999; Nelson, 2000b; Rutter & O'Connor, 2004; van Kesteren & Spencer, 2003). Therefore, significant or persistent dysfunctions in these systems (secondary to early malnutrition) may contribute to abnormal neurological development. Work by Gietzen and others reveals that reductions of specific amino acids result in altered gene expression and changes within various neurotransmitter systems (Blevins, Teh, Wang, & Gietzen, 2003; Gietzen & Magrum, 2001; Gietzen, Ross, Hao, & Sharp, 2004; Jousse et al., 2004; Truong, Magrum, & Gietzen, 2002). These cascading effects provide a plausible mechanism for the effect of macronutrient malnutrition on neurobiology and behavior—i.e., malnutrition causes decreases in important neurotransmitter systems, thus resulting in changes in growth factor concentration and in gene expression, eventually leading to modifications of behavior.

The discussion here has focused on generalized caloric restriction/macronutrient deficiency. The reason for this emphasis is practical in that this is where many researchers have concentrated their efforts. However, as noted in the introduction, certain micronutrient deficiencies are associated with deviant brain development. Therefore, although little research exists directly linking specific micronutrient deficiencies to psychopathological outcomes, it is important to review briefly some of the extant research concerning the effect of specific micronutrient deficiencies on brain development.

Early Life Micronutrient Undernutrition

As stated previously, it is common for deficits in micronutrients to accompany generalized protein energy undernutrition (Gorman, 1995; Kretchmer et al., 1996); conversely, it is possible to have deficits in specific micronutrients without concomitant caloric or protein restriction (Brozek, 1990; Georgieff & Rao, 2001; Fuglestad et al., 2008). The latter scenario is more common in developed versus developing countries (Brown et al., 1996). As discussed already, Brown and colleagues (1996) postulated deficiencies in specific micronutrients (such as folate) more fully explain the findings within the Dutch hunger winter cohort. Numerous studies have repeatedly allied early deficits of iron, zinc, and iodine with aberrant brain development and decreased cognitive skills—thus this brief discussion focuses on these elements (Georgieff & Rao, 2001; Kretchmer et al., 1996; Wachs et al., 2013; Yi-Ming, 1996).

Some studies have stressed the necessity of adequate levels of other micronutrients (such as vitamin B-6, selenium, manganese, copper, and choline) for proper neuronal development; however, they have been studied less extensively, especially with regard to human brain development and cognition (Castano et al., 1997; Craciunescu, Albright, Mar, Song, & Zeisel, 2003; Fisher, Zeisel, Mar, & Sadler, 2002; Fuglestad et al., 2008; Groziak & Kirksey, 1990; Guilarte, 1989, 1993; Keen et al., 1999; McCullough et al., 1990; Prohaska, 2000; Watanabe & Satoh, 1994; Yi-Ming, 1996; Zeisel, 2000). However, several studies have linked decreased periconceptional folate concentration to the development of neural tube defects in the progeny of some individuals (Czeizel & Dudas, 1992; Hibbard & Smithells, 1965). Brown et al. (1996) conjectured an association between prenatal folate deficiency and the development of schizophrenia. Furthermore, investigators have observed lower folate levels in depressed adults, but the etiology or significance of these reductions (i.e., if they represent a symptom or contributor to depression) is unknown (Alpert & Fava, 1997).

Iron

Iron deficiency is one of the most common forms of undernutrition in the world (Lozoff, 1989). Its postnatal cause is chronic undernutrition or consumption of foods low in dietary iron combined with loss of gastrointestinal blood (which contains iron) due to intestinal infestations. This etiology is found primarily in developing countries. Neonatal iron deficiency is also caused by maternal gestational iron deficiency, usually found in developing countries and by conditions such as maternal diabetes or IUGR in developed countries (Georgieff & Rao, 2001; Petry et al., 1992; Siddappa et al., 2007). A significant body of work has connected early iron deficiency (ID) to disturbances in myelination, neurotransmitter systems, metabolism, and hippocampal morphological development (Beard, 2003; DeUngria et al., 2000; Jorgenson, Wobken, & Georgieff, 2003; Kwik-Uribe, Gietzen, German, Golub, & Keen, 2000; Lozoff, 1989; Lozoff & Georgieff, 2006; Roncagliolo, Garrido, Rao, Tkac, Townsend, Gruetter, & Georgieff, 2003; Walter, Peirano, & Lozoff, 1998).

Furthermore, behavioral studies with animals have shown perinatal ID results in impaired performance of hippocampally dependent tasks, lower environmental reactivity, and decreased motor skills (Carlson, et al., 2010; Felt & Lozoff, 1996; Schmidt, Waldow, Salinas, & Georgieff, 2007). Studies conducted with ID infants and

children have revealed deficits in motor skills, sensory processing, recognition memory, visuospatial abilities, language skills, inhibitory control, set-shifting, planning, attention, and academic performance—some of which may persist after iron repletion (Lozoff et al., 2003; Lozoff, Jimenez, Hagen, Mollen, & Wolf, 2000; Lukowski et al. 2010; Nelson, Wewerka, Borscheid, DeRegnier, & Georgieff, 2003; Roncagliolo et al., 1998; Stoltzfus et al., 2001). Lozoff and colleagues (2003) demonstrate that ID children are less socially interactive, display more inefficient information processing, and exhibit reduced activity in their physical environment. Thus, they propose ID infants are less likely to receive sufficient environmental stimulation (Lozoff et al., 2003).

There is well documented evidence that ID in children has a significant influence on cognitive development and intelligence, however there are more recent associations with ID and childhood and adolescent-onset psychiatric disorders. It has been postulated that the alterations in monoamine transmitters and abnormal myelination associated with ID may be related to several psychiatric disorders (Chen et al. 2013). Numerous studies have reported the association of iron deficiency anemia (IDA) with unipolar depressive disorder (Bodnar et al. 2005; Yi et al. 2011; Lozoff et al. 2000). In a longitudinal cohort study of 191 participants, those with IDA in infancy exhibited more depression, anxiety, social problems, and attentional problems later in life (Lozoff et al. 2000; Lukowski et al. 2010). Results of a study of 192 female medical students found the mean ferritin was significantly lower in students with depression than in healthy students (Sharitpanaahi et al., 2007).

Although studies of iron deficiency and the pathophysiology of ADHD, autism, and schizophrenia have been somewhat inconsistent, there have been several important associations demonstrated. Cortese et al. used magnetic resonance imaging to demonstrate that children with ADHD had significantly lower brain iron levels in the thalamus compared to healthy controls (Cortese et al., 2008). An increased risk of ADHD in ID was also shown in a meta-analysis by Tan et al. in 2011. In a study of 96 children with autism spectrum disorder (ASD) by Latif et al., there was an increased prevalence of ID as analyzed by serum ferritin in children with ASD. Up to 30 percent of the children with ASD had significant ID (Latif et al., 2002). Insel et al. studied a population-based cohort born from 1959–1967 and identified that maternal iron deficiency may be a risk factor for schizophrenia spectrum disorders among offspring in adulthood (Insel et al., 2008). Another population-based study in Denmark has identified a similar increased risk of schizophrenia spectrum disorder with maternal iron deficiency (Sorensen et al., 2011). All of these research studies support the emerging evidence that iron deficiency early in life may lead to long-lasting neural and behavioral changes in children.

Iron has been documented to be important in socio-emotional development and therefore ID may lead to alterations in the development of emotion regulation. Mechanisms for ID leading to emotion dysregulation were reported by Phillips et al. (2006) and Stein et al. (2009). Due to ID induced changes in the dorsal and ventral prefrontal cortices, the limbic circuitry, and the hippocampus, ID has been plausibly associated with bipolar disorder, anxiety disorder, and tic disorders. Again in the Lozoff cohort, 25 year follow up demonstrated a direct path for chronic iron deficiency and more detachment and dissociation as adults (Lozoff et al., 2013). Although direct causality between IDA and psychiatric disorders is difficult to prove, the repeated associations identified in these studies warrants further investigation into causality and comorbid effects of ID and psychiatric disorders.

Iodine

Iodine is a necessary for maintaining adequate brain thyroid status. In the late 1990s, estimates indicated that approximately one billion people in the world were at risk for iodine deficiency (Yi-Ming, 1996). Severe maternal iodine deficiency in the preconception period (usually attributed to hypothyroidism) is associated with the development of severe mental retardation secondary to endemic cretinism (Pharoah et al., 1971). Moreover, moderately iodine deficient children display minor (but significant) increases in reaction time and decrements on neuropsychological measures of verbal information processing, attention, and visual-motor integration (Fenzi et al., 1990; Lombardi et al., 1995). These studies suggested that the differences were time-limited and amenable to amelioration with iodine therapy. Additionally, periconceptional injection of iodized oil in at risk populations is effective in attenuating the incidence of endemic cretinism and subsequent mental retardation (Pharoah et al., 1971). Conversely, prolonged childhood iodine deficiency may lead to lower achievement motivation and decreased learning speed, both of which become more striking with increasing age (Tiwari, Godbole, Chattopadhyay, Mandal, & Mithal, 1996). Again, no investigations have specifically examined any possible connections between early iodine deficiency and the development of mental illness (with the well-established connection between maternal iodine deficiency and mental retardation being the exception).

Zinc

Zinc is an important component of many enzyme systems and has been localized to presynaptic vesicles within limbic and cortical regions of the brain (Frederickson & Danscher, 1990; Johnson, 2001; Tuormaa, 1995). Zinc deficiency is associated with growth retardation and impaired hippocampal functioning (Sandstead et al., 1998; Tuormaa, 1995). Zinc is also critical for axonal transport and proliferation during neuronal development (Tuormaa, 1995). Animals made zinc deficient early in gestation commonly experience fetal reabsorption or spontaneous abortion (Tuormaa, 1995). Zinc deficiency in latter gestation or lactation results in decreased forebrain and hippocampal size as well as reductions in total cell numbers (Duamah & Russell, 1984; Tuormaa, 1995).

Some researchers have linked zinc deficiency to increased hyperactivity, apathy, lethargy, sleep problems, poor appetite, aggression, and irritability (Tuormaa, 1995). Others have hypothesized that maternal zinc deficiency during gestation results in permanent alterations of neurological development, which may eventually manifest as psychiatric or neurological conditions (such as schizophrenia, autism, epilepsy, and Parkinson's disease) (Johnson, 2001). Lower serum zinc levels have been demonstrated in unipolar depression (Maes et al., 1994; Manser et al., 1989; Nowak et al., 2005). The severity depression has been negatively correlated with the serum level of the zinc ion as well (Nowak et al., 1999, 2005; Schlegel-Zawadzka et al., 2000). Despite the potential seriousness of zinc deficiency, a study by Sandstead and colleagues (1998) reported that zinc-deficient children showed improved neuropsychological test performance after 10 weeks of zinc supplementation, leaving open the possibility of successful zinc rehabilitation.

Summary of Micronutrient Deficiencies

Overall, data indicate that specific micronutrient deficiencies can affect brain growth, cognitive development, and behavior. Nevertheless, adequate experiments explaining how deficits in these specific micronutrients result in the development of psychopathology (with the exception of mental retardation) have not been conducted. Examples of this approach would include DNA microarray, proteomic, and metabolomic assessments of targeted brain regions or processes (e.g., myelination, migration) following specific timed nutrient deficiencies. The expectation would be to identify genes and gene products that mediate neuronal form and function. For example, studies investigating the hypothesized connection between prenatal folate deficiency, potential migration defects, and the later development of schizophrenia could be addressed using such an approach. Studies of this kind are particularly important, given the significant number of individuals (in both developed and developing countries) affected by early micronutrient deficiencies, both apart from and in combination with generalized malnutrition.

FUTURE DIRECTIONS

A major issue that future research should specifically address is the significance (i.e., magnitude of the effect) of malnutrition in the development of psychopathology. Thus, does early malnutrition independently increase the risk for the development of psychopathology, or is it merely one of many important factors that when combined have a deleterious effect? Similarly, the developmental psychopathology constructs of equifinality (i.e., different developmental pathways leading to the same outcome) and multifinality (i.e., the same precipitating event resulting in numerous developmental trajectories) need to be explored with regards to early malnutrition (Cicchetti & Toth, 2009). For example, it is possible that individuals exposed early in life to less than ideal nutritional circumstances may have different psychopathological or resilient outcomes depending on their genetic predispositions, rearing environments, or level of nutritional supplementation (multifinality). Alternatively, the same psychopathological outcomes could be contributed to by more than one type of nutritional deficiency (equifinality).

Explaining how early malnutrition exerts negative effects on the developing nervous system is also a critical direction for future investigations. Possible neuropathogenic mechanisms of early malnutrition can be broken down into direct and indirect effects. Direct effects refer to those that are the primary result of malnutrition and are considered to underlie the subsequent pathology (e.g., disrupted neurotransmitter function, brain morphology, or myelination). These primary effects could potentially work through direct nutrient contact with DNA promoter regions (as seen with zinc) or at any other post-transcriptional regulatory sites. Indirect effects refer to effects that may potentiate other pathological processes or conditions associated with a pernicious outcome, for example where the nutrient deficiency affects pregnancy integrity, maternal stress levels, or maternal parenting style. Other indirect effects could occur through nutrient deficiency effects on metabolism that in turn influence fetal programming of brain development. It should be noted

that none of the aforementioned mechanisms has been irrefutably linked to the development of psychopathology. They are merely presented here as possibilities to be considered; however, investigating all of these potential mechanisms would be fruitful grounds for future scientific inquiry.

Future research will need to take the knowledge gained at the regulatory level and apply it to physiologic studies at the systems level. For example, many studies have associated disturbances in various neurotransmitter systems (e.g., monoamenergic and glutamatergic) with psychiatric disorders including schizophrenia, depression, and anxiety (Fishbein & Pease, 1994; Kaufman et al., 2000; Konradi & Heckers, 2003). Furthermore, evidence indicates that early malnutrition (or deficiencies in micronutrients such as iron) results in alterations in the development and eventual functioning of certain neurotransmitter systems (Hernandez-Rodriguez & Manjarrez-Gutierrez, 2001; Manjarrez et al., 2003; Tran et al., 2013; Unger et al., 2012). Although it is difficult to speculate on a specific causative mechanism, prolonged increases in neurotransmitter concentrations yielding diminished receptor density or augmented neurotransmitter uptake may significantly alter the neurochemical milieu affecting the functioning of the entire nervous system (Almeida et al., 1996; Pisansky et al., 2013; Wauben & Wainwright, 1999). Additionally, some have postulated neurotransmitter systems interact with each other during development (Benes et al., 2000). Thus, perturbations in one system due to malnutrition may affect the developmental course of other systems (Wauben & Wainwright, 1999). For example, researchers have conjectured that changes within the glutamate, GABA, and norepinephrine systems interact with and contribute to the disregulation of the dopamine system observed in schizophrenia (Friedman, Temporini, & Davis, 1999; Goldman-Rakic & Selemon, 1997; Laruelle, Kegeles, & Abi-Dargham, 2003; Syvalahti, 1994). In addition, dysregulation of certain neurotransmitter systems may adversely affect dendrite formation, gene expression, and neurophysiological functioning all of which would be appropriate avenues to explore in animal models and in human neuroimaging studies (Gietzen et al., 2004; Jousse et al., 2004; Ma et al., 2000; van Kesteren & Spencer, 2003).

The hypothesized relationship between malnutrition and hippocampal dysfunction and between hippocampal dysfunction and psychopathology suggests that this circuit plays a role in the emergence of psychopathology following early nutritional deficits (Pisansky et al., 2013). As highlighted previously, researchers have connected early deficits of protein/protein energy, iron, or zinc to hippocampal malformation and dysfunction (DeUngria et al., 2000; Jorgenson et al., 2003; Morgane et al., 2002; Schmidt et al., 2007; Tuormaa, 1995). This specific brain structure is noteworthy because it has been implicated in various types of psychopathology including schizophrenia, alcohol abuse, antisocial behavior, and anxiety/depression (Brown, Rush, & McEwen, 1999; De Bellis et al., 2000; Heckers et al., 1998; Heim & Nemeroff, 1999, 2001; Korbo, 1999; Korte, 2001; Laakso et al., 2000, 2001; Rajkowska, 2000). However, it is not known whether the hippocampus plays a direct causal role, if it modulates other structures involved in the pathogenesis of the disorder (e.g., frontal lobe structures), or if disruption in this region represents more generalized brain atrophy (Graham, Heim, Goodman, Miller, & Nemeroff, 1999). Moreover, it is possible that although affected, the hippocampus itself is not the crucial contributor to a deviant behavioral outcome. Rather, it is possible that hippocampal dysfunction disrupts projections to/from other brain structures thus deranging the functioning of a wider cortical network (Pisansky et al., 2013).

Another effect of early nutritional deficits (specifically resulting from iron deficiency and essential fatty acid deficiency) is disrupted myelination (Kwik-Uribe et al., 2000; Roncagliolo et al., 1998). This is of note because researchers have reported the occurrence of aberrant white matter structures in various psychiatric disorders (e.g., schizophrenia, mood disorders) (Cotter et al., 2001; Davis et al., 2003; Molnar, Potkin, Bunney, & Jones, 2003; Öngür, Drevets, & Price, 1998). Again, the relationship between the observed white matter abnormalities and the behavioral phenotypes of the disorder are currently unknown; however, they deserve note and future scrutiny because it is conceivable the white matter changes are causally linked to psychopathology (Jones, 1997).

Maternal stress is an example of a more indirect effect that may partly explain the role of malnutrition in the emergence of mental disorders (Monk et al., 2013) and clearly deserves attention from future investigations. For example: more than likely, chronic malnutrition rarely occurs in the absence of significant maternal stress (Gorman, 1995). Therefore, malnutrition could potentiate the effects of maternal stress or vice versa. Moreover, there are clear interactions between stress and nutrition where maternal stress affects who she absorbs and distributes nutrients to the fetus (Monk et al., 2013). The pervasiveness of maternal stress during the Second World War makes it unlikely that this factor alone can account for the pattern of deficits observed in the Dutch famine studies. Nevertheless, maternal stress cannot be ruled out

as a factor contributing (either additively or synergistically) to these findings. Similarly, malnutrition of the child or infant likely occurs along with malnutrition of the mother. Thus, as suggested by the studies of Keys and colleagues (Franklin et al., 1948; Keys, 1946), significant malnutrition affects the psychological functioning of the mother and presumably her ensuing interactions with her child. Therefore, some of the consequences observed following malnutrition could partly result from disordered mother-child interactions (Moffitt & Caspi, 2001). The magnitude of the effects on maternal-child and maternal-fetal interactions—independent of other environmental/biological influences—remains unclear but deserves greater scrutiny by researchers (Moffitt & Caspi, 2001; Monk et al., 2013). However, if the maternal behavior is severely abusive or pathological to the point of being unable to provide the minimal physical, perceptual, and social stimulation required for normal brain development, then a deviant outcome compounded by malnutrition is likely (Guesry, 1998; Jaffee, Caspi, Moffitt, & Taylor, 2004; Raine, Brennan, & Mednich, 1994, 1997; Stein & Susser, 1985; Tully, Arseneault, Caspi, Moffitt, & Morgan, 2004).

The Developmental Origins of Adult Health and Disease (DOHaD) theory states that early intrauterine environment programs the fetus in gestation (Barker, 2001). This mechanism is regarded as an adaptive response helping the fetus to react during gestation to particular stressors such as malnutrition (Barker, 2001; Oliver et al., 1999; Seckl, 1998). This theory argues that these adaptive changes become liabilities when the environmental challenge is no longer present (Barker, 2001; Oliver et al., 1999; Seckl, 1998; Gluckman and Hanson, 2004). Barker and colleagues have invoked this fetal programming hypothesis to explain the relationship between retarded intrauterine growth and the later development of coronary heart disease (Barker, Forsén, Utela, Osmond, & Eriksson, 2001). More recently, researchers have used the fetal programming hypothesis to explain their findings of a link between fetal undernutrition and the later development of depression (Thompson et al., 2001) and reduced cognition (Pylipow et al., 2009). Thus, fetal programming in response to malnutrition could account for many of the descriptive findings regarding prenatal undernutrition; however, a precise mechanism for these alterations is still unknown (Seckl, 1998).

Another potential indirect effect connecting early malnutrition to the development of psychopathology is the decreased cognitive abilities observed in numerous studies. As discussed already, research indicates postnatal malnutrition can result in long-term reduction of intellectual abilities and cognitive skills (e.g., attention) (Galler & Ramsey, 1987, 1989; Galler et al., 1986). These findings are important because intellectual ability measures obtained in middle childhood are highly stable into later life (Deary, Whalley, Lemmon, Crawford, & Starr, 2000; Deary, Whiteman, Starr, Whalley, & Fox, 2004). Other research indicates that low intelligence is an independent predictor of lifetime psychiatric contact in that lower intellectual capacity results in a significantly increased risk for developing psychiatric difficulties including conduct problems and antisocial behavior (Moffitt, Gabrielli, Mednick, & Schulsinger, 1981; Walker, McConville, Hunter, Deary, & Whalley, 2002).

Jacobs and others (2002) found that although childhood cognitive ability and childhood psychopathology are predicted by independent genetic factors, a third genetic factor along with (unspecified) non-shared environmental factors predicts both. Thus, if postnatal malnutrition results in decreases in IQ sustained through middle childhood, these are likely permanent and may in turn lead to increased psychiatric contact. These results may be subtle and relatively small on the individual level. However, slight perturbations in the population IQ will greatly impact the number of individuals classified as mentally retarded and requiring social support services, thus increasing the financial cost to society (Tanner & Finn-Stevenson, 2002). Moreover, reductions in population IQ and specific cognitive skills (such as verbal reasoning) may increase the number of individuals requiring psychiatric support services and engaging in impulsive/delinquent behaviors (Arseneault, Moffitt, Caspi, Taylor, & Silva, 2000; Moffitt et al., 1981; Stevens, Kaplan, & Bauer, 2001; Stevens, Kaplan, & Hesselbrock, 2003).

Finally, early nutritional deficits may make an individual more vulnerable to insults (e.g., hypoxia) that are associated with the development of psychopathology (McNeil et al., 2000; Zornberg et al., 2000). Rao et al. (1999) provided some evidence for this hypothesis by showing prenatally iron deficient juvenile animals sustained more damage to the hippocampus following a hypoxic ischemic insult. Moreover, Fechner and colleagues showed that children admitted to hospital suffering from kwashiorkor exhibited decreased plasma antioxidant levels (Fechner et al., 2001). Decreased antioxidant concentrations likely make these children more susceptible to neuronal damage/death after traumatic injuries such as anoxia or hypoxia-ischemia (Buonocore, Perrone, & Bracci, 2001; Zauner, Daugherty, Bullock, & Warner, 2002).

Similarly, compared with well-nourished children, malnourished children are more susceptible to cell damage and exhibit decreased DNA repair following an injury (Gonzalez et al., 2002). Gietzen and colleagues (1996)

observed that rats with essential amino acid deficiencies displayed heightened seizure vulnerability. Furthermore, research suggests maternal zinc deficiency exacerbates the effects of prenatal alcohol exposure (Flynn et al., 1981).

The previous findings suggest that a nervous system already compromised by malnutrition is more vulnerable to additional insults such as toxin exposure or chronic stress. As discussed in the section on neurobiology, there is a potential for malnutrition or any early insult to alter the fundamental organization or structure of the developing brain. While these modifications may prove beneficial in the short-term (e.g., by conserving energy or reallocating resources) they may prove detrimental in the future—possibly by decreasing behavioral or cellular plasticity (Gluckman & Hanson, 2013).

Thus, malnutrition could serve as a catalyst disrupting normal development, but it may not have an enduring effect, unless occurring proximally with another insult. Furthermore, the consequences of early malnutrition may not be revealed until a future stressor tries the plasticity of the system. This model is analogous to the diathesis–stress theory of mental disorders. In this model, undernutrition could be the stress (second injury) whereas the diathesis (initial damage) could stem from a genetic vulnerability or from other already-present environmental risk factors. Conversely, early malnutrition and its effects could be present first, so that a later infection, toxin exposure, or hypoxic/ischemic event would tip the scales toward an undesirable outcome. As discussed in the introduction, another variable to consider in this system is an individual's ability to maintain homeostasis in response to a challenge. This model may explain some of the discrepant findings in the literature. That is, it posits that each individual has his or her own threshold of how much damage via malnutrition (or other environmental insults) he or she can endure before exhibiting an aberrant phenotype. It also hypothesizes that malnutrition exerts its maximal effect if it occurs in the context of an already compromised system. Again, this is merely a hypothesis and it should be rigorously tested (including the formulation of models that strive to describe this threshold in terms of numerical relationships and which factors are the best predictors of eventual outcome).

TRANSLATIONAL IMPLICATIONS

Studying the impact of early nutritional deficiencies is well-suited to a translational approach because of the various environmental and genetic confounds that are best addressed through multiple levels of analysis. The research reviewed supports the hypothesis that time of onset, dose, and duration of nutritional insults and interventions play critical roles in determining the nature and extent of any deficits (Morgane et al., 1993; Pollitt, 1996; Walker et al., 2011). However, what is not known is how much each of these three factors uniquely contributes to the eventual neurobehavioral outcome. The challenge lies in conjecturing plausible and testable mechanisms for these interactions and deriving maximally precise predictions of which factors contribute in which ways to the eventual outcomes.

Disentangling the various issues at the root of this question highlights the importance of a translational approach that incorporates techniques from basic neurobiology, animal behavioral studies, cognitive and brain-imaging studies with children, and longitudinal, epidemiological studies of affected populations. For example, neurobiological models (concerned with cellular and molecular mechanisms) can inform the development of animal models used to understand behavioral and cognitive correlates. These models would be based on extant relationships between form and function in the brain that are conserved across species and would lend themselves to experimental manipulation. Although there are no convincing animal models of psychopathology, animal studies designed to manipulate time of onset, dose, and duration of early malnutrition would help to understand the relative role of these components on neurochemistry, neuroanatomy, and some basic behavioral constructs (e.g., reward/punishment sensitivity, autonomic arousal, inhibitory control). Using neuroimaging and postmortem techniques, these findings could then be extended to human populations, and combined with evolving knowledge of the neurologic basis of psychopathology may provide insight into the relationship between early malnutrition and the development of mental illness.

Further, these basic studies would be complimented by studies on human participants including longitudinal investigations of the impact of nutrient deficiencies (similar to the types of studies that have already been conducted but with more sophisticated measures of cognitive functioning that are based on current models of brain and cognitive development). Studies with child participants should also include statistical models that seek to explain population and subpopulation relationships among environmental factors to help parse the unique contribution of early nutritional deficiencies. Because criteria for the diagnosis of mental disorders is somewhat arbitrary and may be somewhat culturally determined, a possible way of examining this issue across settings may be to investigate more biological markers of mental disorders (such as dexamethasone suppression in depression or reward/punishment

sensitivity in externalizing disorders). Although the specificity and sensitivity of these types of measures is far from perfect, this approach may provide a useful tool for examining the base rate of psychopathology in undernourished populations—where the current diagnostic system may be less effective for determining the presence or absence of a disorder. This type of a multidisciplinary, multiple levels of analysis approach is the essence of developmental psychopathology and appears very timely given the new emphasis on funding studies that examine psychopathology through the lens of basic neurobiological mechanisms (i.e., the Research Domain Criteria initiative from the National Institute of Mental Health in the United States; Morris, Rumsey, & Cuthbert, 2014).

CONCLUDING REMARKS

The research reviewed in this chapter indicates that malnutrition is associated with disturbances in neurotransmitter systems necessary for normal neuronal maturation, morphological changes in delicate brain structures and reductions in brain growth. Functional behavioral disturbances include deficits in cognitive abilities and an increased risk for psychiatric disorders including schizophrenia and other psychopathological conditions such as externalizing behaviors and internalizing difficulties. These form and function effects persist across various models of malnutrition in animal studies and across demographic factors (country of origin and social class) in human investigations. However, the problem of early malnutrition is significant for both developed and developing countries; thus additional research is necessary to better explicate the long-term consequences of this condition.

The question is not whether severe malnutrition (i.e., starvation) leads to adverse outcomes, because it is obvious that beyond a certain threshold of caloric restriction conception becomes unlikely, miscarriage is inevitable, and death eventually results if adequate energy intake is not restored (Coad, Al-Rasasi, & Morgan, 2002; King, 2003; Stein et al., 1972). Rather, the question that future research should address is: given a limited supply of energy, protein, or specific micronutrients, is an individual at an increased risk for developing psychopathology? Complicating the picture, available research suggests generalized malnutrition rarely exists without micronutrient (iron/zinc) deficits, decreased parental intellectual abilities, deficient psychosocial stimulation, chronic childhood illness, or unsanitary living conditions (Guesry, 1998; Ivanovic et al., 2002; Pollitt, 1969; Stein & Susser, 1985). Even in the case of the Dutch hunger winter, the population was not free from significant wartime and famine induced stress. Therefore, it is difficult to discern if there is a unique contribution of early malnutrition to the development of psychopathology, and what, if any, is the relationship between malnutrition and other risk factors (i.e., mediational, additive, or synergistic).

Early malnutrition appears to be a topic very well suited to the field of developmental psychopathology as it easily lends itself to a multidisciplinary, translational approach. That is, to adequately understand and ameliorate the impact of early nutritional deficiencies on development of psychopathology researchers will need to draw from techniques of basic science (neurobiology and biochemistry) as the foundation, translational research (e.g., using animals to model various paradigms of malnutrition), and finally comprehensive human investigations which include measures of motor, perceptual, cognitive, intellectual abilities, and objective measures of personality and psychopathological symptoms. These human studies should also endeavor to match participants (or otherwise statistically control for) potential confounds such as SES, parental education/IQ, familial history of mental illness, toxin exposure, and living circumstances. Although costly and difficult to conduct a human study which could incorporate all of these components, a study of this kind would provide valuable data which could greatly augment our understanding of the long-term effects of early malnutrition and specify how this condition interacts with other risk factors.

The potential for various gene-environment interactions may explain the relative effectiveness of nutritional intervention programs in developing countries compared to the often modest benefits shown by similar endeavors in countries such as the United States (Pollitt, 1996; Grantham-McGregor et al., 2014). That is, in developing countries, the population is likely to be chronically undernourished but may not exhibit elevated rates of psychopathology, and parents might provide a stable home environment. Conversely, in developed countries, individuals at risk for early malnutrition are more likely to have genetic and additional environmental risk factors—increasing their chance of expressing a deviant phenotype (Grantham-McGregor et al., 2014). This is merely a speculation and is not intended to minimize the potential impact of early malnutrition or the need to address this issue, but rather to emphasize the idea that many malnourished children (especially in developed countries) possess other substantial risk factors such as poverty, unstable home environments, deficient psychosocial stimulation, and

genetic propensities, which may complicate intervention efforts. Again, designing efficient, beneficial interventions is another area that future studies should explore. Implementing successful interventions in countries such as the United States will likely entail carefully designed, targeted procedures (e.g., ensuring proper prenatal care and nutrition, encouraging breastfeeding and parental involvement, better parental and childhood nutrition education, proper vaccinations and postnatal nutrition) that begin early and aim to treat the gestalt of the circumstances and not merely a single destructive component of the milieu (Ramey & Ramey, 1998; Wachs et al., 2014).

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CHAPTER 7

Quantitative and Molecular Behavioral Genetic Studies of Gene–Environment Correlation

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The study of G-E correlation reflects a central premise in developmental psychopathology—the idea that individuals create their own environments, either by evoking some response from the people around them or by actively selecting certain experiences. Thus, G-E correlations can be thought of as a special case of person–environment correlations, highlighting the fact that the individual characteristics that drive this active construction are partially genetic in origin (Defries & Loehlin, 1977). The process by which individuals elicit certain reactions from others, manipulate their environments, selectively attend to features of their environments, or niche-pick their environments on the basis of personality, abilities, or other individual characteristics is what perpetuates and amplifies individual differences in these phenotypes (Caspi & Moffitt, 1995).

From a developmental psychopathology perspective, this process by which person–environment correlations (and the genetic influences that underlie them) drive development is inherently interesting. G-E correlations are additionally relevant to the study of developmental psychopathology, however, because of their implications for understanding causal processes. The goal of social and clinical science is to understand the causes of normal and abnormal development. Features of the environment, ranging from environmental toxicity to relationships with family members, romantic partners, and peers are hypothesized to be among the causes of multiple disorders. The possibility, however, that G-E correlations confound observed effects of exposures or experiences on outcomes is a major challenge to causal inference (D'Onofrio & Lahey, 2010; Foster, 2010; Rutter, 2007). Our goal in

this chapter is to define genotype–environment correlations and then describe efforts to (1) detect and assess the impact of genotype–environment correlations using adoption and twin designs, (2) describe the implications of genotype–environment correlations for understanding developmental processes, (3) describe the evidence for genotype–environment correlations from molecular genetic studies, and (4) use genotype–environment correlations under certain restrictive conditions to make causal inferences about environmental exposures.

GENOTYPE–ENVIRONMENT CORRELATION: DEFINITIONS

Genotype–environment correlation (rGE) refers to genetic differences in the exposure to a particular environment (Kendler & Eaves, 1986; Plomin, DeFries, & Loehlin, 1977). Genotype can be defined as those features of an organism that are encoded in DNA sequence. Environment is defined as the context in which an individual develops over time, including family, neighborhood, peer, school, and work contexts, among others. *Environment* describes not only structural features of these various contexts (e.g., family structure or the percentage of neighborhood residents living below the poverty threshold) but also process-level features (e.g., the quality of parent–child relationships, the amount of praise or criticism provided by teachers). Thus, like other phenomena that are studied in developmental psychopathology, G-E correlations reflect multiple levels of influence on the developing person, with those influences encompassing on the one hand the genes that get outside the skin to increase (or reduce) exposure to specific experiences and, on the other hand, the reciprocal effect of those experiences on a person's affective, behavioral, or cognitive tendencies. Moreover, the study of G-E correlation in the context of developmental psychopathology crosses disciplinary boundaries, requiring that researchers develop expertise in quantitative or molecular behavioral genetics as well as expertise in social epidemiology, clinical science, and development.

Genotype–environment correlation can arise from the causal effects of genotypes as well as from other processes. For example, natural selection and genetic drift give rise to ancestral differences in genotype both within and between populations. Genetic markers for population ancestry will therefore correlate with any environmental and phenotypic features that vary by ethnic group. For example, exposure to malaria-bearing mosquitos over many generations may have caused the higher allele frequency among individuals of African ancestry for the sickle cell hemoglobin (HbS) allele, a recessive mutation that causes sickle-cell anemia, but confers resistance against malaria (Aidoo et al., 2002). In this way, HbS genotype has become associated with the malarial environment. These spurious associations are particularly common in the presence of recent population admixture, and are a potential source of confounding in genetic association studies.

In terms of causal processes that give rise to genotype–environment correlations, psychologists, and psychiatrists commonly refer to three different categories (Figure 7.1). *Passive genotype–environment correlation* refers to the association between the genotype a child inherits from his or her parents and the environment in which the child is raised. In other words, the existence of passive genotype–environment correlation creates the possibility that observed associations between the child's environment and the child's cognitive, behavioral, or physical outcomes are confounded by the genotype shared by parents and children. For example, because parents who have histories of antisocial behavior (which is moderately heritable) are at elevated risk of abusing their children, maltreatment may be a marker for genetic risk that parents transmit to children rather than a causal risk factor for children's conduct problems (DiLalla & Gottesman, 1991; Eaves, Prom, & Silberg, 2010). As another example, reading aloud to young children may be predictive of children's verbal ability because children inherit this capacity from verbally adept parents who tend to enjoy reading to children and have the time to do it.

Evocative (or reactive) genotype–environment correlation refers to the process by which an individual's genotype evokes or elicits some response from the environment. Evocative genotype–environment correlations tend to be behaviorally mediated, meaning that genotype influences an individual's behavior and the behavior is what generates a reaction from others with whom the individual interacts (Jaffee & Price, 2007). For example, although arguing with a spouse may cause someone to become depressed, it is equally plausible that individuals who are highly neurotic and prone to depression tend to provoke arguments with significant others (or other stressful life events), calling into question the direction of the effect (Kendler & Gardner, 2010). In other words, evocative genotype–environment correlations are evidence of heritable person effects on the behavior of others in their milieu.

Active (or selective) genotype–environment correlation refers to the association between an individual's genetic propensities and the environmental niches that individual selects. In other words, active genotype–environment

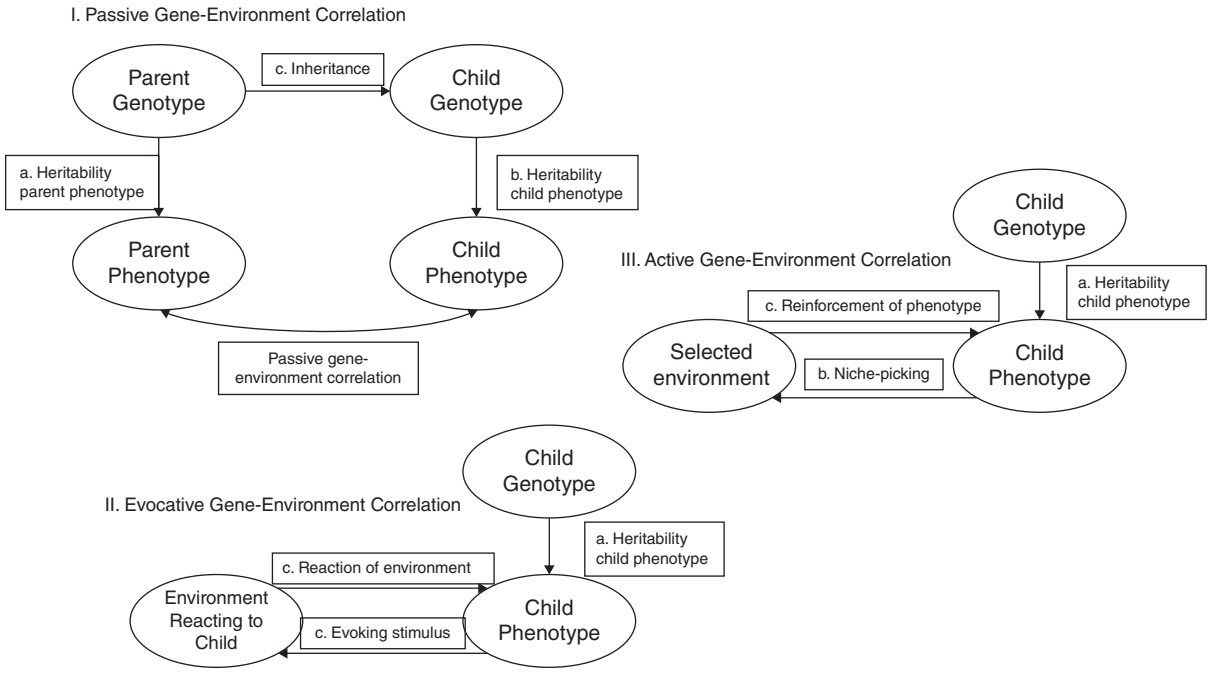


Figure 7.1 Passive, evocative, and active genotype–environment correlations.

correlations are evidence of heritable person effects on the environment due to the person's own actions. For example, individuals who have a genetically based proclivity for antisocial behavior may be especially likely to seek out a delinquent peer group (Kendler, Jacobson, Myers, & Eaves, 2008).

Genotype–environment correlations are often posed as alternatives to causal accounts of the relationships between exposures and outcomes. Indeed, the literature on genotype–environment correlations has led some researchers to conclude that children mainly turn out the way they do because of the genes they have inherited and not because of how they have been socialized by parents or teachers (Harris, 1995). On the one hand, most behavioral geneticists would agree that the existence of genotype–environment correlations undermines a large literature that made causal claims about the importance of parental socialization based largely on correlations between parenting behavior and child behavior (Turkheimer, 2000). On the other hand, most behavioral geneticists also recognize that development is an inherently transactional process between individuals and their environments. That is, even if a parent's use of harsh and coercive discipline is initially a response to a temperamentally difficult child, there is every reason to believe (based on longitudinal data, quasi-experimental data, and data from randomized control trials) that harsh and coercive discipline will amplify preexisting tendencies to engage in antisocial behavior (Jaffee, Strait, & Odgers, 2012; Patterson, DeBaryshe, & Ramsey, 1989).

These forms of genotype–environment correlation differ from gene–environment interaction (GxE), which refers to genetic differences in sensitivity to particular environmental effects (Kendler & Eaves, 1986). Genotype–environment correlations explain why individuals who have a genetic propensity to engage in sensation-seeking behaviors affiliate with drug-abusing peers (Yanovitzky, 2006). GxE explains why heavy drug use is most likely to lead to psychosis only among individuals with a particular genotype (Caspi et al., 2005).

It bears noting that passive, evocative, and active genotype–environment correlations are special cases of more general phenomena in developmental psychology and psychopathology. For example, passive genotype–environment correlations are a specific case of unobserved heterogeneity, in which genes common to parents and children potentially generate spurious associations between exposures and child outcomes. Evocative genotype–environment correlations imply that an individual's behavior actively shapes his or her environment—a process that was described by Bell (1968) in the context of socialization research and was a key tenet of Piagetian theories of cognitive development (Flavell, 1996). The behavioral genetics perspective simply emphasizes

that the behaviors that may evoke specific reactions from the environment have a genetic basis. Finally, active genotype–environment correlations imply that individuals consciously or unconsciously seek specific experiences that are congruent with their genetically based proclivities. Again, this echoes processes of selection and niche picking articulated by life span developmental theories (Elder, 1998), but highlights the genetic basis of the traits driving the selection process.

Evidence for G-E correlations from adoption and twin studies is described in the following two sections. This chapter also describes the strengths and limitations of these designs for (1) detecting G-E correlations and (2) determining the extent to which G-E correlations may account for observed associations between experiences or exposures and measures of emotional or behavioral health. Then it also describes the implications of G-E correlation for understanding developmental process, and evidence for correlations between measured genotypes and measured environments. Finally, it describes efforts to leverage G-E correlations to make stronger causal inferences, concluding with a summary of findings.

GENOTYPE–ENVIRONMENT CORRELATIONS: EVIDENCE FROM ADOPTION STUDIES

Adoption studies are directly informative about the existence of passive genotype–environment correlations. This is because adoptive parents create the environment in which their adopted child is raised, but they are genetically unrelated to their child. In contrast, when parents and their children are biologically related, parents not only create their child's rearing environment, but they also provide their child's genotype. If, for example, an authoritative parenting style is correlated with a child's prosocial behavior, this could reflect at least one of three things. First, it could reflect an effect of the parent on the child, which is how the correlation is often interpreted—parents who are warm, who set consistent, fair, and age-appropriate limits on children's behavior, and who give children age-appropriate levels of autonomy promote (in a causal fashion) the development of prosocial behavior. Second, it could reflect an effect of the child on the parent. Children who are cooperative, empathic, and compliant are more likely to be granted autonomy and to be treated with warmth than are children who are uncooperative, unempathetic, and noncompliant. Third, it could reflect a genetic effect, wherein authoritative parenting style is a marker for a genetic propensity to engage in prosocial behavior that parents transmit to children—that is, a passive genotype–environment correlation. In families where parents and children are *not* biologically related (e.g., adoptive families), any observed association between authoritative parenting and children's prosocial behavior could reflect a parent effect or a child effect, but it could not reflect a passive genotype–environment correlation. If passive G-E correlations (or any other form of G-E correlation) are present, we refer to the association between the exposure and the outcome as genetically mediated in the sense that genes shared by the parent and child account for the observed association. If passive G-E correlations are not present, we refer to the association between the exposure and outcome as "environmentally mediated," recognizing that this does not necessarily mean the exposure has direct effects on the outcome.

When some information is known about an adopted child's biological parents, the adoption design can also be used to identify evocative genotype–environment correlations. In this case, information about the biological parent's mental health or behavior is used as a proxy measure of genetic risk that the adopted child has inherited. To the extent that the child's genetic risk is correlated with how she or he is parented, this is indicative of an evocative genotype–environment correlation. For example, the most parsimonious explanation for why adoptive parents would more frequently use coercive discipline with one child whose biological mother was in prison for assault than with another child whose mother lacked a criminal background is that the first child inherited a genetic predisposition to engage in noncompliant or aggressive behavior and the adoptive parents are responding to this antisocial behavior. Of course it is equally possible that differences in the prenatal environment provided by mothers with versus without a criminal history could account for differences in their children's behavior.

Adoption Studies of Passive rGE

The adoption design has been used to test whether passive genotype–environment correlation accounts for associations between children's behavior and a range of parenting behaviors and family characteristics, including parental divorce or marital conflict, parental psychopathology, and mothers' behavior during pregnancy.

Does Passive rGE Account for Effects of Parental Divorce or Interparental Conflict on Offspring Outcomes?

There is a large literature showing that the children of divorced parents have elevated rates of antisocial behavior

(Emery, 1999), although effect sizes are modest in magnitude (Amato, 2001). Parents who divorce are more likely to have engaged in antisocial behavior in their youth and to engage in antisocial behavior in adulthood compared with parents who do not divorce (Emery, Waldron, Kitzmann, & Aaron, 1999; Fomby & Cherlin, 2007; Lahey et al., 1988) and antisocial behavior is moderately heritable (Rhee & Waldman, 2002). Thus, although the association between divorce and children's antisocial behavior could be causal, divorce could also be a marker for genetic risk for antisocial behavior that parents transmit to children.

Burt et al. (2008) tested whether passive genotype–environment correlations could account for the association between parental divorce and children's behavior using data from a sample of adoptive and nonadoptive families. Consistent with a causal effect of divorce, they found that regardless of whether parents and children were biologically related, children whose parents were divorced engaged in higher levels of antisocial behavior than children whose parents were not divorced. Moreover, children had to have experienced the divorce in order for it to have the predicted effect. Children being raised by two parents, one or both of whom had previously been divorced, had no more behavior problems than children whose parents had never been divorced. Although another study only identified the expected behavioral differences between children from divorced versus intact families if parents and children were biologically related (i.e., consistent with passive G-E correlation), this study included relatively few children who were adopted and whose adoptive parents subsequently divorced (O'Connor, Caspi, DeFries, & Plomin, 2000).

Some adoption studies have shown that interparental conflict is associated with (adoptive) offspring behavior problems and have attempted to identify factors within the family that mediate the association. For example, toddlers engage in relatively high levels of aggressive behavior (Stover et al., 2012) and have more sleep problems (Rhoades et al., 2012) if their adoptive parents' relationship with each other is characterized by relatively high levels of physically and verbally hostile behavior. One reason for this is that parents who are physically and verbally hostile toward each other tend also to be physically and verbally hostile toward their children (Harold, Leve, Elam, et al., 2013; Rhoades et al., 2012; Stover et al., 2012). This pathway from marital hostility to hostile parenting to offspring antisocial behavior problems has also been observed in studies where the inclusion of mothers and fathers who used *in vitro* fertilization technologies (e.g., egg or sperm donation) means that some parents may not be genetically related to the child they are raising (Harold, Elam, Lewis, Rice, & Thapar, 2012).

Does Passive rGE Account for Effects of Parent–Child Conflict on Offspring Outcomes?

Parent–child conflict is characterized by parental criticism of children and frequent arguments between parents and children. Although children and adolescents who have conflictual relationships with parents are at elevated risk for antisocial behavior problems, parent–child conflict, like interparental conflict, could be a marker for genetic risk for antisocial behavior that parents transmit to children. Adoption studies rule out this alternative explanation, however. The association between conflictual parent–child relationships and offspring antisocial behavior is observed both cross sectionally in samples of adoptees and their parents (Klahr, Rueter, McGue, Iacono, & Burt, 2011) and longitudinally (Harold, Leve, Elam, et al., 2013). The association has been observed into young adulthood, where relatively higher levels of conflict between youth and their adoptive parents in early adolescence were predictive of relatively higher levels of conduct problems approximately 4 years later, but early adolescent conduct problems were not predictive of later parent–child conflict (Burt, Klahr, Rueter, McGue, & Iacono, 2011; Klahr, McGue, Iacono, & Burt, 2011). Not only do these results indicate that the relationship between parent–child conflict and child conduct problems is not accounted for by passive G-E correlations, but—given the lack of evidence for child effects on parent–child conflict—they also indicate that the relationship is unlikely to be accounted for by evocative G-E correlations.

Does Passive rGE Account for the Effect of Cumulative Adversity on Child Functioning?

Although most researchers test for passive G-E correlation one risk exposure at a time, psychosocial and physical risk exposures tend to be correlated (Evans, 2004). In developmental psychology and developmental psychopathology research more broadly, it is common for researchers to generate cumulative risk indices instead of focusing on specific risk exposures (Evans, Li, & Whipple, 2013). The concern remains, however, that measures of cumulative risk are markers for genetic risk for psychopathology or other undesirable outcomes that parents transmit to children. These undesirable outcomes may include dysregulation of the stress response system, including the limbic-hypothalamic-pituitary-adrenal axis and its end product cortisol. Individual differences in basal cortisol levels and cortisol reactivity have been associated with

both internalizing and externalizing problems (Gunnar & Vazquez, 2006).

At least one adoption study has shown that cumulative adversity at age 6 years (as indicated by parents' symptoms of depression and anxiety, marital instability, financial need, parents' lack of social support, parents' experience of negative life events, and chaotic family environment) was associated with lower evening cortisol values and less stability in evening cortisol values from age 4.5 to 6 years (Laurent et al., 2014). Thus, although it may be that the association between cumulative risk and cortisol values is accounted for by some unobserved variable, we can rule out the possibility that genetic factors common to parents and children explain the association.

Does Passive rGE Account for the Effect of Parent Psychopathology on Offspring Psychopathology?

There is substantial intergenerational continuity in psychopathology and adoption studies can be informative about the extent to which this reflects environmentally versus genetically mediated pathways. On the one hand, several studies from one sample of adoptive families have shown that even controlling for the biological mothers' symptomatology, adoptive mothers' ADHD symptomatology predicted their children's ADHD symptoms at 6 years of age (Harold, Leve, Barrett, et al., 2013), adoptive mothers' symptoms of anxiety predicted their toddlers' internalizing problems at 18 and 27 months (Brooker et al., 2014), and adoptive mothers' symptoms of depression and antisocial behavior predicted children's internalizing and externalizing symptoms at 18 months, but not change in problem behaviors from 18 to 54 months (Kerr et al., 2013). Studies of adoptees have also shown that the rearing mothers' depressive symptoms are associated with adoptive offspring externalizing problems in toddlerhood (Pemberton et al., 2010) and in adolescence (Tully, Iacono, & McGue, 2008). Maternal depression was also associated with offspring depressive symptoms in adoptive and nonadoptive families (Tully et al., 2008). In contrast, one other study of 402 adoptive and 204 biological families, showed that maternal and paternal antisocial behavior were associated with adolescent offspring externalizing problems only in biological families but not in adoptive families (Bornovalova et al., 2014).

These findings regarding environmental transmission of risk for psychopathology tend to replicate in samples in which parents and children are genetically unrelated because mothers were recipients of donor eggs or sperm or children were born to surrogates (Harold et al., 2011; Harold, Leve, Barrett, et al., 2013; Lewis, Rice, Harold, Collishaw, & Thapar, 2011; Rice, Lewis, Harold, & Thapar, 2013). Findings are less robust for transmission of rearing fathers' psychopathology to his genetically unrelated offspring, however (Harold et al., 2011).

In some cases, the pathways by which parental psychopathology lead to offspring psychopathology are the same, regardless of the biological relatedness of parents and offspring. For example parental hostility has been shown to account for the association between parent and offspring antisocial behavior in both genetically related and genetically unrelated dyads (Harold et al., 2011). In other cases, the pathways differ. For example, high levels of maternal hostility and low levels of maternal positivity account for the association between mothers' and children's depression in genetically related pairs, but these maternal behaviors do not account for links in genetically unrelated pairs (Harold et al., 2011; Rice et al., 2013), though this may have reflected relatively reduced power to detect effects of maternal positivity (if not maternal hostility) in the genetically unrelated pairs.

Does Passive rGE Account for the Effect of Maternal Behaviors While Pregnant on Offspring Outcomes?

In a study of 779 children born through in vitro fertilization whose prenatal environment was either provided by a biologically related mother or a biologically unrelated mother (e.g., a surrogate or the recipient of a donor egg), infants whose mothers smoked during pregnancy had significantly lower birth weights than infants whose mothers did not smoke during pregnancy, regardless of whether the mother and fetus were biologically related (Rice et al., 2009). In contrast, children whose mothers smoked during pregnancy had significantly higher levels of antisocial behavior and hyperactivity than children whose mothers did not smoke only when the mother–offspring pair was biologically related (Rice et al., 2009; Thapar et al., 2009). Thus, smoking during pregnancy is likely to be one cause of low birth weight, but not offspring antisocial behavior or hyperactivity. Interestingly, however, genetically mediated effects of mothers' smoking during pregnancy on offspring conduct problems are observed even when offspring are adopted at birth (Gaysina et al., 2013), suggesting that smoking during pregnancy may be a marker for genetic risk for externalizing problems that mothers transmit to children and that evokes negative interactions with caregivers in the postnatal environment.

Adoption Studies of Evocative rGE

The adoption design can also be used to test for evocative genotype–environment correlations. In this case,

information about the adoptees' biological parents must be available to derive an estimate of the adoptee's genetic risk for some outcome. For example, Ge et al. (1996) used information about antisocial personality disorder and alcohol and drug abuse/dependence among biological parents to identify adoptees at high versus low genetic risk for psychopathology. High-risk adoptees experienced significantly higher levels of harsh, inconsistent discipline and lower levels of warmth and nurturance from their adoptive parents than low-risk adoptees and the relationship between adoptee risk status and adoptive parent behavior was mediated by adoptee antisocial behavior. Thus, a genetic propensity to engage in antisocial behavior made adolescents difficult to manage, resulting in less warmth and more negativity in the parent-adolescent relationship—evidence of evocative genotype–environment correlation.

This finding was replicated in two separate samples. O'Connor et al. (O'Connor, Deater-Deckard, Fulker, Rutter, & Plomin, 1998) showed that adoptive parents of children at high genetic risk for externalizing problems (on the basis of the biological mother's antisocial behavior) consistently used more negative control strategies over a 5-year period from late childhood to early adolescence than did adoptive parents of children at low genetic risk. Follow-up mediation analyses indicated that children who were at high genetic risk also had higher levels of externalizing problems, which explained why their parents were more likely to use negative control strategies. Similarly, Riggins-Caspers, Cadoret, Knutson, and Langbehn (2003) found that adopted adolescents who were at high biological risk (on the basis of the biological parents' psychiatric status) were characterized by relatively high levels of conduct problems, which, in turn, were associated with the receipt of harsh discipline. Interestingly, this evocative G-E correlation was only observed under conditions of moderately high environmental risk (e.g., substance use or other psychological problems in the adoptive family, divorce), suggesting that the broader context modified the degree to which parents reacted with harsh and coercive discipline to their child's externalizing behavior.

Even in the absence of data on biological parents' characteristics, evocative genotype–environment correlations can be ruled out as an explanation for observed associations between children's experiences and their behavior if longitudinal data are available from adoptive families. For example, Klahr et al. (2011) estimated a cross-lagged model of the relationship between parent–child conflict and adolescent conduct problems at two time points, separated by approximately 4 years. They found that parent–child conflict was a much stronger predictor of later conduct problems than the reverse, suggesting that the child's behavior (which had been shown to be moderately heritable in biometric models) was not evoking or escalating conflict with parents.

In summary, results from adoption studies are consistent with the hypothesis that many family-based risk factors, including divorce and interparental conflict, parent-offspring conflict, and parental psychopathology have environmentally mediated effects that are not solely accounted for by genes shared by parents and children. Nevertheless, genetically based child characteristics may play a part in evoking risk exposures such as parent–child conflict (Ge et al., 1996; O'Connor et al., 1998). Finally, the evidence suggests that the association between a mother's smoking during pregnancy and offspring externalizing problems is accounted for by passive G-E correlation, although the process by which a genetic predisposition to engage in externalizing behaviors becomes manifest may involve evocative G-E correlations in the postnatal period (Gaysina et al., 2013).

Limitations of the Adoption Design

Although the adoption design automatically eliminates passive G-E correlations as a source of confounding, it is characterized by various limitations. First, because adoptive parents are closely screened by child welfare services, they tend to be less disadvantaged and less likely to be characterized by psychopathology compared with nonadoptive families (McGue et al., 2007; Stoolmiller, 1999). Thus, the adoption design can be relatively uninformative about the effects of extreme adversity and the restricted range of environments in adoptive families can bias estimates of genetic and environmental influences (Stoolmiller, 1999), although it has been demonstrated that range restriction does not affect the magnitude of adoptive sibling correlations for disinhibitory behaviors and IQ (McGue et al., 2007). Second, the adoption design presumes that adoptive children do not maintain contact with their biological parents. Historically, this assumption has probably been valid, as many samples of adoptees were recruited at a time when both closed and international adoptions were common. However, as open adoptions have become increasingly common, researchers must monitor and quantify the amount of contact between adoptees and biological parents in order to determine whether and how much contact biases heritability estimates (Leve et al., 2007). Moreover, adoptive parents' knowledge of the biological parents' mental or physical health history may color their perceptions of their adopted child's behavior. For example, in comparing the offspring of biological parents

who did versus did not have a history of mental or physical health problems, the former were only shown to have more disruptive behavior problems than the latter (as reported by their adoptive parents) if their adoptive parents knew about the biological parents' history (Riggins-Caspers et al., 1999). In the absence of such knowledge, adoptees' disruptive behavior problems were reported to be low regardless of the biological parents' actual psychiatric or physical health history (Riggins-Caspers et al., 1999).

Research designs that utilize samples of women undergoing assisted reproductive technologies (ARTs) are characterized by similar limitations. Women who use ARTs tend to be older and better educated than women in the population overall (Källén, Finnström, Nygren, & Olausson, 2005; Schieve et al., 2007) and this might not only influence their behavior while pregnant, but also the relationship between their behavior while pregnant and offspring behavior. In addition, although data are limited, women who have taken on the physical, financial, and emotional challenges of ARTs and become pregnant are less likely than other women to engage in behaviors that would put the fetus at risk (Källén et al., 2005). Thus, rates of risky behaviors like smoking or drinking alcohol during pregnancy are likely to be very low in these samples, compromising statistical power, and women who do engage in health-risk behaviors while pregnant are likely to be heavily dependent on substances (Thapar et al., 2009).

GENOTYPE–ENVIRONMENT CORRELATIONS: EVIDENCE FROM TWIN STUDIES

Twin studies have provided much of the evidence for genotype–environment correlations by demonstrating that putative environmental measures are heritable (Plomin & Bergeman, 1991). Twin studies capitalize on the fact that environments vary in the population just like any other phenotype. Some children experience more harsh discipline than others. Some adolescents have more deviant peers than other adolescents. Some adults have happier marriages than other adults. Individual differences in experiences can be decomposed into genetic and environmental components just like variation in any other characteristic. Thus, to the extent that MZ twins have more similar experiences (e.g., with parents or peers) than DZ twins, this is taken as evidence that genetic factors make them more similar. To the extent that MZ twins do not have identical experiences (e.g., one twin is frequently bullied and the other is not), this is taken as evidence that some nongenetic factor is making them different (e.g., they may be in different classes at school). Finally, to the extent that MZ twins are less than twice as similar to one another as DZ twins, this is taken as evidence that shared (or common) environmental factors account for individual differences in experiences. This is because the twin design assumes that their genotype is the only thing that makes MZ twins more similar to one another than DZ twins and, on average, MZ twins are twice as genetically similar to one another as DZ twins. Thus, if genes were the only thing that caused twins to have similar experiences to one another, then MZ twins should be twice as similar to one another as DZ twins. If something other than genes is causing twins to have similar experiences to one another (e.g., a mother's depression is making her prone to use harsh discipline with all her children), then DZ twins will be more than half as similar to one another as MZ twins (Plomin, DeFries, McClearn, & McGuffin, 2008).

Two recent meta-analyses have shown that many of the experiences or exposures that have been investigated in developmental psychology and psychopathology are heritable, including marital quality, social support, parental discipline and warmth, global family environment, and peer relationships (Kendler & Baker, 2007). These also include desirable and undesirable life events, including divorce and exposure to trauma. The weighted heritability of these environments ranges from 6% to 39%, with most ranging from 15% to 35% (Kendler & Baker, 2007). In a meta-analysis focused specifically on parenting, genetic factors accounted for 23% of the variation in measures of maternal and paternal positivity and negativity across 32 studies, with heritability increasing significantly in older versus younger children (Avinun & Knafo, 2014). Finally, other experiences that are thought to be important for children's development including the number of years a person participates in organized sports or music lessons and how frequently children are read to by their parents are also moderately heritable (Vinkhuyzen, van der Sluis, de Geus, Boomsma, & Posthuma, 2010).

Two sets of findings support the hypothesis that genetic influences on putative environments reflect evocative G-E correlations. The first is that genetic influences on experiences that are potentially within an individual's control (e.g., a relationship break-up) are stronger than genetic influences on experiences that are not within an individual's control (e.g., losing one's home in a hurricane) (Kendler, Karkowski, & Prescott, 1999). Relatedly, personal life events (i.e., events that occur directly to an individual) are more highly heritable than network life events (i.e., events that occur to someone within an individual's

social network, thus affecting the individual indirectly) (Bolinskey, Neale, Jacobson, Prescott, & Kendler, 2004; Kendler, Neale, Kessler, Heath, & Eaves, 1993). Together, these findings suggest that something about the individual is evoking or eliciting the event.

The second piece of evidence to suggest that genetic influences on putative environments reflect evocative G-E correlations is that genetic influences on observational measures of parent–child interactions tend to be weaker than genetic influences on parent or child reports of parenting (Avinun & Knafo, 2014; Kendler & Baker, 2007). The presence of an observer and the structure of a parent–child observation session may mean that the parent is reacting more to the situation than to the child's behavior (Avinun & Knafo, 2014).

Behavioral geneticists have never claimed that there are genes for harsh parenting or unhappy marriages per se, so how does one interpret the heritability estimates reported in these meta-analyses? How one interprets the heritability of putative environments depends on who is reporting on the twins' experiences. When twins describe their own experiences (e.g., of receiving parental discipline), then heritability estimates can reflect either of two things: (1) genetic influences on twins' perceptions of their experiences; or (2) genetic influences on twins' behaviors that elicit those experiences. For example, Hanscombe et al. (2010) showed that genetic factors accounted for approximately 20% of the variation in twin children's reports of noise, lack of routine, and chaos in their homes. A subsequent analysis suggested that this heritability estimate was more likely to reflect genetic influences on the twins' perceptions of their environment rather than genetic influences on disruptive behavior problems that could have created a noisy and chaotic environment (Jaffee, Hanscombe, Haworth, Davis, & Plomin, 2012).

When parents report on each of their twin children's experiences, then heritability estimates can only reflect genetic influences on the twins' behavior that elicit those experiences (Ge et al., 1996; Jaffee et al., 2004; O'Connor et al., 1998). For example, Jaffee et al. (2004) found that a common genetic factor accounted for most of the observed relationship between children's antisocial behavior and their experiences of corporal punishment. This suggests that genetic factors are correlated with spanking and smacking because they give rise to oppositional and antisocial behaviors that evoke those behaviors in parents. It bears noting that genetic influences on maternal and paternal positivity are identified not only when parenting is described by each twin in a pair but also when parents report how they treat each of their twins (Avinun & Knafo, 2014).

When *adult* twins report on their (nontwin) children's experiences, the interpretation of the heritability estimate changes. For example, when adult twins describe the disciplinary practices they use with their own children, greater MZ relative to DZ correlations for parental discipline reflect the extent to which the adult's genetic propensities modify or create that experience (Wade & Kendler, 2000).

Using the Multivariate Twin Model to Test for G-E Correlation

The hypothesis that genetic influences on putative environments reflect evocative G-E correlations has been tested most extensively using multivariate twin models. The idea is to identify some behavior or ability that could plausibly evoke the environment and estimate how much of the covariation between the behavior and the environment can be accounted for by genetic influences common to both phenotypes. A range of bivariate (or multivariate) models can be estimated, including Cholesky decomposition models, common factor models, and correlated factor models (Loehlin, 1996).

The Cholesky decomposition model is presented in Figure 7.2 which represents a bivariate model in which Trait 1, might represent some measure of behavior (e.g., aggressive behavior) and Trait 2 might represent

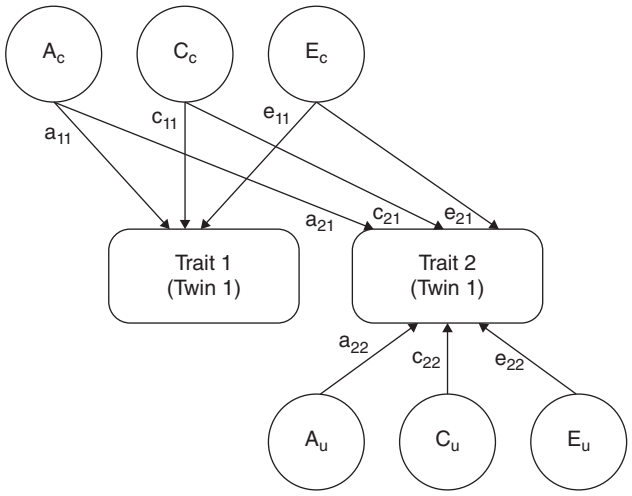


Figure 7.2 Bivariate Cholesky decomposition model. *Note:* A_c refers to genetic factors that account for variation in both phenotypes, C_c refers to common environmental factors that account for variation in both phenotypes, and E_c refers to unique environmental factors (or error) that account for variation in both phenotypes. A_u, C_u, and E_u refer to genetic, common environmental, and unique environmental factors, respectively, that account for variation in only Phenotype 2. The model is presented for twin 1 only. The full Cholesky model (including both twins) would include a correlation equal to 1.0 between the latent C factors (C_c and C_u) for twins 1 and 2 and correlations equal to 1.0 for MZ twins and .50 for DZ twins between the latent A terms (A_c and A_u).

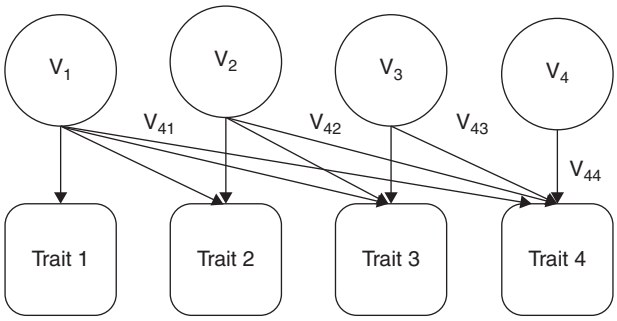


Figure 7.3 Multivariate Cholesky decomposition model. *Note:* Schematic illustrating Cholesky decomposition. Measured traits (Traits 1–4) are regressed on corresponding latent variables (V_1–V_4). V_1 is the total variation in Trait 1 and takes precedence in explaining variance in Traits 2, 3, and 4. V_2 is the residual variance in Trait 2 and has next priority in explaining variance in Traits 3 and 4. V_3 is the residual variance in Trait 3 and has next priority to explain variance in Trait 4. V_4 explains residual variance in Trait 4. Each measured trait is regressed on all preceding latent variables, and all latent variables are uncorrelated. The total variation in Trait 4 is estimated by squaring and summing the paths from V_1 through V_4 to Trait 4 ($v41$ through $v44$, respectively). V_1 through V_4 can be decomposed into additive genetic (A), shared environmental (C), and nonshared environmental (E) components. For example, the total additive genetic variance in Trait 4 would be explained by the squared and summed paths $a41$ through $a44$ from latent variables A_1 through A_4.

some measure of the environment (e.g., delinquent peers). In a Cholesky decomposition, each subsequent observed variable is regressed on the latent A, C, and E variance components of all the previous observed variables. In Figure 7.2, $A_c + C_c + E_c$ explain the total variance in Trait 1. Trait 2 is regressed on the latent variables A_c, C_c, and E_c; in other words, these variance components takes precedence in explaining variance in Trait 2. A_u, C_u, and E_u then explain the residual variance in Trait 2, that is, variance not correlated with A_c, C_c, and E_c. The total genetic variation in Trait 2 is estimated by squaring and summing the genetic paths ($a21$–$a22$). Similarly, shared and unique environmental variation in Trait 2 is estimated by squaring and summing the paths from all C and E components, respectively.

The Cholesky model can be expanded to include additional traits (Figure 7.3). For example, Traits 1 and 2 might represent peer delinquency and aggressive behavior, respectively, measured prior to adolescence. Traits 3 and 4 might represent aggressive behavior and peer delinquency, respectively, measured in adolescence. In this case, V_1 (representing $A_1 + C_1 + E_1$) will have priority in explaining variance in Traits 2, 3 and 4. V_2 will have next priority in explaining variance in Traits 2, 3 and 4. V_3 and V_4 will explain residual variance in Traits 3 and 4, respectively, and are uncorrelated with each other or with V_2 and V_1. Such an analytic approach would allow researchers to temporally order variables and address issues of reciprocal causation.

As an example of this multivariate approach, Jaffee et al. (2012) hypothesized that if the association between chaotic environments and children's disruptive behavior problems reflected a (genetically based) child effect on the environment, then genetic influences on children's disruptive behavior problems at one point in time should account for some of the heritable variation in chaotic environments at a later point in time. Testing this hypothesis involved estimating how much of the variation in the chaotic environment at age 12 was accounted for by genetic factors and then calculating how much of that genetic variation reflected genetic factors that also influenced children's disruptive behavior problems. Although phenotypic cross-lagged regression models had shown that children's disruptive behavior problems predicted increases over time in the level of environmental chaos, the Cholesky decomposition models showed that this child effect on the environment was not genetically based (Figure 7.4). That is, although the chaotic environment was heritable and

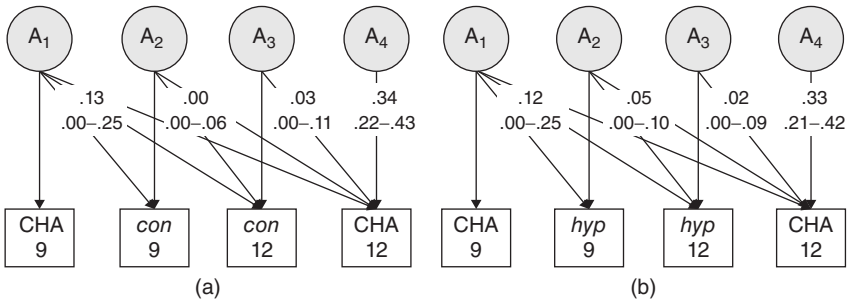


Figure 7.4 Cholesky decomposition showing genetic effects (A) of disruptive behavior on Confusion, Hubbub, and Order Scale (CHAOS) scores at age 12. *Note:* Separate models are shown for the effects of (a) conduct (con) and (b) hyperactivity–inattention (hyp), with both analyses controlling for the genetic effects of CHAOS scores at age 9. A_1 captures the total genetic variation in CHAOS (CHA) scores at age 9; A_2, A_3, and A_4 are the residual genetic variances in disruptive behavior at age 9, disruptive behavior at age 12, and CHAOS scores at age 12, respectively. Standardized (unsquared) path coefficients and 95% confidence intervals are shown.

children's disruptive behavior problems were highly heritable, genetic influences on children's disruptive behavior problems accounted for virtually none of the heritability of the chaotic environment (i.e., the confidence intervals around the A^2 and A^3 paths included zero).

Finally, the basic Cholesky model can be reparameterized to estimate correlated and common factors models which can be useful when there is no logical or theoretical basis for the ordering of variables in the Cholesky decomposition (Loehlin, 1996). Correlated factors models estimate genetic and environmental influences on each trait in a multivariate model and then estimate the correlation between the latent genetic and environmental factors. In the common factors model, genetic and environmental latent factors are decomposed into those that influence all traits in the model and those that are specific to each trait.

In the following section we describe how multivariate twin models have been used to identify behaviors or personality traits that explain genetic influences on putative environments. These efforts generally involve showing that the individual characteristic and the experience or exposure are (1) correlated at the phenotypic level, ideally in fully cross-lagged autoregressive models and (2) heritable in univariate quantitative behavioral genetic analyses. Finally, the multivariate model should show that some significant portion of the genetic variation in the experience or exposure can be accounted for by genetic factors that also influence the behavior or personality trait or that the bivariate heritability is high, indicating that the genes influencing the individual characteristic and the genes influencing the exposure or experience are highly correlated. We focus on five experiences and exposures that have been studied extensively in the literature: parenting, peer relationships, marital status and quality, global family functioning, and classroom characteristics.

Do Genetic Influences on Children's Behavior Account for the Heritability of Parenting Measures?

In child-based twin designs, genetic influences on various measures of parenting have been shown to be at least moderately heritable, including measures of parental hostility (Button, Lau, Maughan, & Eley, 2008; Forget-Dubois et al., 2007; Jaffee et al., 2004; Knafo & Plomin, 2006; Neiderhiser, Reiss, Hetherington, & Plomin, 1999; Shelton et al., 2008; Forget-Dubois et al., 2007; Jaffee et al., 2004); parental warmth (Knafo & Plomin, 2006; Neiderhiser et al., 2004; Neiderhiser, Reiss, Lichtenstein, Spotts, & Ganiban, 2007); and positive parental control strategies (e.g., reasoning or being firm and calm with a child; Knafo & Plomin, 2006).

Parental Hostility. Researchers have hypothesized that children's disruptive, aggressive, and hard-to-manage behaviors evoke harsh or hostile parenting, resulting in G-E correlation. Consistent with this hypothesis, the covariation between parents' use of harsh discipline or hostile parenting and children's antisocial behavior is largely accounted for by a genetic factor common to both phenotypes (Button et al., 2008; Jaffee et al., 2004; Neiderhiser et al., 1999; Shelton et al., 2008).

Genetically based differences in temperament may explain some of these genetic correlations. For example, in a study of approximately 1,300 Swedish twin pairs, genetic influences on aggressive behavior in early adolescence accounted for approximately half of the genetic covariation between parental criticism of adolescent behavior and delinquency in later adolescence, suggesting that genetically based individual differences in the tendency to aggress against others not only elicited criticism from parents, but also promoted delinquent behavior (Narusyte, Andershed, Neiderhiser, & Lichtenstein, 2007).

Longitudinal data potentially shed light on the direction of effects between measures of youth behavior and measures of parenting and can identify the extent to which any cross-lagged associations are accounted for by genetic versus environmental factors. Using data from a longitudinal study of 395 sets of twin and nontwin adolescent siblings, Neiderhiser et al. (1999) estimated cross-lagged associations between measures of adolescent maladjustment (antisocial behavior and depressive symptoms) and measures of maternal and paternal conflict and negativity (e.g., use of coercive and harsh discipline, parent–child conflict, hostility toward child). Parents' reports of conflict negativity at time 1 predicted adolescents' antisocial behavior and depressive symptoms 3 years later, even controlling for stability in adolescent adjustment over time. The reverse was also true: adolescent antisocial behavior and depression predicted change in parental conflict negativity. These cross-lagged phenotypic associations were largely accounted for by genetic factors (Neiderhiser et al., 1999), suggesting that some genetically based temperamental characteristic not only elicited parental conflict negativity but also predisposed adolescents to depression and antisocial behavior.

Parental Control. Although positive parental control strategies (e.g., reasoning, use of firm and calm discipline) are moderately heritable, a study of 9,319 twin pairs assessed at 3, 4, and 7 years of age found that genetic factors

only accounted for a third of the phenotypic correlation, on average, between positive parental control strategies and children's prosocial behavior (Knafo & Plomin, 2006). In contrast, genetic influences on parental negativity (e.g., shouting, smacking) were substantially larger in this study and the correlation between parental negativity and (low) prosocial behavior was largely accounted for by genetic factors (Knafo & Plomin, 2006). Thus, genetic influences on prosocial behavior account for substantially more of the heritability in parental negativity than in parents' positive control strategies.

Overprotective or overcontrolling parenting is another form of parental control that has been shown to be heritable (Eley, Napolitano, Lau, & Gregory, 2010). In a study of 300 8-year-old twin pairs, those who experienced high levels of maternal control during a cooperative Etch-a-Sketch task in which mothers were explicitly instructed to not touch their child's dial (highly controlling mothers disobeyed these instructions) had significantly more symptoms of anxiety compared with children who experienced lower levels of maternal control (Eley et al., 2010). Although genetic influences on child anxiety were correlated with genetic influences on observed maternal control, the absence of longitudinal data makes it difficult to determine whether anxious children were eliciting maternal control or whether overcontrolling mothers were increasing their child's anxiety (Eley et al., 2010).

Do Genetic Influences on Children's Behavior Account for the Heritability of Peer Relationships?

Peer Rejection and Victimization

Peer rejection and peer victimization have been shown to be heritable, with heritability estimates ranging from 16% (Boivin, Brendgen, Vitaro, Dionne, et al., 2013) to 73% (Ball et al., 2008) depending on the child's age, the informant, and the type of peer difficulty (victimization or rejection). Genetic factors account for the stability of victimization experiences from primary to secondary school (Bowes et al., 2013) and the stability of peer difficulties (including rejection and victimization) across middle childhood (Boivin, Brendgen, Vitaro, Dionne, et al., 2013). In a series of studies, Brengden and colleagues (2009, 2011, 2014) have attempted to identify the source of genetic influences on children's peer victimization and rejection. The hypothesis underlying this research is that children are disliked (or actively victimized) partly because their behavior makes them unpopular with other children. For example, children who are aggressive experience more victimization by peers than children who are less aggressive (Brendgen et al., 2011). Similarly children who are depressed are less well liked than their peers who have fewer symptoms of depression (Brendgen et al., 2009). At the phenotypic level, these associations have been shown to reflect both social selection and social causation. For example, although kindergarteners who experienced higher levels of peer difficulties (rejection and victimization) had more disruptive behavior problems in first grade than kindergarteners who experienced lower levels of peer difficulties, the reverse was also true; the more disruptive children were in kindergarten, the more peer difficulties they experienced in first grade (Boivin, Brendgen, Vitaro, Forget-Dubois, et al., 2013).

These relationships between peer difficulties and children's emotional and behavioral problems were shown to be at least partly genetically mediated. For example, genetic factors accounted for approximately a quarter of the variation in peers' reports of how often children in their first grade classrooms were victimized by other children (e.g., hit, pushed, called names; Brendgen et al., 2011) Genetic influences on peer victimization were due entirely to genetic factors that also influenced children's aggressive behavior (Brendgen et al., 2011). In a longitudinal investigation stemming from kindergarten to first grade, 48% of the variation in first graders' peer difficulties was accounted for by genetic factors, with 14% of the heritability attributable to genetic factors that also influenced their disruptive behavior a year earlier in kindergarten (Boivin, Brendgen, Vitaro, Forget-Dubois, et al., 2013). The findings suggested that genetically influenced traits like aggression and disruptive behaviors elicit a negative response from peers.

Similar to the findings for aggression, genetic factors accounted for approximately 30% of the variation in how well-liked children were at the age of 6 years (Brendgen et al., 2009). Approximately half of the genetic variance in 6-year-old children's teacher-reported depressive symptoms was accounted for by genetic factors that also influenced individual differences in how much children were liked or not liked by their peers, suggesting that a genetic predisposition for depression may increase children's exposure to peer rejection (Brendgen et al., 2009).

In contrast to the findings related to aggression and depression, children who were physically unhealthy in the preschool period were not victimized more often in middle childhood (as reported by teachers from age 6 to 12 years) than physically healthier children (Brendgen et al., 2014). Rather, peer victimization in middle childhood predicted physical health problems in adolescence, with genetic influences on peer victimization accounting

for some of the genetic variation in adolescent physical health (Brendgen et al., 2014). Thus, although this study failed to identify the source of genetic variation in peer victimization, it did establish that the association between peer victimization and later physical health was partly genetically mediated.

Prosocial and Deviant Peers

Peer deviance has been shown to be heritable (Harakeh et al., 2008; Hicks et al., 2012; Iervolino et al., 2002; Kendler et al., 2008; Rose, 2002; Samek, Keyes, Iacono, & McGue, 2013), although some studies of early adolescence have identified very small genetic influences on peer deviance (Bullock, Deater-Deckard, & Leve, 2006; Walden, McGue, Iacono, Burt, & Elkins, 2004) and others have identified larger genetic influences in some samples than others (Iervolino et al., 2002). The heritability of affiliation with deviant peers increases from early adolescence to young adulthood, reaching approximately 50% (Kendler et al., 2007; Tarantino et al., 2014). Although many youth who affiliate with deviant peers in mid-adolescence continue to affiliate with deviant peers in young adulthood ($r = .37$)(Tarantino et al., 2014), different factors account for the stability of deviant peer affiliation at different points in time. For example, Tarantino et al. (2014) showed that the phenotypic correlation between deviant peer affiliation at 15 and 18 years was $r = .58$, and that shared environmental factors largely accounted for this stability. In contrast, deviant peer affiliation was equally stable from age 18 to 21 years ($r = .59$), yet genetic factors accounted for stability in the transition from late adolescence to early adulthood (Tarantino et al., 2014).

Researchers have hypothesized that the heritability of deviant peer affiliation reflects genetic influences on aggressive, antisocial, and risk-taking behaviors that cause adolescents to choose delinquent peer groups in which these genetic predispositions can be expressed. If supported, this hypothesis counters social causation theories that propose that affiliating with deviant peers causes youth to initiate antisocial behavior or to increase their antisocial or risk-taking behavior.

There is evidence for genetically mediated selection effects into deviant peer groups. For example, in a sample of nearly 1,800 twins who reported retrospectively on their cannabis use and peer deviance when they were 15 to 17 years old, 18 to 21 years old, and 22 to 25 years old, the best-fitting model was one in which genetic, shared environmental, and nonshared environmental influences on cannabis use and peer deviance were freely estimated and in which a phenotypic regression path ran from cannabis use to peer deviance, accounting for 45% of the variation in the peer deviance (Gillespie, Neale, Jacobson, & Kendler, 2009). Cannabis use accounted for 50% (at ages 15 to 21) to 78% (at ages 22 to 25) of the total genetic variance in peer deviance. This model provided the best fit to the data at all three time points assessed, suggesting that individuals who use cannabis actively select similarly deviant peers.

Similar to the findings for cannabis use, the relationship between conduct problems and peer deviance also appears to be genetically mediated. Using retrospective data on conduct problems and peer deviance at ages 8 to 11 years, 12 to 14 years, and 15 to 17 years, Kendler, Jacobson, Myers, and Eaves (2008) showed that both conduct disorder and peer deviance were heritable, with genetic influences increasing over time. The best-fitting model showed that genetic factors accounted for variation in conduct problems, with aggressive, rule-breaking youth actively choosing to affiliate with deviant peers. At the same time, shared environmental factors accounted for variation in peer deviance, with deviant peer groups promoting conduct problems among twins in the study. Although the genetically mediated pathway by which conduct problems led youth to select deviant peers was constant across adolescence, the pathway by which the effect of the shared environment on conduct problems was mediated by peer deviance was only apparent in early adolescence (Kendler et al., 2008).

In contrast to findings regarding cannabis use and conduct problems, the evidence on alcohol use in adolescence is more consistent with an environmentally-versus-genetically mediated pathway. For example, in a sample of adoptees, the covariation between peer deviance and alcohol use was largely accounted for by shared environmental factors (Samek et al., 2013), suggesting that some third environmental variable explains why youth who affiliate with deviant peers are more likely to use alcohol in adolescence than youth who do not affiliate with deviant peers. Similarly, in a study of 14-year-old twins, Walden et al. (2004) showed that the covariation between measures of peer deviance, parent–child relationship quality, and lifetime substance use (a count of substances ever used) was accounted for entirely by a shared environmental factor. Although Harden et al. (2008) found that genetic variation in best friends' substance use was partly explained by the same genetic factors that accounted for adolescents' substance use (consistent with the possibility that some genetic predisposition causes adolescents to selectively affiliate with substance-using peers), having best friends who frequently smoked cigarettes and drank alcohol was associated with more frequent drinking and smoking among target adolescents, even adjusting for genetic influences on best friends' substance use.

In summary, although there is evidence from twin studies that genetic predispositions—perhaps reflecting aggression or sensation-seeking—cause adolescents to selectively affiliate with deviant peers, the evidence is mixed as to whether peer deviance has causal effects on adolescent behavior, with studies of adolescent cannabis use suggesting not, but studies of adolescent delinquency, alcohol, and cigarette use providing evidence consistent with causal effects, at least in early adolescence.

Finally, variation in the tendency to affiliate with prosocial peers is also heritable (Hicks et al., 2012). Researchers have hypothesized that the heritability of prosocial peer affiliation reflects genetic influences on antisocial behavior (wherein youth who are low in antisocial behavior selectively affiliate with prosocial peers) and this hypothesis is moderately well supported; for example, the correlation between genetic factors influencing adolescent antisocial behavior and youth prosocial peer affiliation was $r_g = -.32$ for boys and $r_g = -.51$ for girls (Hicks et al., 2012). It is possible that genetic influences on adolescent prosocial behavior account for a larger part of the heritability of prosocial peer affiliation.

Shy Peers

Although the majority of research on peer characteristics has focused on peer deviance, Guimond et al. (2014) tested whether socially reticent youth selectively affiliate with socially reticent peers. Having been observed interacting with their peers in an experimental task, kindergarten-aged twins were categorized as being at higher versus lower genetic risk for social reticence (measured by the percent of time they spent in solitary onlooking behavior during the task) on the basis of information about the pair's zygosity and the cotwin's social reticence (Jaffee et al., 2005; Kendler & Kessler, 1995; Ottman, 1994). For example, youth at highest genetic risk for social reticence were MZ twins whose co-twin scored above the 75th percentile on the social reticence measure and youth at lowest genetic risk were MZ twins whose cotwin scored below the 75th percentile on the measure of social reticence (Guimond et al., 2014). Youth who were at higher genetic risk for social reticence were more socially reticent themselves and had more socially reticent friends than youth who were at lower genetic risk for social reticence, indicating an active G-E correlation (Guimond et al., 2014).

Do Genetic Influences on Personality Traits Account for the Heritability of Marital Phenotypes?

Researchers have shown that being married (Jerskey et al., 2010; Johnson, McGue, Krueger, & Bouchard, 2004; Trumbetta, Markowitz, & Gottesman, 2007) and being divorced (Jerskey et al., 2010; Jockin & McGue, 1996; McGue & Lykken, 1992) are accounted for by genetic and nonshared environmental factors, although these tend to be nonoverlapping (Jerskey et al., 2010) and the magnitude of heritability estimates for marriage changes over time, increasing as individuals transition from their twenties to their thirties, but decreasing to near zero as individuals reach their fifties (Trumbetta et al., 2007). Moreover, marriage quality is heritable, with 34% of the variation in marital satisfaction accounted for by genetic factors and the remainder accounted for by nonshared environmental factors (Spotts, Neiderheiser, Towers, et al., 2004).

Researchers have hypothesized that genetic influences on marital status and marital quality can be accounted for by genetic factors that also account for variation in husbands' and wives' personality characteristics. At the phenotypic level, ever-divorced individuals score lower on measures of constraint, but higher on measures of both positive emotionality (the facet of social potency in particular) and negative emotionality compared with never-divorced individuals (Jockin & McGue, 1996). In a study of over 3,000 twins, genetic factors accounted for 55% to 59% of the variation in divorce, with genetic influences on a composite personality score accounting for approximately a third of the genetic variation in divorce (Jockin & McGue, 1996).

Phenotypically, ever-married and never-married individuals also differ in terms of personality, with ever-married men and women scoring higher on measures of positive emotionality and constraint and lower on measures on negative emotionality than never-married men and women (Johnson et al., 2004). Using the same sample of over 3,000 twins that was included in the study by Jockin and McGue (1996), genetic factors accounted for 68% to 72% of the variation in marital status (Johnson et al., 2004). The bivariate heritability was .68 for males and .83 for females, indicating that genetic factors accounted for most of the covariation between the personality composite and marital status (Johnson et al., 2004).

Finally, personality characteristics are correlated phenotypically with marital satisfaction: individuals who are relatively more aggressive, anxious, and relatively less sociable or optimistic tend to report lower levels of marital satisfaction and warmth (Ganiban et al., 2009; Spotts, Lichtenstein, et al., 2005). Moreover, genetic influences on these personality traits account for 50% of the genetic effect on marital quality (Spotts, Lichtenstein, et al., 2005). In an extension of this work, Ganiban et al. (2009) showed that parents who reported lower quality marriages tended to engage in more negative parenting practices as well, with parent personality characteristics accounting for 42% of

this phenotypic association. Moreover, the genetic factors that influenced parents' aggressive, anxious, and sociable personality traits accounted for 57% of the total genetic covariation between marital quality and parenting.

In summary, marital status and marital quality are moderately to highly heritable. Anywhere from a third to half of this genetic variation can be accounted for by genetic factors that also influence personality characteristics.

Do Genetic Influences on Personality Traits Account for the Heritability of Global Family and Interparental Conflict?

Global family conflict refers to the degree of openly expressed anger, aggression, and hostility in a household. Individual differences in global family conflict are moderately heritable (22%) with the remainder of the variance accounted for by nonshared environmental factors (Horwitz et al., 2011). In a study of adult twins, Horwitz et al. (2011) showed that 55% of the genetic variation in global family conflict was accounted for by genetic influences on parents' aggressive personality. Thus, the data are consistent with the hypothesis that parents who have a genetic predisposition to behave aggressively generate and evoke conflict within the family environment.

Whereas parent personality characteristics may evoke conflict within a family, children's personality characteristics filter their perceptions of family conflict. For example, in a study of 600 6- to 11-year-old twin pairs, Nikolas, Klump, and Burt (2013) showed that genetic factors accounted for 2% to 31% of the variation in different aspects of children's perceptions of interparental conflict. Although genetic factors accounted for a small and nonsignificant 2% of the variation in children's perceptions of how frequently and intensely parents argued, they accounted for a significant 31% of the variation in how much children blamed themselves for their parents' arguments. Thus, the data are consistent with the possibility that personality characteristics or social-cognitive biases may influence children's attributions for interparental conflict, but not their perceptions of relatively more objective features of interparental conflict, such as its frequency or severity.

Do Genetic Influences on Children's Behavior Account for the Heritability of Classroom Characteristics?

Multivariate twin models have been used to identify not only G-E correlations within families or peer groups but also how heritable child characteristics evoke reactions within the classroom. For example, 5-year-olds who were rated by parents, teachers, and observers as relatively hostile, oppositional, impulsive, and inattentive required more attention and effort by teachers when they reached early adolescence (Houts, Caspi, Pianta, Arseneault, & Moffitt, 2010). Underlying this relationship was a G-E correlation, whereby genetic factors accounted for approximately 51% of the variation in teacher effort and approximately a third of those genetic factors also influenced children's challenging behavior (Houts et al., 2010).

Adolescents' perceptions of the quality of their learning environment have also been shown to have a genetic basis. Fourteen-year-old twins in the Twins Early Development Study were asked to rate the science learning environment in their classrooms and among their peers with questions such as, "My teacher asks questions that have more than one answer," "I use information to support my answers," "My friends talk about Science outside of class," and "My friends are interested in Science" (Haworth et al., 2013). Genetic factors accounted for 37% of the variation in classroom environment and 39% of the variation in the peer environment with these estimates nearly as large in magnitude as the heritability of a science test taken by participants ($h^2 = 50\%$). Indeed, the phenotypic correlation between science achievement and the science learning environment ($r = .22$) was largely accounted for by genetic factors, suggesting that youth who are genetically inclined to be good at science may perceive the science learning environment differently than youth who are less well inclined (Haworth et al., 2013).

Using the Twin Design to Rule Out Genetic Confounding by Evocative or Active G-E Correlation

The possibility that genetically based individual differences in behavior, temperament, and personality underlie the heritability of parent–child, peer, marital, or classroom relationships, calls into question theoretical models which posit that these relationships or experiences have causal effects on a person's health, behavior, or psychological well-being. The alternative explanation is that individuals evoke or actively select environments or experiences on the basis of the same genetic predispositions that give rise to the phenotype in question (e.g., health, behavior, or psychological well-being). For example, having a warm and trusting relationship with a spouse may decrease a person's risk for depression in a causal fashion. However, the fact that both marital quality and risk for depression are influenced by the same genetically based personality features suggests that individuals who are prone to depression on the basis of their personality

makeup may evoke conflict and lack of trust in their relationships or choose spouses with whom they are unlikely to develop warm and trusting relationships. Such a process would be reflective of evocative or active G-E correlation.

A series of studies have been designed to test whether individual differences in mental, behavioral, or physical health are caused by marital status or marital quality or—alternatively—whether observed associations can be accounted for by genetic selection factors (i.e., the genetic factors that predispose individuals to marry or that influence marriage quality are also involved in health outcomes). In general, these studies show that although there is some selection into marriage (and into highly supportive or highly conflictual marriages), marital status, and marriage quality have causal effects on physical and mental health outcomes. For example, in a sample of 1,566 pairs of same-sex, married twins from Australia, Beam et al. (2011) showed that genetic factors partly accounted for the association between marital support and depressive symptoms in women, but that women (and men) who perceived themselves as having more support from their spouse reported fewer symptoms of depression.

In the Twins and Offspring Study of adult female twins in Sweden, high marital quality (as reported by wives) and social support were both associated with women's well-being and self-worth (Spotts, Pedersen, et al., 2005) as well as women's depressive symptoms (Spotts, Neiderhiser, Ganiban, et al., 2004). Genetic factors accounted for the covariation of marital quality, social support, and women's well-being, self-worth, and depressive symptoms (Spotts, Neiderhiser, Ganiban, et al., 2004; Spotts, Pedersen, et al., 2005). Nonshared environmental factors accounted for the covariation of marital quality specifically and women's well-being, self-worth, and depressive symptoms, indicating that experiences that differed for twins in a family explained why women who were in higher-quality marriages had higher psychological well-being, a higher sense of self-worth, and fewer symptoms of depression than women in lower quality marriages. The data suggested that husbands might have been the source of this nonshared experience, given that nonshared environmental factors accounted for the covariation of husbands' reports of marital quality and their wives' reports of social support and well-being (Spotts, Pedersen, et al., 2005). That is some quality of the husbands themselves that would cause twins in a pair to differ in their psychological well-being and their perceptions of social support might also have explained why some husbands reported higher levels of marital satisfaction than others.

Bivariate twin studies have also been used to test the hypothesis that marital status is related to physical, mental, and behavioral health and that observed associations are not explained by the tendency for healthier and more prosocial adults to marry. Two studies have used data from the National Longitudinal Survey of Adolescent Health (Add Health) to test whether marital status is related in a causal fashion to antisocial behavior, mental health, substance use, or physical health. Both found that married adults were less likely to engage in antisocial behavior than unmarried adults (Barnes & Beaver, 2012), with the benefits of being in a relationship extending to cohabiting couples as well (Horn, Xu, Beam, Turkheimer, & Emery, 2013). Moreover, married and cohabiting adults reported fewer symptoms of depression, less cigarette smoking or alcohol use and less suicidal ideation than young adults who were single (Horn et al., 2013). By estimating genetic and environmental influences on marital status (married or cohabiting versus single) and by controlling for those genetic and family background factors that select individuals into relationships, Horn et al. (2013) showed that the association between marital status and depressive symptoms, suicidal ideation, and alcohol remained significant. In contrast, the association between marital status and cigarette smoking was accounted for entirely by genetic and shared environmental factors that select adults into married or cohabiting relationships. The studies differed with respect to findings on marital status and antisocial behavior, with one showing that being married continued to have a significant (though greatly diminished) effect on reducing antisocial behavior after controlling for genetic factors (Barnes & Beaver, 2012) and the other finding that genetic and shared environmental factors entirely explained why married and cohabiting adults had a lower risk of antisocial behavior than single adults (Horn et al., 2013). Married adults, however, engaged in less antisocial behavior than cohabiting adults and this association was not accounted for by genetic or shared environmental selection factors (Horn et al., 2013).

Finally, the twin design has been used to test whether evocative or active G-E correlations account for the association between various sources of stress (e.g., chronic health problems, employment problems) and symptoms of depression (Schnittker, 2010). Heritability estimates for stressors ranged from $h^2 = .00$ for network life events involving spouses or children to $h^2 = .37$ for perceptions of chronic discrimination. Comparing the fit of models in which the effect of a stressor on depression was estimated (1) in the absence of a genetic correlation and (2) in the presence of a genetic correlation between the two

phenotypes, model fit tended to improve when the genetic correlation was estimated, with the result being that the effect of the stressor on depressive symptoms and on diagnoses of depression tended to be reduced substantially. For example, the correlation between genetic influences on perceived financial strain and depressive symptoms was $r = .38$ and the coefficient for the effect of financial strain on depressive symptoms was reduced from .15 to .08 in the presence of the genetic correlation, both $p < .05$. Thus, the findings suggest that G-E correlations explain some, but not all, of the association between negative life events and depression.

Twin Studies of Passive rGE

Two extensions of the classical twin design are informative about passive genotype–environment correlations: the children of twins (CoT) design and the longitudinal twins and parents design (LTaP).

The CoT design involves parents who are twins and their offspring. The design is premised on the observation that in MZ pairs, the magnitude of the genetic relationship between aunts or uncles and nieces or nephews is the same as that between parents and offspring. For example, a female MZ twin shares 50% of her segregating genes with her own children and with her sister's children. In contrast, in DZ pairs, aunts or uncles are more closely related to their own children than to their nieces and nephews. The design also capitalizes on the fact that twin pairs may be discordant for the circumstances in which they raise their children if, for example, one twin is divorced and the other is not. If the children who are growing up in an intact household have fewer problem behaviors than their cousins whose parents have divorced, then there is a strong basis for presuming that divorce causes offspring maladjustment, because the design automatically controls for genetic differences in pairs discordant for divorce (completely, in the case of MZ pairs wherein the nieces and nephews of the non-divorced twin will have inherited the same genetic liability as the sons and daughters of the divorced twin) and for environmental confounds shared by twins (e.g., ethnicity, socioeconomic background). Figure 7.5a illustrates the pattern of group differences indicative of an environmentally mediated effect of divorce. Comparing the white and black bars, we see that cousins who are discordant for the experience of divorce and whose mothers are MZ twin sisters, differ significantly in their level of behavior problems. The same pattern of effects is observed for the offspring of DZ twins. In contrast, a genetically mediated effect is indicated if differences among cousins whose mothers are discordant for divorce are more pronounced if the mothers are DZ versus MZ twins (Figure 7.5b). This is because genetic sources of confounding are controlled more completely in MZ versus DZ twin families. More formally, a range of analytic approaches is used to model CoT data, including hierarchical linear modeling (Raudenbush & Bryk, 2002), logistic regression models (e.g., Knopik, Jacob, Haber, Swenson, & Howell, 2009), and structural equation models (e.g., Schermerhorn et al., 2011).

Children of Twins and Family Structure and Function

Children of twins studies have tested whether various aspects of family functioning (e.g., marital status, marital quality, family conflict, harsh discipline) are likely to



Figure 7.5 Interpreting patterns of findings in children of twins studies. *Note:* As shown in Figure 7.5a, an environmentally mediated effect of divorce on offspring behavior problems is indicated if children whose mother is divorced have more behavior problems than their cousins whose mother is married and this difference is similar in magnitude regardless of whether cousins come from MZ versus DZ twin families. As shown in Figure 7.5b, a genetically mediated effect of divorce on offspring behavior problems is indicated if differences among cousins whose mothers are discordant for divorce is more pronounced if the mothers are DZ versus MZ twins.

have causal effects on offspring outcomes, even accounting for the possibility of passive G-E correlation. For example, in a series of papers and two different samples, D'Onofrio and colleagues (D'onofrio, Turkheimer, Emery, Harden, Turkheimer, et al., 2007; D'Onofrio, Turkheimer, Emery, Maes, et al., 2007c; D'Onofrio et al., 2005, 2006) compared the offspring of twins discordant for *divorce*. The results were consistent with a causal effect of divorce—particularly before the age of 16—on young adult psychopathology, early sexual intercourse, and educational problems. However, the effects of divorce on early cohabitation and earlier initiation of drug use were genetically mediated (D'Onofrio et al., 2006) and some evidence for genetic mediation was found in the case of offspring tendency to divorce (D'Onofrio, Turkheimer, Emery, Harden, et al., 2007).

In contrast to the causal effect of divorce on offspring psychopathology and some forms of health risk behaviors, the effect of growing up with a stepfather in the household on early age-at-menarche is largely genetically mediated (Mendle et al., 2006, 2009). In a sample of female twins and their daughters, cousins who were discordant for the presence of a stepfather in the household did not differ significantly with respect to age-at-menarche, suggesting that some uncontrolled familial liability accounted for the association between stepfather presence and early age at menarche in the sample overall (Mendle et al., 2006). The sample, however, was underpowered to determine whether the source of the familial liability was genetic or environmental; cousins who differed with respect to the presence of a stepfather may have been similar with respect to age-at-menarche because they were genetically similar or because some other feature of their mothers' backgrounds made them similar to one another.

These findings on stepfather presence and age-at-menarche were replicated in a Children of Siblings sample (Mendle et al., 2009). The Children of Siblings design is a variation of the CoT design that uses information from nontwin sibling dyads who vary in their genetic relatedness (e.g., full siblings vs. half siblings) to estimate the magnitude of genetic and environmental confounds on observed associations between exposures and offspring outcomes. Again, a familial liability explained the association between father absence and age-at-menarche (Mendle et al., 2009). The fact that the difference in age-at-menarche between cousins who were discordant for father absence was greater among the offspring of nontwin siblings than among the offspring of twin siblings suggests that the familial liability was genetic in origin (Mendle et al., 2009).

Two CoT studies have shown that the association between *marital conflict* and offspring externalizing problems is largely accounted for by genetic factors common to both (Harden, Turkheimer, et al., 2007; Schermerhorn et al., 2011), although the model fit was poor and the path estimating common genetic influences on marital conflict and offspring externalizing problems was only marginally significant in one of the studies (Schermerhorn et al., 2011). Schermerhorn et al. (2011) also measured how much parents agreed on how to raise their children and found that youth whose parents shared more similar views had fewer externalizing problems than youth whose parents' views were less similar, but this relationship was partly genetically mediated. In contrast, the greater the level of marital conflict and the greater the level of disagreement about children, the more symptoms of internalizing problems offspring had, even accounting for genetic factors common to marital conflict and internalizing problems and controlling for socioeconomic status (Schermerhorn et al., 2011).

Finally, Lynch, Turkheimer, D'Onofrio, Mendle, & Emery (2006) showed that, within a nuclear family, children who experienced more *harsh physical discipline* than their siblings, had more externalizing problems than their siblings. In addition, children who experienced more harsh physical discipline than their cousins had more externalizing problems than their cousins and the magnitude of this effect was no larger in DZ twin families (where genetic confounds are uncontrolled) than in MZ twin families (where genetic confounds are automatically controlled). Thus, findings were consistent with a causal effect of harsh physical discipline on antisocial behavior.

In summary, the preponderance of evidence from CoT studies supports the hypothesis that divorce, family conflict, and harsh discipline have causal effects on offspring psychopathology, even controlling for genetic factors that could account for observed associations. In contrast, girls who have lived with a stepfather tend to have an earlier age-at-menarche than girls who have not lived with a stepfather and youth whose parents' marriages are conflictual and unsupportive tend to have more externalizing problems than youth whose parents are more happily married because of the presence of passive G-E correlations. Given the high co-occurrence of marital conflict, divorce, and family conflict, it is not clear why only the effects of marital conflict appear to be genetically mediated. More research is needed to determine whether this finding is a function of the samples used to study marital conflict which, to date, have been restricted to intact families (Harden, Turkheimer, et al., 2007; Schermerhorn et al.,

2011). Given that these families may be intact because the parents experience relatively low levels of marital conflict, it would be important to replicate findings in samples that are at higher risk for marital conflict.

Children of Twin Studies of Teen Motherhood

The two CoT studies of adolescent motherhood have shown that the relationship between adolescent motherhood and offspring conduct problems is environmentally mediated and not accounted for by passive G-E correlation. Using data from a sample of Australian twins and their children (Harden, Lynch, et al., 2007) showed that the adolescent and adult offspring of teen mothers reported having had more behavior problems (i.e., conduct, oppositional, attention, and hyperactivity problems), substance use problems, and symptoms of depression compared with their cousins whose mothers delayed childbearing beyond adolescence. However, statistical power was too low to determine whether the magnitude of this effect differed in MZ versus DZ twin families, which would have provided additional information about potential genetic mediation of the observed effect.

Using data from a large Swedish registry sample, Coyne et al. (2013) compared criminal convictions among adult offspring born to twins versus nontwin siblings who were discordant for teen motherhood. Criminal conviction rates varied among cousins as a function of their mother's age at first birth, regardless of whether mothers were full siblings, dizygotic twin, or monozygotic twin siblings. For example, in families where mothers were MZ twins, offspring born to the teen mother were 1.4 times more likely to be convicted of a crime compared to the offspring of her sister who had delayed childbearing beyond adolescence (Coyne, Langstrom, Rickert, Lichtenstein, & D'Onofrio, 2013).

Children of Twin Studies of Parental Alcoholism

Three studies have used the CoT design to test whether the relationship between parent and offspring alcohol use problems is environmentally mediated or can be accounted for by familial factors, including passive G-E correlation. One study produced evidence of an environmentally mediated effect: the offspring of MZ male twins who were alcohol dependent had significantly greater risk for alcohol use disorder than their cousins whose father was not alcohol dependent (Jacob et al., 2003). In contrast, another study found that the offspring of MZ twins who were discordant for alcohol use disorders had equally high levels of alcohol use disorder symptoms regardless of whether their own parent was affected by alcohol use disorder (Slutske et al., 2008). Power was too low to determine whether genetic or environmental factors shared within twin families primarily accounted for the intergenerational transmission of risk for alcohol use disorders (Slutske et al., 2008). Differences between the two studies were potentially accounted for by the use of different statistical approaches. Slutske et al. (2008) explicitly estimated the effect of 0, 1, or both twins in the family having alcohol use disorder whereas Jacob et al. (2003) did not. This between-twin-families effect was a stronger predictor of offspring alcohol use problems than the within-twin-family effect (Slutske et al., 2008), suggesting that the differences observed by Jacob et al. (2003) among offspring of discordant twin pairs may have been reduced with controls for twin-family-wide alcohol use density. Moreover, a follow-up study of the sample included in Jacob et al. (2003) failed to detect evidence of an environmentally mediated effect of childhood exposure to paternal alcohol dependence (i.e., before age 12 years) and offspring risk for alcohol use disorder (Duncan et al., 2006).

Several other studies have tested whether the relationship between parental alcoholism and offspring conduct problems or ADHD is environmentally mediated or can be accounted for by familial factors. Two studies, both using data from an Australian twin sample, have shown that the relationship between maternal alcohol use disorder and symptoms of ADHD (Knopik et al., 2006) and parental alcohol use disorder and symptoms of externalizing problems (Waldron, Martin, & Heath, 2009) is likely to be genetically mediated. Similarly, data from a study of male MZ twins, discordant for alcohol dependence or abuse found that offspring of the unaffected twin had equally high levels of conduct disorder symptoms compared with their cousins whose father was alcohol dependent (Haber, Jacob, & Heath, 2005). Paternal alcoholism, in contrast, was only weakly related to offspring ADHD and this effect was completely reduced in a model that controlled for maternal characteristics (Knopik et al., 2009). Across studies, the weight of evidence supports the hypothesis that the association between parental alcohol use and offspring psychopathology is genetically rather than environmentally mediated.

Children of Twins and Parental Depression

Parents' symptoms of depression and offspring perceived self-competence were measured in a sample in which the mothers and fathers were members of 909 same-sex adult twin pairs (Class et al., 2012). In the sample overall, adolescent and young adult offspring tended to have lower perceived self-competence the more symptoms of depression their mothers or fathers had. Compared with

their cousins, however, with whom they shared a familial liability for depression and associated phenotypes, the offspring of the sister who was relatively more affected by depression had poorer perceived self-competence if the sisters were dizygotic rather than monozygotic twins. In contrast, the offspring of the brother who was relatively more affected by depression did have poorer perceived self-competence than the offspring of the relatively less affected brother, regardless of the pair's zygosity (Class et al., 2012). Thus, the environment created by fathers who suffer from depression is likely to have adverse effects on their children's perceived self-competence, although the mechanism is unclear. In contrast, the observed association between mothers' depression and offspring perceived competence is likely to result from an underlying genetic liability rather than anything about the environment in which depressed mothers raise their children.

The relationship between parent and offspring depression was shown to be environmentally mediated in a sample of nearly 1,300 adult twins from Australia and their spouses and offspring (Singh et al., 2011). Even controlling for the spouse's history of depression, the offspring of the depressed twin in a pair had higher rates of depression than the offspring of the nondepressed twin, regardless of the pairs' zygosity (Singh et al., 2011). In contrast, the association between parental depression and offspring conduct problems was genetically mediated, whereby the offspring of the depressed twin only had higher rates of conduct disorder than the offspring of the nondepressed twin if the pair were DZ, but not if they were MZ (Singh et al., 2011).

Strengths and Limitations of the CoT Design

Strengths of the CoT design include strenuous controls for genetic and environmental factors correlated with the candidate environment, automatically ruling out most unmeasured confounders. However, the design is also characterized by a number of limitations. First, it does not automatically control for unmeasured environments that are correlated with the candidate environment and that are *not* common to both twins. These nonshared factors must be measured explicitly and included as covariates in the design. Second, when the candidate environment is likely to be influenced by both parents (i.e., the twin and his or her spouse), the design may not reliably distinguish between direct and genetically mediated effects of the candidate environment on the offspring phenotype (Eaves, Silberg, & Maes, 2005). This problem might be mitigated by including measured characteristics of spouses as covariates (D'Onofrio et al., 2005; Rutter, Pickles, Murray, & Eaves, 2001). Third, the design does not control for reciprocal effects of the child's behavior on the family environment, although the direction of effects can be addressed in the extended children-of-twins design (see below).

Fourth, the design—like all twin designs—assumes the absence of assortative mating, even though assortative mating is moderately high for most psychiatric disorders and antisocial behavior (Galbaud du Fort, Bland, Newman, & Boothroyd, 1998; Krueger, Moffitt, Caspi, Bleske, & Silva, 1998; Maes et al., 1998). Assortative mating could confound correlations between the twin parent and his or her offspring if the spouse's behavior is strongly associated with the twin parent's behavior. Assortative mating in the grandparental and twin parental generations could also lead to violations of the assumption that DZ twins share half of their segregating genes, on average, and that the offspring of DZ twins will share an eighth of their segregating genes, on average. With assortative mating, DZ twins and or cousins who are offspring of DZ twins will have a greater coefficient of genetic relatedness with corresponding implications for estimates of genetic and environmental influences on phenotypic variance.

Fifth, the design assumes an intergenerational version of the equal environments assumption—namely that adult MZ twins do not spend more time together (and with their nieces and nephews) than adult DZ twins and, as a result, the offspring of MZ twins are not exposed more than the offspring of DZ twins to the environments in which their cousins reside. An explicit test of this assumption found that adult MZ twins did have more contact with each other than adult DZ twins, but that level of contact did not interact with zygosity to predict offspring externalizing problems (Koenig, Jacob, Haber, & Xian, 2010).

Sixth, in the absence of extremely large samples and large parent-offspring correlations, the CoT design cannot reliably estimate which confound—genetic or environmental—accounts for the largest portion of the association between the environment and offspring behavior (Slutske et al., 2008).

Extended Children of Twins Design

Comparing genetic and environmental influences on exposures or experiences in child- versus adult-twin–based designs can be informative about the extent to which passive versus evocative G-E correlations account for associations between putative measures of the environment and outcomes (Neiderhiser et al., 2004). For example, evidence for passive G-E correlation would be obtained if genetic factors accounted for variation in a measure of how frequently adult twins monitor their children and if shared environment factors accounted for variation

in parents' reports of how frequently they monitor each of their twin children (Neiderhiser et al., 2004). Using this logic, Neiderhiser et al. (2004) reported that mothers' positivity and monitoring reflected passive G-E correlation whereas mothers' negativity and control mainly reflected evocative G-E correlations, although patterns of genetic and environmental effects changed somewhat depending on whether mothers, children, or observers were the informants. A somewhat different pattern was found for fathers' behavior; fathers' negativity and monitoring reflected both passive and evocative G-E correlation whereas fathers' positivity and control mainly reflected evocative G-E correlation (Neiderhiser et al., 2007).

The extended children-of-twins design combines data from samples of adult twins and their offspring and child twins and their parents (Narusyte et al., 2008). The design estimates direct effects of parenting (or other exposures in the family) on children, direct effects of child characteristics on parenting (or other exposures in the family), and passive and evocative genotype–environment correlation. The ability to distinguish passive from evocative genotype–environment correlations is a unique characteristic of the model. A simulation study established that the extended CoT model was stable and recovered the true parameter values with high precision under the assumption that individual differences in parenting were entirely accounted for by additive genetic and nonshared environmental factors (Narusyte et al., 2008). The model was able to detect relatively small genotype–environment correlations. Applying the model to data, the relationship between maternal over-involvement and offspring internalizing problems was shown to be accounted for by evocative G-E correlations (Narusyte et al., 2008), as was the relationship between maternal criticism of offspring behavior and offspring externalizing problems (Narusyte et al., 2011). Data from the same sample showed that the association between parental negativity more broadly (including conflict with the adolescence, parental coercion, and parental punitiveness) and adolescent externalizing problems was accounted for by evocative G-E correlations (Marceau et al., 2013).

Finally, an ECoT study involving (1) adult twins and their offspring and (2) child twins who were approximately age-matched to the offspring of the adult twins identified a significant environmental pathway from parent antisocial behavior to youth conduct problems, even accounting for the fact that some of the genetic factors that influenced youth conduct problems were shared with genetic influences on adult antisocial behavior (Silberg, Maes, & Eaves, 2012). A small passive G-E correlation was identified accounting for just over 3% of the variation in youth conduct problems (Silberg et al., 2012).

As reviewed by Narusyte et al. (2008), the requirement that the combined samples be comparable in terms of size, participant characteristics, and measured constructs is a major limitation of the extended CoT design. Samples of twin children and their parents on the one hand and twin parents and their children (who are cousins) on the other hand may produce correlations among youth behavior or parenting constructs that differ in magnitude simply because cousins are likely to be less similar to each other than siblings and because cousins will vary in age while twin siblings will not. Such differences could result in larger residual error terms and poorer model fit. Many researchers will not have access to data that meet these requirements for comparability. The design also assumes that the genes that influence the parent phenotype are the same as those that influence the child phenotype. This assumption is likely to be violated when the parent and offspring phenotypes reflect behavior at different points in development. For instance, it has been shown that gene variants associated with alcohol dependence in adulthood are associated with symptoms of conduct disorder rather than alcohol dependence in adolescence (Dick et al., 2006) and longitudinal data from Eaves et al. (2010) showed that genetic influences on juvenile antisocial behavior were largely different from genetic influences on adult antisocial behavior in the same individual. To the extent that different genes influence the parental versus the child phenotype, passive genotype–environment correlation may be underestimated.

Twins and Parents Design

This design estimates the magnitude of genetic and nongenetic pathways by which a parental phenotype (e.g., parental antisocial behavior) is associated with the corresponding phenotype among offspring. Measured environments (e.g., maltreatment) can be included in the model and their direct effects on the child phenotype can be estimated. The design also estimates the degree of assortative mating between parents. As with the ECoT design, the TaP design assumes that the (genetic and environmental) sources of variation in the parent phenotype are the same as in the offspring phenotype and that the magnitude of the variation in the phenotype is the same in both generations (Fulker, 1982).

Eaves et al. (2010) used the LTaP design to test whether the association between childhood adversity (indexed by retrospectively reported parental neglect, exposure to interparental violence, and inconsistent parental discipline) and

offspring antisocial behavior (as measured by adolescent conduct problems and adult antisocial behavior) was genetically or environmentally mediated.

The use of longitudinal data in this model circumvents some of the more problematic assumptions of the standard TaP model. First, the LTaP design includes measures of the candidate environment (i.e., childhood adversity) and both parents' antisocial behavior, thus providing information about assortative mating and the size of the association between parent antisocial behavior and childhood adversity. Second, the LTaP design includes information about twins' antisocial behavior in adolescence and adulthood, thus providing information about the magnitude of genetic and environmental influences on these behaviors at two different points in development. Third, a model incorporating information on parent antisocial behavior and *adult* offspring antisocial behavior provides information on the extent to which genetic differences in parental behavior account for the relationship between childhood adversity and adult offspring antisocial behavior. Because antisocial behavior is measured at the same point in development for parents and offspring, this model is unlikely to violate the assumption that the same genes influence parent and offspring phenotypes (assuming there are not sizable cohort effects). This model can then be used to identify a model that measures the influence of parental genotype and childhood adversity on juvenile antisocial behavior, including the measure of passive genotype–environment correlation.

Using the LTaP design, Eaves et al. (2010) found that nongenetic effects of parent antisocial behavior on the shared environment were largely mediated by parental treatment of children and that childhood adversity directly accounted for shared environmental effects on offspring antisocial behavior, providing evidence for an environmentally mediated effect of parental treatment. Moreover, effects of the shared environment (including parental treatment) on offspring antisocial behavior persisted from adolescence into adulthood. Very small passive G-E correlations were detected.

Discordant MZ Twins Design

The discordant MZ twin design is not used to estimate G-E correlations directly, but rather to rule them out as a potential confounder of observed associations between experiences and behavior. To the extent that within-pair differences in experience are correlated with within-pair differences in behavior, one can be confident that the effect of the experience is environmentally rather than genetically mediated (i.e., does not arise from evocative, active, or passive genotype–environment correlation). This is because MZ twins are genetically identical, so differences in their experiences cannot logically arise from genetically based differences in their behavior.

The discordant MZ pairs approach has been used to examine 4 categories of exposures: (1) parenting (or parent–child relations); (2) peer relationships; (3) health risk behaviors; (4) and stressful life events and life course transitions. We discuss each of these in turn.

MZ Pairs Discordant for Parenting

In a study of 5-year-old twins, Caspi et al. (2004) showed that the twin about whom the mother expressed more negative feelings was also the twin with more externalizing problems at age 5 and 7 years. Other studies have shown that within-pair discordance for parental negative feelings and parental criticism is associated with within-pair differences in conduct problems in middle childhood (Larsson, Viding, Rijsdijk, & Plomin, 2008; Mullineaux, Deater-Deckard, Petrill, & Thompson, 2009), in a sample of 8- to 16-year-olds (Carbonneau, Eaves, Silberg, Simonoff, & Rutter, 2002), and in a sample of adolescents, even controlling for within-pair differences in conduct problems measured 8 years earlier (Shelton et al., 2008). Studies focused on harsh discipline show a similar pattern wherein the twin who has experienced more harsh discipline also has more conduct problems and lower levels of prosocial behavior (Asbury, Dunn, Pike, & Plomin, 2003; Asbury, Dunn, & Plomin, 2006; Deater-Deckard et al., 2001; Pike, McGuire, Reiss, Hetherington, & Plomin, 1996). In contrast, within-pair differences in mothers' use of criticism or praise in a parent–child interaction task were shown to be unrelated to within-pair differences in 3-year-olds' conduct or emotional problems, although the twin who received more criticism was also the twin who was reported to have lower levels of prosocial behavior (Deater-Deckard et al., 2001). Finally, in a study in which parents of preschoolers were asked to report on their over-protective and hostile parenting, within-pair differences in over-protective parenting were associated with within-pair differences in boys' socially reticent behavior in kindergarten whereas within-pair differences in fathers' hostile parenting were associated with within-pair differences in girls' social reticence, particularly when their fathers also reported high levels of depressive symptoms (Guimond et al., 2012).

When combined with longitudinal data involving repeated measures of experiences and youth behavior, the discordant MZ pairs approach offers a strong test of the

direction of effects. For example, Burt et al. (2006) measured parent-adolescent conflict and adolescent antisocial behavior in a study involving 486 MZ twin pairs assessed at ages 11, 14, and 17 years. They found that among twins highly discordant for the experience of parent–child conflict (as well as for twins highly discordant for antisocial behavior), the twin who experienced higher levels of conflict at age 11 had significantly higher levels of antisocial behavior at age 14 than his co-twin, controlling for both the stability of within-pair differences in antisocial behavior from early to middle adolescence as well as the stability of within-pair differences in parent–adolescent conflict. The results were consistent with the interpretation that parent–adolescent conflict was causally associated with youth antisocial behavior in middle adolescence, although the effect was only present for highly discordant pairs. In a similar analysis, Cecil, Barker, Jaffee, and Viding (2012) identified bidirectional effects across four time points from early childhood into early adolescence between harsh discipline and children's self-control. The twins who experienced higher levels of harsh discipline in early childhood had lower levels of self-control at subsequent waves. Conversely, the twins with lower levels of self-control subsequently experienced more harsh discipline. MZ pairs also differed in the degree to which their mothers expressed negative feelings about them and these within-pair differences were predictive of within-pair differences in self-control, although the reverse was not true.

MZ Twins Discordant for Peer Relationships

In a study of school-age children from Canada, MZ twin differences in peer rejection in kindergarten and the quality of their relationship with their kindergarten teacher predicted within-pair differences in academic achievement in first grade, with the rejected twin (or the twin who had a poorer relationship with his or her kindergarten teacher) showing lower academic achievement than the better-liked twin (or the twin who had a better teacher relationship) (Vitaro, Boivin, Brendgen, Girard, & Dionne, 2012). Moreover, the twin who had relatively more aggressive friends in kindergarten was relatively more aggressive in first grade, partly as a result of peer victimization, presumably at the hands of those very friends (Vitaro et al., 2011).

In a sample of twins from the UK, MZ twins who were bullied had significantly more internalizing problems at age 10 years than their nonbullied cotwin, even controlling for preexisting internalizing problems at age 7 years (Arseneault et al., 2008). Data from the same sample showed that the pathway by which bullying victimization gets under the skin is also environmentally mediated, with the bullied twin in a pair showing blunted cortisol reactivity to a public speaking task relative to the nonbullied twin (Ouellet-Morin, Danese, et al., 2011). Among youth who were bullied or maltreated, blunted cortisol reactivity was shown to be associated with elevated social and behavioral problems (Ouellet-Morin, Odgers, et al., 2011).

Burt, McGue, and Iacono (2009) estimated fully cross-lagged models of the relationship between externalizing problems and peer delinquency at ages 14 and 17. The sample included MZ twins and results showed that controlling for the stability of externalizing problems and peer deviance, the twin who had more externalizing problems at 14 years of age was also the twin with more deviant peers at 17 years of age, regardless of whether twins did or did not share most of their friends. In contrast, within-pair differences in deviant peers at 14 years of age was unrelated to within-pair differences in externalizing problems at 17 years of age. Thus, regardless of any shared genetic liability for externalizing problems, adolescents were actively selecting themselves into particular peer groups on the basis of their actual attitudes, beliefs, or behaviors, although exposure to deviant peers was not increasing their externalizing problems. In contrast to these findings, Loehlin (2010) reported that MZ and DZ adolescent twins who shared fewer friends were also less similar in their drinking, suggesting that something about the composition of the peer group was causing within-pair differences in alcohol use even though there was also some indication that the association sharing friends and alcohol use partly reflected active G-E correlation in female (but not male) pairs.

MZ Twins Discordant for Health Risk Behaviors

The discordant MZ twin approach can also be used to test whether differences in twins' behavior lead to differences in their development. For example, Lynskey et al. (2003) reported that MZ twins who used cannabis by age 17 years had elevated rates of drug use, alcohol dependence, and other drug abuse/dependence in young adulthood relative to their cotwin who did not use cannabis by age 17 years. These associations were not accounted for by other known risk factors for young adult substance use or abuse and the findings imply that the effect of early cannabis use on later substance use is not accounted for by a common genetic or environment liability to use substances.

In a study of 189 young adult MZ twin pairs, male twins who had better sleep quality than their cotwins also had better self-reported health and female twins who had better sleep quality than their co-twins also reported higher

levels of relationship satisfaction (Barclay, Eley, Buysse, Maughan, & Gregory, 2012). Within-pair differences in sleep quality were unrelated to other experiences that were nonshared by twins in a pair (Barclay et al., 2012).

MZ Twins Discordant for Stressful Life Events and Life Course Transitions

The experience of stressful life events is a robust risk factor for depression, but observational studies are typically unable to determine whether some individuals have certain characteristics (e.g., high levels of neuroticism) that (1) make them more likely than others to experience stressful life events and (2) increase their risk for depressive disorder. This hypothesis was ruled out in a study of MZ twins who were discordant for their recent experience of stressful life events. Consistent with a causal effect of stressful life events on increasing risk for depression, the twin who had experienced more recent stressful life events had a greater risk of developing major depressive disorder than the twin who had experienced fewer recent stressful life events (Kendler & Gardner, 2010).

Burt et al. (2010) used longitudinal data from a study of 289 29-year-old monozygotic (MZ) and dizygotic (DZ) twin pairs to test whether active genotype–environment correlations (or other environmental factors) accounted for the association between marital status and men's antisocial behavior. They found that in both MZ and DZ pairs, the married twin in a pair had significantly lower levels of antisocial behavior compared with his unmarried cotwin. Similarly, in a study of middle-aged and older MZ twins from the Midlife in the United States Study, the twin who reported more social support from friends and family also reported higher levels of happiness than the twin who reported less social support from friends and family (Schnittker, 2008). However, within-pair differences in many other characteristics including marital status, social support from spouses, schooling, employment, income, and personal wealth were unrelated to within-pair differences in happiness although the measures were associated with happiness in the overall sample of unrelated individuals (Schnittker, 2008). Thus, to the extent that—in the population—high socioeconomic position, being married, and perceiving one's spouse to be supportive are associated with an individual's happiness, these associations are likely to be accounted for by genetic and family background factors.

Finally, in a sample of Danish adult male twins, the twin who was widowed or divorced reported lower cognitive abilities and more symptoms of depression than the married twin (Osler, McGue, Lund, & Christensen, 2008). Among female twins, the twin who was divorced or widowed also reported more symptoms of depression (Osler et al., 2008). Although within-pair differences in marital status were associated with within-pair differences in men's cognitive abilities and women's depression symptoms in DZ, but not MZ pairs, the confidence intervals around estimates of the marital status effect were largely overlapping in DZ and MZ groups (Osler et al., 2008). Thus, it is not clear whether the smaller effects of marital status observed in MZ pairs reflect a lack of statistical power to detect within-pair differences or whether they show that controlling completely for genetic differences within pairs eliminates associations between marital status and certain outcomes.

Criticisms of the Discordant MZ Twins Design

As discussed by Vitaro, Brengden, and Arseneault (2009), the discordant MZ twins design—especially when it is embedded within a longitudinal design—can allow researchers to make powerful causal inferences about the relationship between experiences and behavior. This is because it eliminates genetic differences within pairs as well as other potential family-wide confounds that might otherwise explain the relationship. A limitation of the design is that it requires there to be sufficient within-pair variability in experiences or outcome and that this reflect true variability rather than measurement error. This requirement is especially challenging for research on adolescents because adolescents have greater autonomy than younger children to select and create their own experiences. To the extent that such selection is driven by genetically influenced characteristics of the adolescent, MZ twins will become increasingly similar for their experiences as they transition from childhood to adolescence. In addition, because the design eliminates so many potential confounds, the variance in outcome accounted for by within-pair differences in experience is often modest (less than 5%).

Finally, the design estimates within-pair differences in exposure (e.g., to cannabis or parental criticism) which it presumes to be the cause of within-pair differences in outcome (e.g., later drug use, delinquency), but the design cannot rule out the possibility that some other event not shared by twins is the real culprit. For example, twins may differ with respect to their peer relationships, with one twin associating with peers who promote both cannabis and later drug use and the other twin associating with a more salubrious social group. Thus, although the design rules out the possibility that genetic differences within pairs account for the relationship between within-pair exposures and within-pair outcomes, it cannot definitively identify

the exposure as the causal agent of within-pair differences in outcome.

GENOTYPE–ENVIRONMENT CORRELATIONS AND DEVELOPMENT

Developmental psychopathologists have long been interested in correlations between persons and environments because of their potential to amplify individual differences as, for example, personality traits evoke reactions from family members, peers, and teachers, cause individuals to actively select certain kinds of experiences, make individuals selectively attentive to information about themselves and others, and influence the ways in which individuals seek to manipulate their environments (Caspi & Moffitt, 1995).

Like person–environment correlations, G-E correlations are also hypothesized to underlie developmental processes. In a simulation study, Beam and Turkheimer (2013) showed that the apparent increase in the heritability of many human traits (e.g., intelligence, personality traits) can be explained by G-E correlations that lead to increasing differentiation of DZ twins relative to MZ twins. Thus, small genetically based individual differences in behavior and abilities become amplified over time as individuals expose themselves to experiences for which they have some affinity and those experiences in turn reinforce and widen preexisting individual differences. Failing to model G-E correlations leads to an apparent increase over time in the heritability of a phenotype when, in fact, genetic influences on the phenotype remain stable over time.

Hicks et al. (2013) provided an empirical example of how G-E correlations underlie the process by which personality can be amplified into psychopathology. In their sample of 11-year-old twins, Hicks et al. (2013) measured the tendency to follow rules and endorse conventional norms—a construct they named *socialization* that shares many features with the Big 5 factor of conscientiousness (Costa & McCrae, 1992). Youth with lower scores on the measure of socialization subsequently experienced higher levels of contextual risk in mid-adolescence, such as a deviant peer group or a conflictual relationship with parents. The relationship between socialization and contextual risk was largely accounted for by genetic and shared environmental factors common to both constructs, indicative of an active G-E correlation. Moreover, youth with lower scores on the socialization measure in early adolescence tended to engage in higher levels of substance use in late adolescence, an association that was mediated by their exposure to contextual risk factors. Thus, genetically based individual differences in personality increased the likelihood that some youth would be exposed to higher levels of contextual risk than others, with implications for the emergence of substance use problems in late adolescence.

Another such example was provided by Klahr et al. (2013), who observed 546 mothers interacting with each of their 6- to 10-year-old twin children during a structured cooperative task. Interactions were coded in real time for maternal and child warmth and control using a joystick method. From minute to minute, children's efforts to exert control in the interaction were countered by mothers' efforts to retain their own control or relax the child's control, with the same genetic factors accounting for these correlations. The reverse was also true, highlighting the reciprocal nature of parent–child interactions over even a brief structured interaction. Thus, mothers and children were responding to genetically influenced tendencies towards submission or dominance. Although maternal and child warmth were also stable across the course of the interaction, nonshared environmental factors accounted for their covariance on a minute-to-minute basis and from one minute to the next (Klahr, Thomas, Hopwood, Klump, & Burt, 2013). Thus, whatever was causing some children or mothers to engage in higher levels of warmth than other children or mothers was specific to the situation and nonshared by twins in a pair.

Finally, studies of G-E correlation reflect and potentially shed further light on processes of developmental change. For example, it is understood that the behaviors that elicit parental irritability or hostility change as children develop. Parents may become frustrated with an infant who is difficult to soothe, a toddler who is prone to temper tantrums, a school-aged child who is oppositional, and an adolescent who breaks rules. Theories of heterotypic continuity assume that these diverse behaviors reflect some underlying construct that is likely to have some common origin. At least one twin study forces us to reexamine this assumption, however—at least in very early childhood. When hostile-reactive parenting behaviors were measured repeatedly over the first 2.5 years of life in a sample of Quebecois twins, genetic influences on these behaviors were only weakly correlated (Forget-Dubois et al., 2007). Thus, on one hand, the data were consistent with the hypothesis that hostile-reactive parenting would be evoked by different behaviors at different ages; on the other hand, the data ran contrary to expectations in showing that there was little common genetic basis to whatever behaviors were eliciting hostile-reactive parenting over time.

GENOTYPE–ENVIRONMENT CORRELATION: EVIDENCE FROM THE MOLECULAR GENETIC LITERATURE

In contrast to quantitative genetic studies, which infer genetic influences from familial correlations, molecular genetic studies measure genotype directly. Although the majority of studies that measure genotypes and putative environments fail to detect significant genotype–environment correlations (and there may be reasonable explanations for this pattern of null findings; Jaffee & Price, 2007), there is a small but growing set of positive findings that highlight issues worthy of further consideration.

Much of the recent work to demonstrate associations between measured genotypes and environments has involved relationships between maternal and child genotype and either reported or observed parenting behaviors. A growing number of studies have focused on interpersonal relationships more broadly, including partner relationships. Researchers interested in genetic influences on parenting have focused primarily on dopamine genes because of the role dopamine has been shown to play in facilitating affiliative behaviors in humans (Barrett & Fleming, 2011; Depue & Morrone-Strupinsky, 2005) and animals (Numan, 2007; Spielewoy et al., 2000) and because dopamine genotypes have been associated with externalizing child behaviors (Gizer, Ficks, & Waldman, 2009; Schmidt, Fox, Rubin, Hu, & Hamer, 2002) that may evoke sub-optimal parenting practices. Researchers have also focused on oxytocin genes because of the demonstrated role of oxytocin in pair bonding, including bonds between parents and children as well as between partners (Numan, 2006; Saltzman & Maestripieri, 2011).

Maternal Dopamine Genotype and Parental Behavior

Lee and colleagues (2010) identified a nonadditive association between maternal dopamine transporter 1 (DAT1) genotype and observed negative parenting behavior in a sample of 207 mother–son pairs, ranging in age from 3 to 7 years. DAT1 is a 40 base pair (bp) variable number tandem repeat located in the 3' untranslated region in exon 15 of the dopamine transporter gene (SLC6A3). The 40-bp sequence is typically repeated 9 or 10 times and the majority of individuals are either homozygous for the 9- or 10-repeat variants (i.e., 9/9 or 10/10) or heterozygous for the 9- and 10-repeat variants (9/10).

In analyses that controlled for parental psychopathology and child disruptive behavior during the parent–child observation, results showed that mothers with the 9/10 genotype engaged in more negative parenting (e.g., using critical and negative statements, using negative physical contact) compared with either homozygous group (9/9 or 10/10), with effect sizes that were small to moderate in magnitude ($d = .35$ for 9/9 vs. 9/10 and $d = .19$ for 10/10 vs. 9/10). Mothers with the 9/9 genotype issued fewer commands to the child compared with mothers who carried the 10-repeat allele ($d = .33$). Maternal genotype was not correlated with positive parenting (e.g., praising child, positive affect, positive physical contact). Moreover, the relationship between maternal genotype, negative parenting, and maternal commands was strongest when children engaged in high levels of disruptive behavior during the parent–child interaction task. When children engaged in lower levels of disruptive behavior (e.g., at the median or lower), levels of negative parenting and the number of commands issued were uniformly low for all maternal genotype groups.

Although main effects of maternal genotype on maternal behavior have been detected infrequently, the finding that the relationship between maternal genotype and maternal behavior is conditional on individual or contextual features is one that has been replicated by other researchers. For example, three studies have shown that the relationship between maternal dopamine receptor D4 (DRD4) genotype and observed maternal sensitivity depends on characteristics of the infant or other features of the mother's environment. One found that mothers who carried the 7-repeat DRD4 allele behaved more sensitively with fussy infants than with nonfussy infants. In contrast, mothers who did not carry any 7-repeat alleles were equally sensitive to their infants, regardless of infant temperament, with this interaction accounting for nearly 3% of the variation in maternal sensitivity (Kaitz et al., 2010). The second study found that mothers who carried the 7-repeat allele were more sensitive with their 3.5-year-olds if, as newborns, their children had lower versus higher levels of birth risk (as indexed by gestational age, birth weight, and admission to the neonatal intensive care unit). Again, mothers who did not carry any 7-repeat allele were equally sensitive to their children regardless of infant birth risk, with this interaction accounting for 5% of the variation in maternal sensitivity (Fortuna et al., 2011). The third study found that the combined effects of DRD4 and catechol-O-transferase (COMT) genotype on how sensitively mothers engaged with their toddler-age children depended on the level of daily hassles mothers reported experiencing. Mothers who had a combination of COMT and DRD4 genotypes associated with the least efficient dopamine transmission engaged in the least sensitive

parenting in the context of high levels of daily hassles, but the most sensitive parenting in the context of low levels of daily hassles, with this interaction accounting for approximately 2% of the variation in maternal sensitivity (van IJzendoorn, Bakermans-Kranenburg, & Mesman, 2008). Taken together, these studies suggest that the behavior of mothers who do not carry the 7-repeat *DRD4* allele is relatively consistent, regardless of child characteristics or other features of the environment. In contrast, the behavior of mothers who do carry the 7-repeat allele (perhaps in combination with specific *COMT* genotypes) is highly responsive to context, with two of the three studies showing that under optimal conditions (e.g., low levels of daily hassles, low levels of infant birth risk) these mothers are more sensitive with their children than 7-repeat-absent mothers, but less sensitive than 7-repeat-absent mothers under less optimal conditions.

Child Dopamine Genotype and Parental Behavior

At least three studies have estimated the relationship between the dopamine receptor D2 (DRD2) allele in the child and parenting behavior. DRD2 has a restriction length fragment polymorphism called TAQ1A (rs1800497) located on chromosome 11q. Taq1A has two alleles, known as A1 and A2 (Eisenberg et al., 2007). Postmortem studies and studies using positron emission topography have shown that individuals who carry the A1 allele (A1 +) have fewer D2 dopamine receptors than individuals who are homozygous for the A2 allele (A1-) (Jonsson et al., 1999; Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991; Pohjalainen et al., 1998; Thompson et al., 1997). In addition, children who carry the A1 allele have been shown to be more anxious and to have higher levels of negative emotionality compared with children who are homozygous for the A2 allele (Hayden et al., 2010; Marino et al., 2004; Mills-Koonce et al., 2007). Thus, Taq1A has been the focus of research on the genetic basis for child effects on parent behavior.

Two studies have shown that A1 + children receive less sensitive and supportive parenting compared with A1– children, as observed during parent–child interaction tasks (Hayden et al., 2010; Mills-Koonce et al., 2007). Effect sizes were small to moderate in magnitude ($d = .25$ for Hayden et al., 2010; $d = .40$ for Mills-Koonce et al., 2007). In addition, in their sample of 473 3- to 4-year-old children, Hayden et al. (2010) showed that the relationship between *DRD2* genotype and supportive parenting was partially mediated by child negative emotionality. Although Mills-Koonce et al. (2007) found a main effect of child (but not maternal) *DRD2* genotype on maternal sensitivity in their sample of 172 mother-infant pairs participating in the Durham Child Health and Development Study, this effect was not moderated by other child, maternal, or family characteristics nor was it mediated by child negativity.

Other dopamine gene variants have been implicated in the genetic basis of child effects on maternal behavior. A separate analysis of children in the Durham Child Health and Development Study showed that DRD4 genotype was also associated with maternal sensitivity; children with the long DRD4 allele (6–8 repeats or 7-repeats) experienced lower levels of warm-responsive parenting than children with the short form of the allele ($d = .34$) (Propper, Willoughby, Halpern, Carbone, & Cox, 2007). When followed up at school-age, DRD4 genotype was also associated with girls' academic outcomes, with mediational analyses showing that low levels of sensitive parenting in the preschool years explained why girls who carried the long form of the DRD4 allele scored lower on a standardized achievement test and were judged by teachers to perform more poorly in the classroom compared with girls who carried the short form of the allele (Propper, Shanahan, Russo, & Mills-Koonce, 2012). For boys, DRD2 genotype was associated with parental sensitivity and school performance (Propper et al., 2012). Finally, in an age-6-year follow-up of children who participated in the study reported by Hayden et al. (2010), those who carried the DAT1 9-repeat allele experienced more hostility ($d = .22$) and received less guidance ($d = .28$) from their caregivers during a structured task compared with 10/10 homozygotes and this association was partly explained by elevated levels of negative emotionality directed at the caregiver by children who carried the 9-repeat allele (Hayden et al., 2013).

Oppenheimer et al. (2013) estimated the association between child COMT genotype and parental sensitivity in a sample of 263 third, sixth, and ninth graders. Although no main effects of youth genotype on parental sensitivity were identified, there was a significant interaction between youth genotype and parental personality characteristics. If parents were high in extraversion or low in neuroticism, the more copies of the Val allele youth carried, the more sensitive parenting they received. In contrast, if parents were low in extraversion or high in neuroticism, youth genotype was unassociated with parental responsivity. These interactions accounted for 1% to 2% of the variation in parenting. Thus, the extent to which genetically influenced characteristics of youth evoke sensitive or insensitive parenting may depend on characteristics of the parents.

Child Dopamine Genotype and Peer Relations

Homophily refers to the tendency to bond with similar others. Heterophily, in contrast, reflects the tendency to gather in diverse groups. These processes have been shown to have a genetic basis, such that adolescents' genotype for the Taq1A polymorphism in the DRD2 gene was positively predictive of their friends DRD2 genotype (i.e., genetic homophily) and adolescents' cytochrome P450 2A6 (CYP2A6) was negatively predictive of their friends' CYP2A6 genotype (i.e., genetic heterophily; Fowler, Settle, & Christakis, 2011). To the extent that these genotypes are associated with personality and social behavior, they may explain why genetically similar (or dissimilar) others are drawn to each other (Fowler et al., 2011).

In an extension of these results, Boardman, Domingue, and Fletcher (2012) demonstrated that genetic homophily for the Taq1A polymorphism in DRD2 was strongest in schools characterized by the highest levels of socioeconomic inequality, suggesting that friends' genetic similarity may not reflect the active selection by one adolescent of a genetically similar friend but rather structural factors (e.g., tracking within school curricula) that sort genetically similar individuals into similar environments. Thus, genetically-based homophily under these circumstances may reflect evocative G-E correlations (e.g., teachers responding to a youth's innate ability by tracking them along a more or less advanced curriculum) as opposed to active G-E correlations (Boardman, Domingue, & Fletcher, 2012).

Finally, measured genotype has been associated with peer delinquency. Two studies, both using data from the National Longitudinal Study of Adolescent Health reported that the 10-repeat variant of DAT1 was associated with adolescent reports of peer delinquency (Beaver, Wright, & DeLisi, 2008) as well as reported delinquency from the adolescent's peer network members (Yun, Cheong, & Walsh, 2011). However, these associations were only detected for White males from high-risk family backgrounds in stratified analyses, calling into question the robustness of the effect.

Serotonin Genotype, Parenting, and Peer Relations

Because of the role that serotonin plays in the regulation of anxious, depressed, and impulsive behavior, researchers have hypothesized that variants in serotonin system genes may be related to parenting behavior, although the only genome-wide association study of children's anxiety did not identify variants in the serotonin system (or anywhere else in the genome) that met genome-wide levels of significance (Trzaskowski et al., 2013) and serotonin system gene variants have inconsistently been associated with children's depressed or anxious behaviors in candidate gene studies. Nevertheless, in a study of 376 3.5-year-old children, Pener-Tessler et al. (2013) reported that boys who carried at least one copy of the short allele of the serotonin transporter gene-linked polymorphic region (5-HTTLPR) were observed to experience less positive parenting from their mothers and this was because 5-HTTLPR genotype was associated with lower levels of boys' self-control.

Maternal Oxytocin Genotype and Maternal Behavior

Oxytocin is a hormone that plays an important role in facilitating affiliative maternal behavior in animals (Numan, 2006; Saltzman & Maestripieri, 2011) and is a focus of investigation in a growing number of studies of human maternal behavior (Galbally, Lewis, van IJzendoorn, & Permezel, 2011; Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010; Naber, van IJzendoorn, Deschamps, van Engeland, & Bakermans-Kranenburg, 2010). For these reasons, researchers have investigated whether common polymorphisms in oxytocin genes are related to maternal sensitivity. In a sample of 176 mothers, the oxytocin receptor gene *(OXTR;* rs53576*)* was associated with maternal sensitivity, accounting for 3% of the variation; mothers with the GG genotype behaved more sensitively in observed parent–child interactions with their toddlers than mothers with the AG or AA genotypes (Bakermans-Kranenburg & van IJzendoorn, 2008). In an effort to identify physiological mediators of genetic effects, Riem and colleagues (2011) exposed 40 women without children to recordings of infant crying bouts and recorded their heart rate. Women with the GG genotype had greater heart rate reactivity to infant cries, but only if they did not have high levels of depressive symptoms, with this interaction accounting for 20–25% of the variation in autonomic arousal. The authors hypothesized that, for nondepressed women at least, high levels of autonomic arousal underlie quick responding to infants' needs.

Oxtyocin and Pair-Bonding Behavior

Variation within the OXTR gene has also been associated with other forms of pair-bonding. For example, in a study comprising three independent samples of Swedish adult and child twins, one of 12 SNPs genotyped across the *OXTR* gene (rs7632287) was associated with a measure of marital quality, support-seeking behavior, and marital instability in the sample of older adult twins (Walum et al., 2012). The association between rs7632287 and affectionate

relationship quality was also observed in the 323 young women (but not the 142 young men) who were in romantic relationships in the younger adult twin sample. In both samples, women who carried one or two copies of the A allele had poorer relationship quality scores than women who carried two copies of the G allele. Moreover, in the older adult twin sample, women who carried one or two copies of the A allele were approximately 50% more likely to have reported a marital crisis or threat of divorce in the past year than women who carried two copies of the G allele. Finally, the *husbands* of women who carried one or two copies of the A allele reported significantly lower marital satisfaction than the husbands of women who carried two copies of the G allele.

In the younger adult sample, women in romantic relationships who carried one or two copies of the A allele scored significantly higher on the CBCL Social Problems Scale when they were 8 to 9 years old compared with women in romantic relationships who carried two copies of the G allele, with Social Problems, in turn, predicting poor relationship quality in young adulthood (Walum et al., 2012). Thus, a variant in the OXTR gene was associated not only with pair-bonding behavior in adulthood but also with developmental precursors of pair-bonding behavior.

Using data from a sample of 909 adult twins, Walum et al. (2008) reported that a polymorphism (RS3) in the arginine vasopressin receptor subtype 1a (AVPR1a) gene was associated with pair-bonding behavior in men, such that men who were homozygous for the RS3 334 allele reported less marital satisfaction, support seeking, and poorer relationship quality than men who carried 1 or 0 copies of RS3 334. Moreover, carrying two copies of the 334 allele was associated with double the risk of having experienced a marital crisis in the past year compared with carrying 0 copies of the 334 allele.

Genome-Wide Association Studies

Although genome-wide association studies of complex physical and mental disorders have become common, genome-wide association studies of putative environments are still rare. Butcher and Plomin (2008) conducted a two-stage analysis that first involved pooling DNA from 4-year-old twins whose families were selected for inclusion because they scored at the high versus low extremes on a measure of chaotic family environment. A comparison of allele frequencies in the high versus low chaos groups was then used to inform the selection of SNPs ($n = 48$) for individual genotyping at the second stage of analysis, which involved one twin from each of the remaining pairs in the sample ($n = 3,529$). However, none of these 48 SNPs was associated with chaotic family environment (Butcher & Plomin, 2008).

Recently, researchers in the social sciences have adopted the practice of consolidating data from multiple data sets that include genetic as well as social science data (Rietveld et al., 2013; van der Loos et al., 2013). By conducting GWAS meta-analysis, SNPs have been identified that are associated with educational attainment, though any given SNP accounted for less than 1% of the variance in educational attainment and even a linear combination of all measured SNPs explained only about 2% of the variance (Rietveld et al., 2013). Another GWAS meta-analysis failed to identify individual SNPs that exceeded genome-wide levels of significance and that were associated with the tendency to be self-employed (van der Loos et al., 2013). The data were consistent with the possibility that multiple genes of small effect additively account for variation in this phenotype (van der Loos et al., 2013).

Summary of Findings from Molecular Genetic Studies and Future Directions for Research

Although the field remains small, a growing number of studies have identified correlations between maternal or child genotype and maternal behavior or between individual genotype and pair-bonding behavior more generally. These associations are typically modest in magnitude, accounting for as little variation in outcome as any single construct typically does in studies of developmental psychopathology. Often these associations are conditional on other features of the interaction, including characteristics of the child, the mother, or the broader context. In some cases, the data are consistent with the notion that some individuals are more susceptible than others to their environments in a for-better-and-worse fashion (Fortuna et al., 2011; Kaitz et al., 2010; Oppenheimer, Hankin, Jenness, Young, & Smolen, 2013).

The field of molecular genetic research into genotype–environment correlation faces three major challenges. The first is to produce a body of replicated findings. This goal is undercut by the fact that a great number of researchers who publish papers on measured genes and measured environments still fail to report genotype–environment correlations, possibly because the research is usually focused on identifying gene × environment interactions. As just one example, in the 10 nonexperimental studies of differential susceptibility to environment reviewed by Bakermans-Kranenburg and Van IJzedoorn (2011), only

five reported whether child (or maternal) genotype was correlated with the environmental measure. Thus, in many cases it is not clear whether a finding has been replicated because the test of genotype–environment correlation has not been reported.

Moreover, as has been observed in the literature on genotype × environment interaction, efforts to replicate findings have been challenged by the use of heterogeneous measures of the environment (Uher & McGuffin, 2010), making it unclear whether a specific genotype × environment interaction has not been replicated because the original finding was a false positive or because the replication sample involved a measure of the environment that was substantially different from the measure used in the original sample. In the first instance, replication attempts should involve measures of the environment that are operationalized as closely as possible to the original measure. Once it has been established that the original finding is replicable under these narrow conditions, the field can proceed to test the sensitivity of the genotype–environment correlation to alternative specifications of the environment.

The second major challenge to the molecular genetic study of associations between genotype and environment is for this enterprise to articulate its raison d'être. This research demonstrates an important proof of principle—that genes and environments do not just act additively and interactively to influence behavior, cognition, or psychopathology, but that (in the words of Richard Dawkins; Dawkins, 1982) genes get "outside the skin" to affect the environment itself (Kendler, 2011). A critic might take the position that beyond such generalizations this research does not tell us anything we did not know already. That is, the idea that *person–environment* correlations are important in shaping development has long been recognized in life span developmental psychology and developmental psychopathology (Elder, 1998; Rutter & Pickles, 1991). The primary focus of attention should remain the specific behaviors that serve to influence environments, not the genotypes that cause those behaviors (Moffitt, Caspi, & Rutter, 2005).

However, if molecular genetic studies of genotype–environment correlation do not have immediate translational implications, they may still merit study. There is often a long span of time before the translational benefits of epidemiological and basic research are realized (Rutter & Plomin, 2009) and the more immediate pay-off may be in a better understanding of the biological basis of behaviors that shape environments crucial for our survival and healthy development. For example, how do we optimize the chances that children will be sensitively nurtured by their caregivers? Many clinicians already screen for difficulties that caregivers might face in providing sensitive care, including a lack of social support, substance use problems, postpartum depression, and domestic violence, although beyond making caregivers aware of relevant services, there is generally little follow-through to ensure that caregivers are actually coping. A current lack of joined-up services aside, imagine that as our understanding of the biological basis of children's difficult temperament advances, researchers can identify a panel of biomarkers which exceeds some threshold of sensitivity and specificity for identifying children who fail to establish regular sleeping or feeding routines, react strongly and negatively to novelty, frequently fuss and cry, and are difficult to soothe. Combining this information about children's biological risk with information about their social circumstances may help clinicians and social service workers identify particularly vulnerable infant-caregiver dyads and provide caregivers with adequate support and training to cope with challenging infants. This combination of screening and parent training could potentially circumvent evocative genotype–environment correlations in which difficult children elicit harsh and insensitive care from adults and it could potentially do so before clinically significant child behavior problems emerge.

A third challenge in this research is methodological. To date, research on measured genes and measured environments has generally proceeded on a gene variant by gene variant basis. In some cases, researchers have combined information from two genes (Oppenheimer et al., 2013; van IJzendoorn et al., 2008). However, the prior probability of an association between a genetic polymorphism and an environment is exceedingly low (Davey Smith et al., 2007). Genome-wide association studies (GWAS), with their measures of hundreds of thousands of single nucleotide polymorphisms (SNPs) provide the means to test hypotheses about genetic influences over the environment on a scale that is appropriate to our lack of knowledge about how genes act (Butcher & Plomin, 2008). These vast yet affordable studies also provide opportunities to conduct pathway analyses and to group genes in functionally similar sets (Sun et al., 2010) or to aggregate multiple genes of small effect (Purcell et al., 2009).

The problem with these approaches is that GWA studies often require tens of thousands of participants to generate sufficient statistical power to detect genetic main effects and, consequently, there are practical limitations as to the kinds of environmental measures that can be collected. For example, observational assessments of parents and children would not be feasible in a sample of

20,000 participants. One possible solution is to use the information generated from GWAS of personality traits and behaviors that are hypothesized to mediate relationships between genes and environments. For example, the Five Factor Model of Personality can be evaluated with a relatively brief paper-and-pencil instrument that could be administered to large numbers of individuals. These individuals could be genotyped and statistical approaches could be used to generate polygenic scores (i.e., SNP sets) that predicted substantial amounts of variance in personality factors. If one hypothesized that individuals who were high in negative emotionality and low in agreeableness were especially likely to elicit hostile reactions from their romantic partners, then one could genotype those SNP sets in a smaller sample that allowed for intensive observations of interactions between couples and test for associations between the polygenic score and couples' behavior with each other.

Several caveats bear noting with the proposed approach. The first is that once researchers move from candidate gene approaches to polygenic scores, the possibility of testing mechanistic hypotheses is eliminated. Because they aggregate information across thousands of SNPs, polygenic scores are no more informative about the mechanisms by which genes influence brain and behavior than black box genetic risk estimates derived from family data (e.g., knowledge of a relative's diagnostic status). Moreover, they are usually far less predictive of outcome—although, unlike family history, polygenic scores are able to predict disease risk within as well as between families (Ruderfer et al., 2011). The second caveat is that although GWAS of personality traits are underway, results have been mixed and variants that reach genome-wide statistical significance generally account for less than 1% of the variation in personality traits (Shifman et al., 2008; Terracciano et al., 2010; van den Oord et al., 2008; Verweij et al., 2010).

Finally, some of the findings described in this section underscore the complexity of G-E interplay—specifically, the coexistence of genotype–environment correlations and genotype–environment interactions. For example, in the study conducted by van IJzendoorn et al. (2008), mothers with Val/Met or Val/Val COMT genotypes reported experiencing more daily hassles than mothers who were homozygous for the Met genotype—a genotype–environment correlation. Moreover, when compared with mothers who were homozygous for the Met allele, their parenting was also more adversely affected by these daily hassles, particularly if they also carried the DRD4 7-repeat allele—a genotype × environment interaction. As another example, although mothers who were homozygous for the 9-repeat allele of DAT1 engaged in lower levels of negative parenting than mothers who carried the 10-repeat allele (Lee et al., 2010), child DAT1 genotype was unassociated with negative parenting in the same sample (Lahey et al., 2011). However, the adverse effect of negative parenting on boys' conduct problems was strongest when the sons were homozygous for the 9-repeat allele (Lahey et al., 2011). Here, then, the same genotype that was associated with lower levels of negative parenting was associated with higher levels of child conduct problems but only when boys were exposed to high levels of negative parenting.

USING GENOTYPE–ENVIRONMENT CORRELATIONS TO UNDERSTAND CAUSAL MECHANISMS

As reviewed so far, genotype–environment correlations have been a focus of study by quantitative and molecular genetic researchers who want to demonstrate that putative environments are under genetic influence. In quasi-experimental studies, genotype–environment correlations are treated as potential confounds that must be rejected as alternative explanations for observed associations between exposures and outcomes. A third reason investigators are interested in genotype–environment correlations is because they can be used to determine whether specific exposures (e.g., diet, health-related behaviors, toxins) have causal effects on disease. Genetic associations can be interpreted as causal. The processes that determine one's genotype—meiosis and possibly mutation in the parental germ-line cells, followed by fertilization—are causally prior to outcomes. This excludes the possibilities of reverse causality and transactional relationships between genotypes and outcomes like psychopathology. For example, an episode of depression cannot cause changes in the structure of DNA (although it could lead to epigenetic changes). Since the process by which the maternal and paternal chromosomes in each cell are reshuffled during meiosis to produce gametes is random, most kinds of confounding are also excluded. The major confound is population ancestry, the effects of which can be controlled for statistically if genotype data is collected on a sufficient scale (Devlin, Bacanu, & Roeder, 2004; Price et al., 2006).

Risk genotypes do not necessarily have direct effects on outcomes, however, and often their effects will be mediated by measurable environments. This phenomenon can sometimes be exploited to show causal environmental effects. Let us imagine that there exists a genetic variant whose biological function mimics that of the environment,

or indeed directly influences the degree of exposure. Under certain circumstances, the genotype can act as a proxy variable or *instrument* for the environmental exposure, but one that is untroubled by confounding and reverse causality. As a consequence, association between the genetic proxy and an outcome can be interpreted as evidence for a causal effect of the environment. (It bears noting that the term *environmental exposure* in this context can mean nutritional or toxin exposures or sometimes health behaviors that are more typically studied as outcome variables in psychology and psychiatry.)

Although the concept of instrumental variables and the related statistical methodology originates in the field of econometrics, its application to genetic epidemiology has been dubbed "Mendelian randomization" (MR) (Davey Smith & Ebrahim, 2003). The technique is premised on Gregor Mendel's second law—the law of random assortment—which states that traits are inherited independently of each other. A genotype that influences exposure, but has an independent effect on the outcome—or is linked to another genotype that does—would confound their association, rather than measure it. Mendel's second law does not operate in the presence of pleiotropy or linkage, and neither does MR. (In technical terms, these are violations of the requirement that an instrumental variable be *exogenous*—that is, its value is determined by factors that are external to the causal system under study). These conditions are difficult to guarantee because we do not usually know the full range of effects of any particular genotype, not to mention the many nearby genotypes that may have correlated effects due to linkage disequilibrium. In addition, the range of exposures that could be considered for a MR experiment is restricted to those with documented genetic proxies that have reasonably strong effects—and this is currently a very short list.

The aldehyde dehydrogenase 2 (ALDH2) gene has been used as a genetic proxy for alcohol exposure in many studies because it fulfills these assumptions. ALDH2 metabolizes an ethanol byproduct, acetaldehyde, into acetate. Homozygotes for the mutant ALDH2*2 allele have negligible ALDH2 activity and, after drinking alcohol, they experience an unpleasant flushing reaction with associated nausea, drowsiness, and headache as a result of acetaldehyde accumulation. Heterozygotes have reduced ALDH2 activity and experience less severe flushing. The ALDH2*2 allele is common in East Asian populations and there is clear evidence of a correlation between ALDH2 genotype and alcohol exposure, with alcohol intake increasing as a function of the number of ALDH2*1 alleles (Lewis & Smith, 2005).

Although ALDH2 has primarily been used as a genetic proxy for alcohol exposure in studies of cancer, Irons, McGue, Iacono, and Oetting (2007) used MR to test the gateway hypothesis that alcohol use in adolescence leads directly to other forms of drug abuse and disinhibited behavior. Critics of the gateway hypothesis argue that alcohol use (or marijuana use) is correlated with the use of harder drugs because of a general propensity to try drugs and that the reason adolescents tend to try alcohol and marijuana before trying harder drugs is because opportunities to try the former tend to present themselves before opportunities to try the latter (Morral, McCaffrey, & Paddock, 2002). MR provides a test of the gateway hypothesis because ALDH2 will be associated with alcohol use, but the law of random assortment means that it is unlikely to be associated with other individual factors (e.g., delinquency, sensation-seeking, socioeconomic status) that are also correlated with alcohol use and could explain observed associations between alcohol use and later drug use.

Using data from a sample of 180 East Asian adolescents, they found that ALDH2 deficient adolescents (i.e., those who were homozygous or heterozygous for the ALDH2*2 allele) used alcohol less often than ALDH2 nondeficient adolescents, thus establishing that ALDH2 genotype was associated with alcohol exposure. However, youth who carried the ALDH2*2 allele (i.e., the proxy for low alcohol exposure) did not engage in significantly less lifetime or past-year use of other drugs (including tobacco, marijuana, or other illicit substances) or less disinhibited behavior compared with youth who were homozygous for the ALDH2*1 allele. The findings suggest that alcohol use per se is not a gateway to the use of other drugs or to disinhibited behavior.

MR may have applications in other areas of developmental psychopathology where researchers are interested in the role of dietary factors and toxin exposures in disorders like attention deficit/hyperactivity disorder (ADHD) and in neurodevelopmental disorders (Froehlich et al., 2011; Nigg, 2010). For example, Mendelian randomization could be used to test whether folate supplementation in early pregnancy causes reductions in neurodevelopmental and behavioral problems in early childhood, potentially via epigenetic changes in gene expression involving methylation (Glymour, Veling, & Susser, 2011). Folate triggers a metabolic process by which homocysteine is converted to methionine, which plays a role in DNA methylation (Lucock, 2000). MR studies of the association between folate intake and neurodevelopmental outcomes would require the identification of a functional gene variant that mimics the effects of folate intake. With some caveats,

the gene methylenetetrahydrofolate reductase (MTHFR) meets this condition. MTHFR has a common variant (MTHFR C677T) that influences the speed at which homocysteine is converted into methionine. The *677TT* allele encodes an enzyme that is associated with a slower conversion of 5, 10 MTHF to 5 MTHF. Consequently, the conversion of homocysteine into methionine is also slowed, a process that mimics the effects of folate restriction. Thus, MTHFRC677T status can potentially be used as a proxy for folate status, although the validity of this approach has been questioned based on the observation that very high folate concentrations effectively silence the effects of MTHRF677TT (Schatzkin et al., 2009).

As a final example, there is some evidence that iron deficiency (and a range of other micronutrient and toxin exposures) is associated with ADHD (Froehlich et al., 2011). The biological plausibility of this association is bolstered by the observation that iron status affects myelination, dopamine neurotransmission, and cortical fiber conduction (Froehlich et al., 2011). Gene variants that influence serum iron concentrations, such as the hemochromatosis allele (HFE C282Y) could serve as genetic proxies for serum iron status (Schatzkin et al., 2009). Associations between these gene variants and ADHD would be strongly suggestive of a causal role for iron status in ADHD.

Mendelian randomization makes a number of assumptions, some of which may be more defensible than others. Thus, Mendelian randomization, like other quasi-experimental methods, cannot be considered a gold standard, but the findings from studies using MR must be viewed in the context of findings from other research designs that make different assumptions and have different strengths and weaknesses.

As genome-wide association studies identify more and more of the genetic determinants of a range of biomarkers, the potential for using MR in the context of developmental psychopathology is likely to expand. However, MR will only be a promising methodological prospect to the extent that researchers understand the biological mechanisms by which specific exposures "get under the skin" to influence behavior. Clearly, the potential for using MR is limited by the nature of the exposure, such that those involving physical effects on the organism are likely to be more empirically tractable than those involving psychological (as well as) physical effects. For example, researchers hoping to use MR to test hypotheses about the relationship between abusive parenting or social deprivation and psychopathology are unlikely to identify plausible genetic proxies. Although there have been relatively few efforts to date to identify genes associated with social environments (Benjamin et al., 2012; Butcher & Plomin, 2008; Rietveld et al., 2013; van der Loos et al., 2013), this may be changing as social scientists join consortia devoted to consolidating data sets that include information on genotype and social science traits (e.g., education, income, attitudes).

TRANSLATIONAL IMPLICATIONS

Research designs that can measure and potentially rule out G-E correlations as potential sources of confounding are valuable from an intervention standpoint because they provide data on which exposures or experiences are likely to have causal effects on development. Such designs can be important complements to randomized control trials, which are characterized by their own strengths and limitations. Because they control for observed and unobserved heterogeneity, genetically sensitive designs (more so than observational studies) can identify upper and lower limits on the size of the effects that are likely to be observed in randomized control trials and they can potentially be informative about the breadth of effects that are likely to be observed. For example, interventions to reduce parental substance use may be effective in achieving that aim, but reductions in offspring externalizing problems are unlikely to be a serendipitous by-product of such interventions because the association between parent substance use and offspring externalizing problems appears to be genetically rather than environmentally mediated (Table 7.1).

CONCLUSIONS

The recognition that genes get outside the skin to shape the environment has important implications for research in developmental psychology and psychopathology. Namely, genotype–environment correlations over-turn conventional models of the determinants of individual differences in health, behavior, and cognitions. Genes and environments do not always act independently (additively or interactively) to influence phenotypes. Rather, our genes shape our behaviors and cognitions and these, in turn, shape our environments. Thus, social causation theories must explicitly rule out the alternative hypothesis that genotype confounds the relationship between exposures and outcomes. Otherwise, researchers run the risk of misidentifying the true causal agent in the relationship between a given exposure and a given outcome.

As summarized in Table 7.1, the data are largely consistent across research designs in the conclusions they draw

TABLE 7.1 Summary of Findings from Across Twin and Adoption Studies Testing Genetic Versus Environmental Mediation

	Adoption	Bivariate twin	Children of Twin	Twins & Parents	MZ Difference
Harsh parenting	ENV (Harold et al., 2012; Harold, Leve, Elam, et al., 2013; Rhoades et al., 2012; Stover et al., 2012)		ENV (Lynch, Turkheimer, D'Onofrio, Mendle, & Emery, 2006)	ENV (Eaves et al., 2010)	ENV (Asbury et al., 2006; Asbury et al., 2003; Cecil, Barker, Jaffee, & Viding, 2012; Deater-Deckard et al., 2001; Pike et al., 1996)
Parental criticism and parent–child conflict	ENV (Burt et al., 2011; Harold, Leve, Elam, et al., 2013; Klahr et al., 2011)		GEN (Marceau et al., 2013; Narusyte et al., 2011)		ENV (Burt, McGue, Iacono, & Krueger, 2006; Carbonneau et al., 2002; Caspi et al., 2004; Cecil et al., 2012; Larsson et al., 2008; Mullineaux et al., 2009; Shelton et al., 2008)
Interparental conflict	ENV (Harold et al., 2012; Harold, Leve, Elam, et al., 2013; Rhoades et al., 2012; Stover et al., 2012)		GEN (Harden, Turkheimer, et al., 2007; Schermerhorn et al., 2011)		
Divorce					
On externalizing and internalizing	ENV (Burt, Barnes, McGue, & Iacono, 2008) GEN (O'Connor, Caspi, DeFries, & Plomin, 2000)		ENV (D'Onofrio et al., 2005; D'Onofrio et al., 2006)		
On internalizing			ENV (D'Onofrio et al., 2005; D'Onofrio et al., 2006) GEN (D'Onofrio, Turkheimer, Emery, Maes, et al., 2007)		
On substance use			GEN (D'Onofrio et al., 2006) ENV (D'Onofrio et al., 2005; D'Onofrio, Turkheimer, Emery, Maes, et al., 2007)		
On cohabitation and transmission of divorce			GEN (D'Onofrio et al., 2006; D'Onofrio, Turkheimer, Emery, Harden, et al., 2007)		
Intergenerational transmission depression/anxiety	ENV (Brooker et al., 2014; Kerr et al., 2013; Tully et al., 2008)		ENV (Singh et al., 2011)		
Maternal depression to offspring conduct problems	ENV (Kerr et al., 2013; Pemberton et al., 2010; Tully et al., 2008)				

(*continued*)

TABLE 7.1 (*Continued*)

	Adoption	Bivariate twin	Children of Twin	Twins & Parents	MZ Difference
Intergenerational transmission antisocial behavior	ENV (Kerr et al., 2013) GEN (Bornovalova et al., 2014)		ENV (Silberg et al., 2012) ENV (for boys) (D'Onofrio, Slutske, et al., 2007) GEN (for girls) (D'Onofrio, Slutske, et al., 2007)		
Intergenerational transmission substance use			ENV (Jacob et al., 2003) GEN(Duncan et al., 2006; Slutske et al., 2008)		
Parental substance use to offspring ADHD and conduct problems			GEN (Haber et al., 2005; Knopik et al., 2006; Waldron et al., 2009)		
Peer victimization and rejection					ENV (Arseneault et al., 2008) (Ouellet-Morin et al., 2011a) (Vitaro et al., 2011) (Vitaro et al., 2012)
Peer deviance					
On cannabis use		GEN (Gillespie et al., 2009)			
On antisocial behavior		GEN (Kendler et al., 2008)			Nongenetically- mediated child effect (Burt, McGue, & Iacono, 2009)
On nicotine or alcohol use		ENV (Harden et al., 2008; Samek et al., 2013; Walden et al., 2004)			(Loehlin, 2010)
Marital status					
On antisocial behavior		ENV (Barnes & Beaver, 2012) GEN (Horn et al., 2013)[1]			ENV (Burt et al., 2010)
On depression		ENV (Horn et al., 2013)			ENV (Osler et al., 2008)
On happiness					GEN (Schnittker, 2008)
Marital quality		ENV (Beam et al., 2011; Spotts, Pedersen, et al., 2005)			GEN (Schnittker, 2008)
Smoking in pregnancy on externalizing problems	GEN (Gaysina et al., 2013; Rice et al., 2009; Thapar et al., 2009)				

Note: ENV = environmentally mediated effect; GEN = genetically mediated effect (via passive, evocative or active G-E correlation).
[1]The genetically mediated effect was specific to the comparison of married and cohabiting versus single respondents; reduced antisocial behavior in married versus cohabiting individuals was not confounded by genetic or shared environmental selection factors (Horn et al., 2013).

about whether observed associations between exposures (or experiences) and outcomes are environmentally or genetically mediated. Such consistency is crucial, given that each method of identifying and accounting for G-E correlations has its own weaknesses. For example, there is no question that genetic factors partially explain why some parents more frequently use harsh discipline or express hostility toward their children than other parents; such evidence of genetic effects is obtained when adult twins report on how they parent their own children and when (nontwin) adults report on how they parent their twin children. The existence of these G-E correlations implies that observed associations between parents' use of harsh discipline and offspring conduct problems are inflated in magnitude when estimates are based on samples of genetically related parents and offspring. Despite the existence of G-E correlations, however, significant associations between harsh parenting and offspring conduct problems are observed in children of twins designs (which control for passive G-E correlation), twins and parents designs (which also control for passive G-E correlations), MZ difference designs (which control for all forms of G-E correlation), and adoption designs (which control for passive G-E correlation). Consistent evidence of environmentally mediated effects implies that researchers can usefully focus research on efforts to identify mechanisms by which harsh parenting increases risk for offspring conduct problems as well as conditions under which this mechanism would not be observed.

The old nature–nurture dichotomy—while alive and well in newspaper headlines—fails to capture the complexity by which genes and environments act together to influence normal and abnormal behavior. Genetic risk factors modify sensitivity to environmental risk factors (GxE) and—as described extensively in this chapter—they influence a person's exposure to environmental risk factors (rGE). Although not covered in this chapter, the environment also has the potential to regulate gene expression (Cole, 2011) and the epigenome (Mill, 2011). Advances in genetic epidemiology are therefore conditional on advances in environmental epidemiology (Moffitt et al., 2005). We have noted an important corollary: advances in genetic epidemiology can also *prompt* advances in environmental epidemiology.

A number of research designs are also available that are capable of ruling out genotype–environment correlations as alternative explanations for associations between risk exposures and outcomes. Although many of these designs require genetically sensitive data (e.g., measured genotypes or data from individuals who vary in their genetic relatedness), not all do. For example, studies of within-individual change merely require longitudinal data to test the hypothesis that a given event can change a person from one point in time to the next. More analytically sophisticated versions of these models allow researchers to account for simultaneous change in other aspects of the person's environment that may—alongside the focal exposure—change the individual's behavior (Sampson, Laub, & Wimer, 2006). In addition, genotype–environment correlations can be—under some conditions—leveraged to identify genetic proxies for environments and used to make causal inferences about environmental exposures. In summary, although genotype–environment correlations have received relatively less attention than G-E interactions, they are likely to play a key role in development. Taking account of genotype–environment correlations in research on putative environments is likely to enhance our understanding of environmentally mediated causes of individual differences in normal and abnormal development.

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CHAPTER 8

The Trilogy of GxE: Conceptualization, Operationalization, and Application

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INTRODUCTION

From the beginning of the quest to comprehend the forces of human development (i.e., their typology and etiology), there was a notion that these forces had different sources: there is something that a child gives to this world (i.e., through abilities to be developed into competencies and expertise), and there is something that the world gives to the child (i.e., proximal adults, various experiences, or chance). Justifiably or not, these sources have been viewed as distinct entities and labeled as nature and nurture, respectively. Throughout the history of the developmental sciences, whether embedded in other sciences or forming sciences themselves, nature and nurture and their relationship have been defined across a continuum, from being independent to interdependent, with all possible variations in between.

Fast-forward to today, where the prevailing view in the developmental sciences is that nature and nurture are intertwined. This means that, although separable via extreme main effects, nature and nurture shape developmental trajectories together through co-action, whether at the level of a cohort or an individual. The separation of nature and nurture arises only in relatively rare situations, in fact, in which nature overrides nurture—e.g., severe genomic lesions resulting in high mortality regardless of environmental circumstances, or in which nurture overrides nature (e.g., severe nutrient deficiency resulting in high mortality regardless of the exposed genotype). In other words, it is now commonly recognized that the structural variation in

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[1]Color versions of Figures 8.1 and 8.8 are available at http://onlinelibrary.wiley.com/book/10.1002/9781119125556

the genome alone cannot explain most cases of inherited diseases/disorders. Similarly, it is widely accepted that environments, however defined, cannot explain most cases of acquired diseases/disorders. It is far more probable that environments as well as self-determined behavior (e.g., lifestyle), interacting with the structure of the genome, result in the manifestation and dynamics of these diseases and disorders as well as normative development.

This nature–nurture co-action is exemplified plentifully in numerous phenomena in the developmental sciences, including, but not limited to, the manifestation of differential responses to environments that are demonstrated by humans throughout the life span. Illustrations of such differential responses are abundant and are exemplified, primarily, in the literature on responses to different early rearing conditions in general (e. g., Cicchetti, Rogosch, Gunnar, & Toth, 2010; Lawler, Hostinar, Mliner, & Gunnar, 2014) and variation in caregiving quality in particular (Kochanska, Askan, & Joy, 2007; Suomi, 1997); moreover, these responses are traceable, although manifested in different forms, throughout the life span (Aron & Aron, 1997; Evans & Rothbart, 2007; Posner & Rothbart, 2007). Differential responses are acknowledged when the removal of either nature or nurture susceptibility factors negates the outcome (Caspi & Moffitt, 2006; Rutter, 2006).

These differential responses, whether with regard to typical or atypical development, have been theorized about in a number of models, most notably, the transactional/dual-risk model (Sameroff, 1983) and the diathesis–stress model (Meehl, 1962; Monroe & Simons, 1991; Zubin & Spring, 1977; Zuckerman, 1999). The main theme of these models is that, even upon their initial arrival to this world, children already differ in vulnerability, and those who are deemed vulnerable are likely to be adversely affected, disproportionally or even selectively, by environmental stressors (e.g., child maltreatment, inadequate parenting or schooling, negative life events). Thus, atypical development (or psychopathology) is a systemic outcome of co-effects or synergisms of inherent vulnerabilities (diatheses) and negative environments (stressors). This theme has been further developed in what is known as the differential susceptibility (Belsky, 1997, 2014; Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Belsky & Pluess, 2009; Pluess & Belsky, 2013) and biological sensitivity to context (Boyce & Ellis, 2005; Boyce, Sokolowski, & Robinson, 2012; Ellis, Essex, & Boyce, 2005; Ellis, Jackson, & Boyce, 2006) hypotheses, stipulating that the very same individuals who are deemed vulnerable and suffer the most from adversity, are also the ones who will profit the most from the amelioration of adversity and enrichment of their environment. These hypotheses, although similar in their position on the importance of the co-action of nature and nurture and their inclusion of the notion of developmental plasticity (Belsky & Pluess, 2009), differ in their accents. Thus, in the nature–nurture co-dynamics of the development and emergence of individual differences, the former hypothesis accentuates the part of nature, whereas the latter accentuates the part of nurture. Both hypotheses are grounded in the theory of evolution, emphasizing the rationale for differential responsiveness in a continually volatile environment (Wolf & Krause, 2014; Wolf, van Doorn, & Weissing, 2008) and, correspondingly, for maximizing fitness through diversity (Belsky, 1997) by programming, prenatally and postnatally, hyperreactivity and hypersensitivity to stress to adaptively match those unpredictable environments (Boyce & Ellis, 2005).

Empirically, these hypotheses are rooted in the large literature known as the gene–environment interaction literature (e.g., Bakermans-Kranenburg & van IJzendoorn, 2006, 2011), which captures an ongoing quest of ever-gaining momentum (Hunter, 2005) for the understanding of the empirical and mechanistic texture of nature–nurture co-action. In this chapter, we intend to introduce this literature and highlight its particularly distinct facets. As an introduction, by definition, is not a comprehensive overview of the field, this chapter is segmented into three parts: the first presents the concept of gene–environment interaction; the second discusses various aspects of the operationalization of the concept; and the third exemplifies issues arising in the actual implementation of the operationalization and application of GxE in empirical research. Thus, the chapter introduces the trilogy of gene–environment interaction (i.e., the presentation and discussion of the phenomenon's conceptualization, operationalization, and implementation).

THE CONCEPT

The most intuitively appealing conceptualization of gene–environment interaction (GxE) is the dependence between two factors—the genetic (G) and environmental (E) in their effects on a trait. The presence of GxE is posited when the effect of the genome depends on the immediate environment in which it exists or when, vice versa, the effect of the environment depends on the genome (Duncan & Keller, 2011). In other words, biologically, GxE interactions signify all of the different ways that

a genetic structural variant may give rise to a particular phenotype within a particular environment, or vice versa (Manolio, Bailey-Wilson, & Collins, 2006). Statistically, GxE indicates differential associations between the genotype and the phenotype in the presence, absence, or dosage of a particular environmental exposure.

From a public health perspective, GxE interactions are highly important (Thomas, 2010a). Broadly speaking, their importance is two-fold, as they have negative and positive facets. The negative facet of GxE is that it can mask a main effect (either G or E), so that the research generates false negatives or inconsistent results (Bos et al., 2005; Ko, Hsu, Hsu, Ko, & Lee, 2004; Ordovas et al., 2002; St-Pierre et al., 2003; Tai et al., 2003). The positive facets of GxE are thought to be numerous (Le Marchand, 2005; Le Marchand & Wilkens, 2008); these aspects reflect both future promises and current shortcomings of this concept. Specifically, first, understanding the mechanics of GxE may produce insights into the biological pathways of typical and atypical development (Thomas, 2010a). Thus, it is possible that many genetic risk factors act synergistically, but do not demonstrate marginal effects (i.e., do not appear to have an impact when examined individually). If so, understanding related interactions would be pursued not for the sake of the discovery of the interaction per se (Kraft, Yen, Stram, Morrison, & Gauderman, 2007), but for the sake of identifying the genetic risk factors. The same logic applies to understanding environmental hazards and their deleterious effects (Hunter, 2005). Second, in situations when both the susceptibility genetic factor and environmental exposure should be present for a disorder to manifest, GxE interactions are viewed as instrumental in altering or diverting the effects of harmful genes by avoiding exposure to harmful environments (Manolio et al., 2006). Third, understanding GxE might aid in both qualifying and quantifying the degree of etiological heterogeneity, whether genetic or environmental (Greene, Penrod, Williams, & Moore, 2009; Ioannidis, 2007). Fourth, ideally, if GxE interactions are of substantial magnitude, they could be incorporated into risk prediction models with consequences for practice in both the domains of public health and personalized medicine (Thomas, 2010b).

Although relatively young, the field of studies of GxE has had an impressive trajectory (Thomas, 2010a). It was formulated prior to the discovery of the structure of DNA, that is, when G was not measurable, and prospered through quantitative genetic (e.g., twin) studies. The field has since learned how to measure G in stages, initially through the utilization of single polymorphisms[2] and now through high-throughput technologies capturing the variation in the whole genome. With the subsequent development of relevant measurement tools (e.g., genotyping and sequencing), the field has flourished. Initially, the GxE field was dominated by candidate–gene (or, more precisely, candidate-polymorphism) studies. The premise for this hypothesis-driven or inferential approach in general, as well as for the selection of gene candidates, was the existence of a known connection between a given environmental factor and the genetic pathway that carried that factor on (e.g., metabolized it, such as the metabolic pathway of alcohol or tobacco).[3] Then, a particular gene within a specific pathway or a particular polymorphism within a specific gene could be singled out and nominated as a candidate gene or a candidate polymorphism, deemed to serve as a proxy or a marker for a specific biological process. As the field's sophistication has grown, the focus of GxE studies has moved from single polymorphisms and single genes to entire pathways, along with the genes, exposures, and various cofactors deemed relevant to these pathways. The same technological and theoretical advancements that increased the complexity of the hypothesis-driven approach to GxE have triggered a hypothesis-free or agnostic approach to studies of GxE. This approach is rooted in the availability of large amounts of genetic data generated, initially, by genome-wide association studies (GWAS, which allow testing for associations between common genetic variants and phenotypic traits) and now by genome-wide sequencing studies (GWSS, which allow the discovery of new rare variants accounting for phenotypic variation). Although the initial investigations of these data intended and attempted to investigate main effects, there is now an increasing interest in investigating interactive effects (Cordell, 2009). Although not all, many GWASes and GWSSes, either by design or by the nature of samples (e.g., in cohort studies), include relevant indicators of environment and, thus, the data they produce might be utilized in GxE studies. These studies might be of two

[2]In whatever type these polymorphisms (i.e., genetic variants at a particular position of the DNA sequences) were available, namely, restriction fragment length polymorphisms—RFLPs, variable number tandem repeat—VNTRs, or single nucleotide polymorphisms—SNPs.

[3]Of note is that there is a certain field specificity in how this approach is manifested in medical (e.g., psychiatry) and behavioral (e.g., developmental psychopathology) candidate–gene GxE studies. The former, in fact, are much more hypothesis oriented than the latter.

kinds: the first aimed at exploring signals that do not reach genome-wide significance in the context of main-effect analyses, but might in the context of interaction-effect analyses (Holmans et al., 2009); and the second aimed at mining patterns of interaction effects to identify novel biological pathways (Sebastiani, Ramoni, Nolan, Baldwin, & Steinberg, 2005).

As the number of GxE studies, conducted either in old (i.e., candidate gene or polymorphism) or new (i.e., whole genome) style, has been increasing exponentially, there has been a push to establish and propagate a set of systematic requirements to guide GxE discovery and replication. Although this chapter is not the forum for setting such requirements, our intention is to highlight and discuss issues that have been flagged as important and problematic in GxE research, and that require understanding and reflection by any individual who aims to be an informed reader and/or a qualified contributor to the GxE literature.

Both historically and currently, the literature contains many different notions of the term *interaction*; the multiple meanings of the term have been and are likely to remain a source of confusion (Clayton & McKeigue, 2001). Due to such ambiguity, it is customary to see disclaimers in the literature that differentiate a *statistical* form of an interaction (i.e., statistical interaction—a quantitative description of the joint effects of multiple factors) from a *biological* form of an interaction (i.e., biological interaction—the causal and biological mechanisms; Cox, 1984; Rutter, Moffitt, & Caspi, 2006; Thompson, 1991). There are historical and conceptual reasons for differentiating these concepts.

Tabery (2007) distinguished so-called biometric and developmental concepts of GxE. He attributed the former to R. A. Fisher and put forth an interpretation of the concept of GxE (GxE_B) within Fisher's general biometric paradigm aimed at partitioning total phenotypic variance into its components, including genetic and environmental ones. As his paradigm was defined by a particular set of assumptions, the concept of GxE was neither native to it nor readily assimilated by it, being viewed as a potential source of bias[4] for other components of the decomposition of phenotypic variance equation. Being aware and concerned about biases, Fisher investigated the concept of GxE quite closely, but in a single empirical investigation, and arrived at the conclusion that, in fact, the magnitude of effects associated with this concept were not impressive and, therefore, not substantial; in fact, it could be eliminated with a transformation of scale.

Tabery (2007) contrasted Fisher's biometric concept of GxE with the *developmental* concept of GxE (GxE_D) conceived by L. Hogben. For Hogben, GxE was a facet of the natural course of events that is as embedded in nature as development itself. In other words, GxE is omnipresent and the question is whether our statistical apparatus can detect it and appraise its magnitude. According to Tabery, the tension between these two interpretations of GxE has shaped the relevant literature in the last century and remains highly present today.

It so happened, as is often the case in science, that these two different interpretations arose from the fact that the two scientists followed rather different scientific and personal pathways to the derivation of GxE interaction, both conceptually and statistically. Fisher, working on the foundations of what is now known as quantitative genetics and behavior genetics, first viewed the environmental variable as randomly distributed (Fisher, 1918). Yet, his later experiences at the Rothamsted Agricultural Research Station, where, reportedly, his charge was to evaluate environmental variation, challenged his view on this randomness and triggered his thinking on the possible "interaction of causes" (Fisher, 1925). To follow up on his thinking experimentally, Fisher examined different combinations of various sorts of potatoes with various types of manure. He stated, as a result of his single experiment, that the deviations from additivity observed in his potato-compost system were not significant; that is, the potato varieties did not exhibit differences in their reaction to different types of manure (Fisher & Mackenzie, 1923), and, therefore, there was no reason to believe that the "interaction of causes" should create important complications to his approach to the decomposition of phenotypic variance. Thus, for Fisher, genetic and environmental forces, especially the former, remained the major causes; any co-action between them, however defined, constituted mere nonstatistically significant deviations from additivity, (i.e., possible qualitatively, but not essential to account for quantitatively)—of "possible, but unproved, importance" (Tabery, 2007, p. 967).

Hogben's (1932) conceptualization of GxE interaction was very different. In part, it was inspired by his own scientific journey while teaching at the London School of Economics (Tabery, 2007). Although unequivocally recognizing the usefulness of differentiating genetic and environmental factors in understanding causality of development, he was highly critical of their separation, even if only for the sake of deriving testable statistical models.

[4]Where bias is defined as "any process at any stage of inference which tends to produce results or conclusions that differ systematically from the truth" (Sackett, 1979, p. 60).

In fact, Hogben underscored the critical nature of a third type of variance, which manifests itself when a particular combination of genetic factors interacts with a particular combination of environmental factors. In doing so, he postulated both the ubiquitous character of GxE in development and the flaw in statistical representations of G and E when their interaction term is omitted.

The ubiquity of GxE comes from the very fact that the genome does not exist without an environment; thus, the developmental version of the GxE concept, or, specifically, GxE_D (Tabery, 2007), is as important a player in human development as G or E individually. The GxE_D interaction could be studied experimentally (Krafka, 1920), although the options for such studies are limited with regard to research on humans. Although not directly referenced by Hogben, similar ideas were developed by Richard Woltereck in Germany in the early twentieth century with regard to his concept of *Reacktionsnorm*, or norm of reaction—a complete set of developmental outcomes that could emerge when the same genotype is immersed in different environments (Sarkar, 1999 & Peirson, 2012).

To summarize, for Fisher, the phenomenon of GxE (GxE_B, today referred to mostly as statistical GxE) did not exist unless it was explicitly detectable (i.e., representable by a statistical term in his variance decomposition equation) and statistically significant. Moreover, even if there were evidence for the significance of the term, the interaction might be removable by transformation of variables and the corresponding portion of the variance manifested on the side of G.

For Hogben (1932), the GxE phenomenon ($Gx E_D$, today referred to mostly as biological GxE) existed a priori, and, if statistical rather than experimental approaches mattered at all, they needed to be perfect to capture it. Thus, Fisher (1925) argued that his biometric machinery could detect the interaction if it was there, while Hogben argued that, in most cases, it was there, even if it was not detectable statistically. After an exchange of letters and a number of cross-referencing debates in the literature, neither conceded. Fisher's position was that the burden of proof was on the opposition; one needed to show that something exists before the discussion of how to assess or measure it could meaningfully take place.

This debate has not been resolved, and, moreover, its essence has framed much of the relevant research today. The relevant discussions have gone through a variety of different stages, engrossing many scientists, and generating many new concepts. Highly engaging, both theoretically and historically, this debate will be represented in this chapter only by a limited number of highlights. Fisher's view of GxE as a mere phantom whose existence needs to be proved has been adopted by many scientists in a number of different contexts (Jensen, 1969, 1973; Lush, 1937). Whatever the phenotypic trait at the focus of discussion, the meagerness of the GxE interaction term, as estimated in a Fisher-style decomposition of variance approach, was compared to the substantial main effects of G and E (and the error term) and, therefore, dismissed. In turn, Hogben's ideas both inspired and framed the thinking of C. H. Waddington, who, pursuing the premise of the developmental preeminence of GxE, introduced the concepts of epigenetics and an epigenetic landscape (i.e., a physical and temporal map of the genetic regulation of development; Waddington, 1957, 1975). The indisputable reality of GxE has also been endorsed by R. Lewontin (1974), who, in his discussion of the biometric approach to phenotypes, asked a very important question about the limitations of this approach for making inferences about the magnitude of genetic effect on a trait (i.e., heritability estimates, or the proportion of phenotypic variance accounted for by genetic variance) in environments that have not yet been encountered (Feldman & Lewontin, 1975).

The debate crystallized in the distinction of two extreme positions, often referred to as *interaction versus interactionism*, where the former represented Fisher's views and the latter—Hogben's. A new interpretation of this debate has surfaced more recently in the work of M. Rutter and colleagues, who discussed the narrow sense (i.e., statistical concept) and broader sense (i.e., biological concept) of the GxE phenomena (Rutter, 2006; Rutter & Pickles, 1991). Regardless of the terms used, the crystallization of this debate recognizes the importance of both conceptualizations of GxE and argues that they often, yet do not always, function sequentially. The ongoing nature of this debate also illuminates the different stages of the field's understanding of how genomes and environments co-act (i.e., in that they are inseparable within an individual, but can be statistically isolated when considered at the population level). In other words, a registration of statistically significant GxE at the population level can be followed up with an investigation of the underlying biological mechanism, either at the individual or group/population level, just as the registration of a biological phenomenon in a particular individual/group can be later investigated at the population level, so that its role as a risk factor in the larger population can be appraised. A recognition that both types of GxE are important may help to reconcile the two extreme views; such an appeasement would be supported by many scientists (e.g., Vreeke, 2000).

THE OPERATIONALIZATION

From Concept to Term

Conceptually, interaction refers to the co-participation of two factors in a causal mechanism (Rothman, 1986). A GxE interaction transpires when subsets of a population (or a specific sample, if not representative of the population), distinguished by a specific genotype (e.g., a polymorphism, a risk-associated haplotype, several causal variants within a gene, or even some complex index of genetic risk, constructed from several causal variants, Thomas, 2010a), differentially respond to varying environmental conditions (Rowe, 2003). This observation is translated into statistical terms, according to which GxE interaction is present when the impact of a specific genotype on one's susceptibility to a disease or disorder depends on exposure to a specific environmental factor; the reverse (from environment to genotype) is also true (Clayton & McKeigue, 2001). Specifically, G and E demonstrate dependence such that genetic influences on the phenotype are conditioned on the environmental context, whereas an organism's phenotypic response to the environment is conditioned on the genotype. Rephrased, GxE interaction can be defined as *differences in the effect* of an environment on disease/disorder risk in carriers of different genotypes or, equivalently, *differences in the effect* of a genotype on disease/disorder risk in persons with different environmental exposures (Ottman, 1996).

In general terms, an interaction is qualitatively indicated when an effect is explained, not merely by independent and relative contribution of one or more variant(s) within a gene (or many variants within many genes) and one or more environmental exposures, but by the joint contribution of these two (G and E) factors. Correspondingly, tests for interaction (GxE) address the fit between a chosen model and the data. A test for the main effect (or the average effect) of exposure assumes the null hypothesis of no difference between risk in exposed and unexposed subgroups, and for genotype assumes the null hypothesis of no difference between risk associated with genetic variability. A test for interaction assumes the null hypothesis of the co-action of these two factors, as described by a specific statistical model. Conventionally, when testing for GxE, a multiplicative model is used, which assumes that the product of functions of the genetic and environmental risk factors explain the relative risk of manifesting a disease/disorder. A joint effect that differs from the predicted value of the specified model is deemed a form of interaction. Or, in other words, the presence of interaction is marked by lack of fit to the statistical model (Clayton & McKeigue, 2001; Thomas, 2010a).

A common measure of effect is the ratio of the incidence of a disease or disorder in exposed to unexposed subgroups, which can be captured (in a case–control study, for example) by an odds ratio. In this context, a multiplicative model for the joint effects of risk factors (e.g., G and E) assumes that the risk ratio between exposed and unexposed subgroups (i.e., subgroups of E) does not vary over subgroups defined by the genetic factor (i.e., subgroups of G). As the presence of interaction entails differences in the risk ratio across different subgroups, statistically, it will mean a lack of fit to the multiplicative model. Of note, the detection of statistical interaction might or might not aid in understanding the underlying biological mechanics associated with GxE. In order to contribute to this understanding, the null hypothesis needs to have a clear biological interpretation. Moreover, the same statistical model for the risk ratio could be associated with many different biological models or mechanisms. In fact, the registration, by statistical means, of the presence of interaction does not imply the strengthening of any corresponding theory of pathogenesis (Eaves, 2006; Rothman & Greenland, 2005; Rothman, Greenland, & Walker, 1980; Thompson, 1991).

The central issue here is that of biological validity, as biologically essential interactions can typically be detected without statistical techniques. An oft-cited example of a biologically valid interaction is that of phenylketonuria (PKU)—a disorder resulting from an interaction of homozygous loss-of-function mutations in the gene encoding the phenylalanine hydroxylase enzyme, and dietary exposure to phenylalanine. As phenylalanine is abundant in the human diet, under typical conditions (i.e., when a baby is exposed to typical early care) the interaction is not statistically detectable because the exposure variable is fixed (i.e., every human baby is exposed to phenylalanine). Yet the knowledge of this interaction is critical as it determines both prevention and intervention.

As evident from the previous historical notes, the field of GxE started with the statistical estimation of the corresponding term, defined within Fisher's model of phenotypic variance decomposition (i.e., the so-called quantitative-genetic model), in which case many components of the equation were unmeasured. Specialized statistical models (Andrieu & Goldstein, 1998; Eaves & Erkanli, 2003; Purcell, 2002) to test for the variance components of GxE have been developed over time. These black box statistical approaches have undoubtedly made a substantial contribution to the fields of quantitative and behavior genetics. However, these advances in statistical modeling have had much less relevance for researchers wanting to utilize the results of the GxE studies to make specific practice-related recommendations. Gradually, different

versions of the general variance-decomposition model have been developed, so that unmeasured terms have been replaced with measured terms (in different combinations).

In this part of the chapter, we will comment on the issues that arise when both of these approaches (i.e., one with unmeasured and the other with measured terms are exercised). The discussion will primarily focus on the concept of statistical interaction, as this is what is utilized in the majority of studies in the developmental sciences in general, and developmental psychopathology in particular.

When Terms Are Unmeasured

In quantitative-genetic (also often referred to as behavior-genetic) studies, GxE interactions are reported primarily in attempts to understand how genetic influences are moderated by different aspects of the environment. In other words, these studies allow researchers to appreciate the magnitude by which the impact of a specific genotype is either augmented or limited by exposure to a specific environmental factor. Yet, depending on what particular model of moderation is assumed, rather distinct types of results and interpretations are expected. Carlson, Mendle, and Harden (2014) exemplified these expectations as follows. One model of moderation is the diathesis-stress model (see above). According to this model, individuals differ in the degree to which they can be negatively affected by adverse environments, and this differential risk can be attributed to individual variations in genetic vulnerability (Monroe & Simons, 1991). In other words, such environments may moderate the role of the genetic factors associated with disease/disorder risk by magnifying the likelihood that genetically vulnerable individuals will develop negative outcomes. This translates into an assumption that genetic variance will be higher in low-quality, adverse environments, and lower in high-quality environments.

Conversely, some models focus on the relationship between specific genetic predispositions and their capacity to benefit from advantageous environments (Bronfenbrenner & Ceci, 1994; Pluess & Belsky, 2013). This translates into the assumption that genetic variance will be higher in high-quality environments and lower in lower quality environments.

Finally, the differential susceptibility model (Belsky et al., 2007; Ellis et al., 2005) assumes the existence of genetic predispositions that are marked by greater plasticity overall, so that both adverse and advantageous environments differentiate these genotypes and magnify the resulting outcomes as more negative or positive than those for carriers of less-sensitive genotypes in negative and positive environments, respectively. This translates into an expectation that genetic variance will be maximized at opposing extremes of the moderating environmental factor (Ellis, Schlomer, Tilley, & Butler, 2012), but will be negligible in average environments (South & Krueger, 2013).

The literature provides a number of illustrations of quantitative-genetic studies of GxE (Jaffee, Price, & Reyes, 2013). For example, it has been demonstrated that in environments that facilitate substance use—that is, those that impose lower taxes on substances (Boardman, 2009), have greater alcohol availability (Boardman, 2009; Kendler, Gardner, & Dick, 2011) or are characterized by greater existence or dominance of social norms encouraging drinking (Boardman, Saint Onge, Haberstick, Timberlake, & Hewitt, 2008; Timberlake et al., 2007), increased affiliation with deviant peer groups in adolescence (Kendler et al., 2011), urban (vs. rural) environment (Dick, Rose, Viken, Kaprio, & Koskenvuo, 2001), avoidance of organized religion (Timberlake et al., 2006), and lower levels of parental monitoring (Dick et al., 2007)—genetic variance in alcohol and tobacco use is higher.

A similar pattern of greater amount of genetic variance has been observed for youth externalizing problems when adolescents are exposed to a broad range of adversities in their environment (Hicks, South, DiRago, Iacono, & McGue, 2009). Otherwise, adverse childhood environments appear to suppress genetic influences, compared to more advantaged environments (Carlson et al., 2014), predisposing youth, over and above their genetic differences, to earlier initiation of sexual activity (Belsky, Steinberg, Houts, Halpern-Felsher, & the NICHD Early Child Care Research Network, 2010; Coley & Chase-Lansdale, 1998).

Conversely, a suppression of genetic variance in substance abuse has been demonstrated in environments imposing high social control (Kendler et al., 2012), high parental monitoring (Dick et al., 2007), religious upbringing (Koopmans, Slutske, van Baal, & Boomsma, 1999), and positive marital relationships (Dick et al., 2006). Recently, such a list of positive environments has been extended to include that of competitive, achievement-oriented, high-quality schooling (Benner, Kretsch, Harden, & Crosnoe, 2014), shedding light on the nature of previously reported overlapping genetic influences between, for example, nicotine use and educational attainment (McCaffery et al., 2008), academic mastery and alcohol dependence (Bryant, Schulenberg, Bachman, O'Malley, & Johnston, 2000; Crosnoe, 2006; Kiecolt, Aggen, & Kendler, 2013), and verbal ability and alcohol dependence (Latvala et al., 2009).

Of note, aligned with both the expectation regarding the diversity of possible GxE patterns and the theoretical assumptions outlined above, there are traits and genotypes that benefit from relative social advantage. Thus,

it has been shown that genetic influences on age at the initiation of sexual activity are greater in contexts of relative social advantage and suppressed in more adverse conditions (Carlson et al., 2014; Waldron et al., 2008). Similarly, greater genetic variance has been registered in more advantageous environments for traits of intelligence (i.e., higher levels of SES; Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003) and early reading (i.e., higher teacher quality; Taylor, Roehrig, Soden Hensler, Connor, & Schatschneider, 2010).

When Terms Are Measured

The term that researchers started to measure first in GxE studies was that of environment. One (although not the only) reason is that by the beginning of the 21st century, the field of epidemiology had accumulated enough data (Hemminki, Lorenzo Bermejo, & Forsti, 2006) to demonstrate that environmental factors have amplified the background incidence of so-called common complex diseases and disorders in high-income countries to over 10 times the level observed in low-income countries (Buchanan, Weiss, & Fullerton, 2006; Colditz, Sellers, & Trapido, 2006; Willett, 2002). This observation corresponds to the growing recognition that combinations of these environmental factors, characteristic of high- compared to low-income countries, with specific genetic predispositions, are responsible for the most recent epidemics of chronic disease. The challenge of epidemiological research today is to identify these combinations (Weaver, Buckley, & Groopman, 1998) so that the course of the epidemic can be reversed (Chakravarti & Little, 2003). One example of such a combination is the interaction between today's environment of overabundance of calories with presumed famine-protective genetic predispositions, which is argued to have contributed to the current obesity epidemic in the United States (F. S. Collins, 2004).

Although quite often in GxE research genetics (G) and environmental (E) have been conceived, rather simplistically, as dichotomous variables, both G and E factors, in reality, are complex and multidimensional (Thomas, 2010a). Consider, for example, air composition, which can be specified as polluted/unpolluted dichotomous E, but whose indicators, in reality, represent a multifarious brew of gases and particles with different properties (Ghio, Carraway, & Madden, 2011; Nieuwenhuijsen, Gómez-Perales, & Colvile, 2007), so that types of polluted air may vary dramatically with regard to the level of danger associated with exposure. In addition, G and E might have other sources of variability, such as time and intensity. With regard to the former, many environmental risk factors can be modified by such time-based factors such as age at or duration of exposure (Thomas, 1988). With regard to the latter, the intensity and number of exposures could be a much more important source of information than whether or not an exposure has occurred (Miller, Schlosser, & Janszen, 2000).

The technological developments in the measurement of both the genome and the environome (i.e., the combination of aspects of the environment that can be systematically extrapolated such as nutritional intake, amount of physical exercise, amount of sleep, level of stress and so forth) coupled with the development of computational capacities, has resulted in a dramatic shift away from GxE studies in which none of the terms are measured toward those in which all of the terms are measured. In addition, the development of robust analytical methods for assessing both main effects and interactions has permitted the interrogation of these complex effects on a population scale (van den Oord, 1999). Yet, this change has also brought up a number of new concerns not previously voiced in the GxE literature. These concerns are many and they will be discussed primarily in the next section of this chapter. Here we mention only those that are relevant to the measurement of genes and environments in the context of GxE studies.

First, as the broader field of genetics (both quantitative and molecular) transitioned from unmeasured to measured G and E, the problem of missing heritability of common traits (Maher, 2008; McCarthy & Hirschhorn, 2008) arose. The field anticipated a translation of the high heritability estimates obtained from quantitative-genetic studies into similarly high heritability estimates obtained from molecular-genetic studies. However, this did not happen. In fact, the latter were estimated to be nowhere near as high as the former. The major effort to qualify and quantify genetic variation triggered, in part, by the Human Genome Project, had produced an ocean of genome-wide association studies (hereafter, GWAS will refer to the method and GWASes will refer to studies carried out using the GWAS method). These studies led to the identification of >1,200 loci whose genetic variants were shown to be associated with >165 common human diseases/disorders and complex traits; collectively, these variants implicated many previously unknown or unconsidered roles for numerous biological pathways (Hirschhorn, 2009; Lander, 2011; Manolio, Brooks, & Collins, 2008). It was expected that these very first GWASes (measuring the genome in this case with single nucleotide polymorphisms, SNPs) would result in the translation of previously obtained

heritability estimates into effect sizes for measured G (i.e., specific genetic variants). The GWAS-based estimate of heritability is the ratio of the heritability due to the variants used in the GWAS (specified as the numerator), estimated directly from their observed effects, to the total heritability (specified as the denominator), obtained either from previous studies or from the same study (if the sample is comprised of related individuals), or inferred indirectly from population data (Zuk, Hechter, Sunyaev, & Lander, 2012). However, these first GWASes and all subsequent ones (until recently, when the data-analytic approach changed and genomewide complex-trait analysis, GCTA, was introduced, e.g., Plomin et al., 2013), reportedly accounted for only a small proportion of the previously published heritability estimates of diseases/disorders and complex traits. This discrepancy between what was expected based on results from quantitative-genetic studies and what was observed based on the results from molecular-genetic studies was labeled as the "missing heritability" problem. As GWASes have become bigger (i.e., larger samples) and better (i.e., denser coverage of the genome), results have improved, with the referenced amount of variance reaching 20–30% or even 50% in isolated cases. However, the puzzle remains, as only a smaller portion of the previously obtained heritability estimates have been mapped onto specific genetic variants measured by GWASes (Lander, 2011).

As the problem of missing heritability became apparent, the dominant explanation was that it arose from incomplete coverage of the genome, i.e., the assumption that there were still some (or many) undiscovered variants not included in the numerator, leading to estimates biased on the lower side. Yet another possibility pertains to the overestimation of the denominator: the phenomenon referred to as *phantom heritability* (Zuk et al., 2012). Such an overestimation can arise, for example, if models do not take into account epistatic genetic interactions within loci (in that effects of each loci may not merely be additive but interact with each other to predict disease/disorder risk) (Zuk et al., 2012). To illustrate their point, Zuk and colleagues (2012) referenced Crohn's disease—an inflammatory bowel disease that impacts various components of the digestive tract. For this disease, in a traditional GWAS paradigm, 71 risk-associated loci have been identified (Franke et al., 2010). If an additive model is assumed, then these loci account for only 21.5% of the heritability, which was previously estimated at 50% (Halme, Paavola-Sakki, Turunen, Färkkilä, & Kontula, 2006), yet, if an epistatic model is assumed, then these loci explain 80% of the adjusted heritability (the phantom heritability was estimated at 62.8%). Unfortunately, it is estimated that very large sample sizes (~500,000) are required to detect genetic interactions even for such a relatively heritable disease as Crohn's. The authors (Zuk et al., 2012) concluded that current estimates (and, therefore, the whole discussion) of missing heritability might not be meaningful, as these estimates were obtained without taking into account genetic interactions. This observation is quite congruent with the worry that most previously reported heritability estimates are, indeed, artificially elevated. In fact, most of these estimates come from twin studies, which tend to provide an upper limit to the genetic component of the variance of a disease/disorder or a trait, and thereby may lead to invalid conclusions (Wallace, 2006).

The second concern relevant to the measurement of G and E, as mentioned above, is with the selection of the candidate genes and candidate environments used in GXE studies. For most, if not all, common complex diseases and disorders, even main effects of G and E are still rather mysterious (see the discussion for psychiatric disorders in Flint & Munafò, 2008). In fact, almost two decades of candidate gene association studies have produced, arguably, little or no unequivocally accepted findings regarding genetic effects (Burmeister, McInnis, & Zöllner, 2008). This observation is especially worrisome given that most (if not all) hypotheses about specific candidate genes emerged from strong neuroscience research that uncovered the putative properties and functions of these genes (Hebebrand, Scherag, Schimmelmann, & Hinney, 2010); these candidate genes, most of which are protein-coding, were selected because they were found to have functional variants that somehow changed the properties of synthesized proteins, which were implicated in complex diseases and disorders. Given the lack of prior success in uncovering main effects of G for a given complex disease or disorder, there is understandable skepticism regarding the possibility that more complex associations, such as between a specific variant in a specific candidate gene (or any other type of genotype) and a specific facet or a general characteristic of a particular environment (Duncan & Keller, 2011; Ioannidis, 2005), will also be uncovered.[5]

The GWAS approach is fundamentally different and hypothesis-free. Correspondingly, it is not surprising that

[5]A prior probability distribution (the prior) of an uncertain quantity *p*, in Bayesian statistics, is a distribution capturing expectations about *p* prior to the accumulation of the relevant evidence.

thus far, results of GWAS do not align with hypotheses generated by candidate–gene research. In fact, out of 531 SNPs labeled as the most robustly associated (SNPs) to various medical and psychiatric phenotypes in GWAS studies, 45% are intronic, 43% are intergenic, and only 11% are exonic (Hindorff et al., 2009). Moreover, when specific polymorphisms in specific candidate genes are investigated (i.e., those that have been featured in numerous candidate gene studies, such as the serotonin transporter gene promoter polymorphism) in GWAS designs, they reportedly do not demonstrate performance above the level of chance (Bosker et al., 2011; Lasky-Su et al., 2008; Need et al., 2009; Sullivan et al., 2008). To summarize, GWASes do not appear to be converging on the expected candidate genes, and the SNPs that GWASes are illuminating are mostly not exonic. This state of affairs has been referred to as a failure of both candidate gene studies (Little et al., 2009) and GWASes (McClellan & King, 2010), as their respective findings do not converge.

Yet several considerations are important to mention here. Many fashionable polymorphisms that are used in GxE candidate gene studies are not present (and cannot be present due to their biological makeup) in GWASes; thus, they need to be imputed. For example, the polymorphism in the promoter region of the serotonin transporter gene may be imputed in Caucasian samples with high (~93–95%) accuracy using multiple SNPs present in some GWAS arrays (Knodt, 2012; Lu et al., 2012). Conducting such imputations for groups other than Caucasians is much more difficult. Importantly, GWASes are designed primarily to investigate main effects of G (or its specific variants). However, the polymorphism in the promoter region of the serotonin transporter gene has not been registered to exert substantial main effects on various aspects of psychopathology and is known primarily through publications on GxE. As GWASes routinely do not test for interactions, perhaps it is not surprising that this polymorphism (or its imputed proxy) is not associated with phenotypic variation in these studies. Finally, often phenotypes used in GWASes and phenotypes used in GxE studies are quite different, even if they might be stated to tap into the same disease/disorder (e.g., depression). GWASes' phenotypes tend to be substantially less detailed and elaborate than the phenotypes showcased in GxE studies. Correspondingly, criticisms that GWASes have not implicated specific candidate genes that have been featured in GxE studies have to be examined carefully with specific caveats (e.g., what polymorphisms and what phenotypes) in mind.

The third concern is self-evident: the nonconvergence of findings from different methodologies is not encouraging and seems to indicate lack of insight into the genetic mechanisms underlying complex human diseases/disorders, at least at the level of formulating specific and verifiable hypotheses pertaining to candidate genetic polymorphisms and candidate genes (Hebebrand et al., 2010). It has been stated (Colhoun, McKeigue, & Davey Smith, 2003) that the overwhelming majority (up to 95%!) of main effect findings obtained in genetic association studies appear to be false positives. This estimate, under the assumption of statistical power between 10% and 90%, in turn, is translated to a prior probability of a true association being 0.3–3.0%. Furthermore, this estimate might well be inflated, as testing main effects demands less statistical power than testing GxE interaction effects, meaning the prior for the latter might be even lower than 0.3–3.0%. In light of these considerations, Duncan and Keller (2011) concluded that under the relatively expectant assumptions of a prior of 5% and power of 55% (which seem rather unrealistic, as small sample sizes are the norm rather than the exception among GxE studies), approximately 63% of positive findings are likely to represent Type I error. These researchers argued that if these assumptions are altered to be more realistic—i.e., a prior of 1% and statistical power of 10%—the false discovery rate is likely to be at 98%. This problem of dealing with false positive findings is quite familiar to epidemiologists, who for a long time and with little satisfaction have been engaged in detecting subtle effects, whether for environments (Taubes, 1995) or genes (Crow, 2011).

Commenting on this situation, Clayton and McKeigue (2001, pp. 1357–1358) noted the following:

> If we could specify in advance that the effect of the environmental factor on disease risk would be restricted to a subgroup of individuals with a particular genotype, there would, of course, be a gain in power from testing only this subgroup for the effect of the environmental factor. In practice, such an extreme situation is unlikely to be frequently encountered in the study of complex diseases, and entails a level of knowledge of underlying biology that would probably render epidemiological studies redundant. In less extreme situations, and where previous knowledge is more limited, a combined test would need to be done for the main effect of environmental exposure and its interaction with genotype. Since such tests have multiple degrees of freedom, the gain in power is much reduced; indeed, power might even be lost.

Fourth, there is both conceptual and statistical uncertainty as to whether the terms, as defined, are really G, E, or GxE, particularly given the findings from earlier quantitative genetic studies (Burton, Tobin, & Hopper,

2005). For example, it has been shown that if the environment, E, is separated into shared (common, C) and nonshared (unique, E) components, then the term GxC will inflate the estimate of G, whereas the term GxE will inflate the estimate of E (Molenaar, Boomsma, & Dolan, 1997). These uncertainties were brought to the forefront in GxE discussions: "Importantly, however, we must acknowledge an almost complete ignorance of the relevant gene–environment interactions—as data accumulate, causes that now seem to be environmental could turn out to be gene–environment interactions" (Hemminki et al., 2006, p. 961). Such interactions could erroneously inflate heritability estimates (Hemminki et al., 2006).

A final concern is that both the genotypic frequency (i.e., the observed frequency of particular genotypes, including those associated with risk) and frequency of exposure (i.e., the observed frequency of encountering the risk environmental factor) are crucial for discovery as well as replication (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010), as the same GxE phenomenon might (1) not manifest when the prevalence of exposure is very low; (2) manifest via statistical interaction when the prevalence is moderate; and (3) manifest via main effect when the prevalence is very high. To maximize statistical power, it is recommended that the distribution of genotypes and exposure within a given sample follow a so-called balanced design, when rates of both derived (i.e., minor) allele frequencies and exposure are at ~50%. However, such a balance is often unrealistic, especially when utilizing a case–control design or considering more than one polymorphism. Moreover, the number and nature of subgroups resulting from the joint distribution of genotypes and environment is often unknown. Facing such a situation, researchers may be tempted (Flint & Munafò, 2008) to search for the best outcome, exhausting all analytic possibilities in a drive to register nominal statistical significance, in response to publication bias toward positive results (Ioannidis & Trikalinos, 2007). As the number of subgroups and sub-subgroups is large, so is the number of comparisons (Ioannidis, 2006; Patsopoulos, Tatsioni, & Ioannidis, 2007). Such comparisons have been used, for example, in situations when the original effect of GxE failed to be replicated in the whole sample, but was registered to operate in particular subgroups (Eley et al., 2004). Yet, extensive subgrouping is highly susceptible to false positive findings (Brookes et al., 2001).

For the brave who are willing and able to take on GxE studies in spite of the above caveats, specific recommendations have been offered (Moffitt, 2005). These recommendations include seven distinct steps.

The first step assumes a survey of the existing quantitative-genetic literature. It is always helpful if there are studies in which the specific GxE interaction in question has been evaluated already and deemed to be substantive and important, particularly if there is an explicit biological mechanism that has been coupled with this statistically significant interaction. If the relevant publications have not explicitly tested for GxE, particular attention should be given to the estimates of G (in particular, the additive genetic component, A) and E (in particular, the nonshared component of E). As discussed earlier (Molenaar et al., 1997), if GxE is not explicitly modeled, GxC can look like G (A) and GxE can look like E (E). Therefore, moderate-to-large estimates of A and E can signify the presence of potentially large GxE interaction effects (Purcell, 2002).

The second step is to identify a candidate environmental factor, the exposure to which is known to have a (preferably strong) main effect on the phenotype (trait, behavior, disease, or disorder) in question. To illustrate such a factor, Moffitt (2005) referenced early maltreatment for antisocial behavior, arguing that the former is particularly relevant through its association with biological correlates of the latter (DeBellis, 2001), although the behavior itself has been associated with multiple environmental risks (Loeber & Farrington, 1998). As a substep, Moffitt urged researchers to ensure the environmental mediation of the selected risk factor (for an illustation, see Fujisawa, Yamagata, Ozaki, & Ando, 2012). Otherwise, the selection of the environmental risk factor may be misguided, as it might capture the interaction between different genotypes rather than between genotype and environment (which could, in fact, be an issue with the maltreatment—antisocial behavior connection, Schulz-Heik et al., 2007).

The third step provides recommendations for the selection of specific measurements to be used to capture the exposure. Indeed, minimizing measurement error is associated with enhanced power (Luan, Wong, Day, & Wareham, 2001; Wong, Day, Luan, & Wareham, 2004). However, Moffitt's reference to the possibility of related reduction of sample size in situations when near flawless assessments of exposure are used is misguided.

At the fourth step, attention is switched from environments to genes. The main recommendation here is to stay in touch with the literature, as the knowledge of various gene–behavior associations advances rapidly, through the addition of new candidates and the elimination of old candidates (via nonreplication) from the list (Insel & Collins, 2003). Other recommendations are aligned with those that are present in many writings on GxE, and are discussed in

this chapter. Specifically, the genotypes of interest should be relatively prevalent in the general population. Both high and low prevalence of genotypes of interest, although they may be reflective of particular evolutionary dynamics (Hill, 1999; Searle & Blackwell, 1999), can generate various statistical biases (Lachance & Tishkoff, 2013; Vinkhuyzen, Wray, Yang, Goddard, & Visscher, 2013). Similar to the expectations for exposure, it is desirable that the candidate genetic factor be previously implicated as exerting a main effect on the phenotype of interest, although this expectation may not be realistic, given the general landscape of nonreplicability of such main effects. Finally, it is always recommended to look for a candidate that permits the formulation of a biologically plausible hypothesis as a counterpart to the statistical hypotheses. In illustrating these points, Moffitt references the polymorphism in the promoter region of the serotonin transporter (see Illustrations), arguing that the plausibility of the selection of this candidate polymorphism was substantiated by evidence from studies in psychopathology (Caspi et al., 2003), animal models (Bennett et al., 2002; Murphy et al., 2001), and human brain imaging research (Hariri et al., 2002). She also references both experimental research (e.g., Sayette, Griffin, & Sayers, 2010) and large-scale efforts documenting the range of responses of different genotypes to various environmental risks (Kaiser, 2003) as particularly important sources of nomination of candidates for GxE studies.

The fifth step is the statistical test itself. Although a reference is made, in passing, to a variety of designs used in the field (Moffitt, Caspi, & Rutter, 2005; Ottman, 1990; van Os & Sham, 2003; Yang & Khoury, 1997), the representative population-based cohort is endorsed as the most informative. It is argued that this type of design allows not only an appraisal of the presence or absence of the interaction (by the statistical test of GxE), but also an evaluation of the magnitude of this interaction. Of note is that such population-based cohorts require large sample sizes in order to capture a full distribution of E and provide enough power for various statistical tests.

The sixth step is to ensure the specificity and robustness of the registered effect by exploring the model via substitution of different candidates, both genetic and environmental. It is argued that, although it is vital to be hypothesis-driven in setting up the evaluation of GxE, having registered it, it is important to evaluate the original hypothesis among other plausible hypotheses (Licinio, 2003).

The seventh and final step calls for replication, although it is not specified whether this request pertains to replication within the same research effort (i.e., with a different sample by the same investigator), by different investigators on the same data, or some other form of replication. This recommendation acknowledges the tentative nature of an isolated GxE discovery but argues that its presentation (whether the interaction is ultimately true or not) should trigger both attempts at replication and collateral research.

So far, we have presented the literature on GxE focusing on the emergence and history of the concept and its operationalization. In the next part of this chapter, we will summarize the literature through the lens of the current state of affairs in the field of GxE.

THE ANALYSES

Almost 15 years of intensive research into GxE have generated many published reports, which, in turn, have provided the foundation for meta-analyses, systematic reviews, targeted literature reviews, and opinion pieces (e.g., Calati, Gressier, Balestri, & Serretti, 2013; Decoster, van Os, Myin-Germeys, De Hert, & van Winkel, 2012; Duncan & Keller, 2011; Eaves, 2006; Flint & Munafò, 2008; Gressier et al., 2013; Karg, Burmeister, Shedden, & Sen, 2011; Keller, 2014; Modinos et al., 2013; Munafò, Durrant, Lewis, & Flint, 2009; Munafò & Flint, 2009; Risch et al., 2009; Uher & McGuffin, 2008). In general, the field is in a curious state. On one hand, the number of empirical reports on GxE, whether positive or negative, has been growing both overall and annually, as exemplified by studies of the specific polymorphism in the promoter region of the serotonin transporter gene. Figure 8.1 captures the studies discussed in the following illustrations and listed in the Appendix; the x axis shows the number of publications, and the y axis shows the year of publication. In other words, this research is still widely funded, which motivates researchers to engage with it and

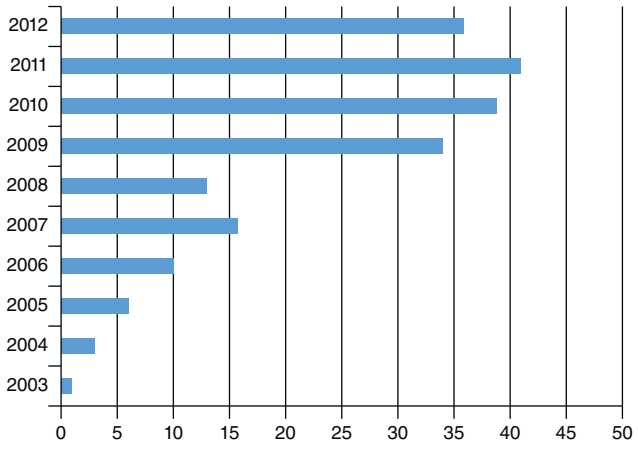


Figure 8.1 Number of publications GxE, by publication year. See footnote 1.

publish extensively on it. On the other hand, meta-analyses and literature reviews on GxE have generated results and comments that are unabashedly skeptical. It seems that the larger the literature grows, the more incredulity it generates; yet, it still keeps growing! This incredulity stems from concerns pertaining both to the content (definitional) and the formal (analytical) aspects of this literature. As the former has been discussed already, this section of the chapter will focus on the latter.

As for analytical concerns, observations have been made with regard to the following. First, en masse, the literature on GxE is characterized by a low replication rate (Kaufman, Gelernter, Kaffman, Caspi, & Moffitt, 2010; Munafò, Durrant, Lewis, & Flint, 2010). Second, although low even in the published literature, the replication rate is, probably, even lower among all attempts to replicate due to publication bias toward positive findings but not null findings. That is, it is impossible to know how many attempts at replication have failed and therefore have not been published (i.e., the file drawer problem), and the specific magnitude of this capitalization is difficult to appraise (Munafò & Flint, 2009). In fact, it has been argued that the false discovery rate in the GxE literature is substantially higher than the Type I error rate of .05 (Duncan & Keller, 2011; Flint & Munafò, 2008) commonly utilized in inferential statistics. Third, as a whole, studies conducted on small samples are common in this literature, thereby adding additional complications associated with insufficient statistical power to detect effects, especially statistical interactions. This can, somewhat counterintuitively, serve to inflate the rate of false-positive results reported in the literature, as null findings are less likely to be published in small-sample underpowered studies relative to the likelihood that positive findings are reported in such samples, whereas the likelihood of reporting both null and positive findings is more equal in sufficiently powered, large sample studies (Burmeister et al., 2008).

In essence, there is an expectation that the fate of GxE findings will be similar to that of GWAS findings (Murcray, Lewinger, & Gauderman, 2009) when the GWAS field leapt from small- to large-sample studies and was not able to replicate the majority of its previously celebrated findings (Bosker et al., 2011; Collins, Kim, Sklar, O'Donovan, & Sullivan, 2012; Need et al., 2009; Sanders et al., 2008; Sullivan et al., 2008). Although such a situation is anticipated, we certainly hope that it will not transpire. Yet if it does, it is important to understand why it has transpired and, moreover, be as accurate and comprehensive as possible in appraising the findings that are in the literature on GxE. In the next part of the chapter, we consider a number of characteristics of GxE studies that may explain why successful replications have proven difficult to realize.

Measurement Error

As discussed already, GxE studies are highly susceptible to measurement error in the assessment of genetic (Wong et al., 2004) and environmental exposure (Caspi et al., 2010; Luan et al., 2001) indicators. The former is viewed as less threatening, as quality control for genetic data is typically set at a threshold of 1% or less, and error per se can be quantified exactly by genotyping the same individuals on the same markers twice. The latter is thought to be much more concerning, as the magnitude of measurement error in exposure can be large, especially if captured by retrospective self-reports. Moreover, if measurement error around the exposure variable is high, even relatively small genotyping errors can result in a discernible impact on interaction estimates. In turn, poor measurement leads to a substantial loss of information. For example, it has been demonstrated that the mode of measurement of exposure (e.g., stressful life events) can have an overpowering effect on indicators of both frequency of occurrence and predictive power of this exposure (Monroe & Reid, 2008), which can bias the results of the interaction regression. Thus, care must be exercised in determining how indicators of exposure are ascertained. There is a direct connection between reducing measurement error and improving the statistical power of a study, which suggests that minimizing measurement error may be a more cost effective alternative in conducting GxE analyses than increasing the sample size. In quantifying environment or exposure, it is suggested that precise objective measures be used, such as environmental sampling or observational measures and experimental techniques capturing biological indicators of stress, rather than subjective reports.

It has been argued that smaller GxE studies tend to use these higher precision prospective measures, whereas larger ones tend to use lower precision retrospective reports (Caspi et al., 2010; Lotrich & Lenze, 2009). While this may be true, sufficient sample size for a study depends on a number of indicators, measurement error being only one of them. Even with the use of these more precise measurement tools, small studies can still be underpowered, and therefore more susceptible to either inflated false positive rates or publication biases, than larger ones, and it is generally difficult to justify a certain sample size without the use of comprehensive statistical power calculations. It is important to note that the presence of measurement error does not signify only one type of bias. The problem

is that if either factor (G or E) has been measured with error, the relation between them will be altered and biased toward a multiplicative model (Clayton & McKeigue, 2001). Specifically, Clayton and McKeigue illustrated that if the presence of interaction is established through lack of fit to a multiplicative model, the test for interaction will be conservative if there is measurement error, such that if the null hypothesis is correct, the test will not yield significant results more often than expected by chance. If any other definition of interaction is used, the bias of the test (conservative or liberal) in the presence of measurement error is difficult to predict.

There are ways to correct for measurement error in environmental variables (Thomas, Stram, & Dwyer, 1993), but these corrections typically require clear ideas of what the errors are, how they arise, and what their time-based properties are. Of note, in large-scale studies, exposures might not even be measured at the individual level, but rather, may be assigned based on some other information indicating ecologic-level exposures (e.g., exposure to natural disaster as a mere fact of having a registered address in the area where the disaster occurred, even though a given person might or might have not been in the area at the moment of the disaster), or obtained from another prediction model. Such uncertainties can lead to the manifestation of unpredictable biases, which may be especially detrimental to the model's accuracy if these biases are differential with respect to the phenotype. As a result, spurious interactions can be introduced (Holmans et al., 2009).

It is worth noting that even though there are methods of correction for measurement errors in indicators of G and E that are well established in studies testing for main effects, they have rarely been used in studying GxE (Lobach, Carroll, Spinka, Gail, & Chatterjee, 2008; Wong, Day, Luan, & Wareham, 2004). Nevertheless, interactions are less likely to be biased than main effects, except when the measurement errors are differentially associated with both exposure and genotype and, as a result, the measurement error is not equal for G and E factors (Thomas, 2010a).

Confounders

Yet another relevant issue that has been comprehensively addressed in the recent literature (Keller, 2014) pertains to controlling for potential confounders. The general point that an interaction term of interest should be adjusted for the effects of confounding variables has been put to force in other behavioral sciences (Hull, Tedlie, & Lehn, 1992; Yzerbyt, Muller, & Judd, 2004), but has not penetrated the field of GxE research. In its typical form, the analytical facet of GxE studies includes three variables—the genetic polymorphism (typically dummy-coded), the environmental factor (typically either continuous or somehow categorized), and the interaction effect (typically captured by the product of the two main effect variables). These variables are then placed in a linear or logistic regression with a predicted variable of conceptual interest (e.g., delinquent behavior, academic achievement, mental health indicator). Keller (2014) and others (Hebebrand et al., 2010) rightfully noticed, however, that there are additional variables—race/ethnicity, gender, age, socioeconomic status, education, IQ, among many—known to be predictive of outcomes of interest, as main effects or members of other interaction terms, that are often treated by GxE researchers as noise to be controlled for. To that end, these potentially important variables are either residualized out prior to fitting the regression, or else they are included as covariates. Keller, however, argued that the proper account for the confounding effects of these additional variables can be achieved only if the full factorial model is tested, specifically, if all of the covariate × environment and covariate × gene interaction terms are tested for in the same model where the GxE interaction is featured. For example, to adjust the GxE term for gender and general cognitive ability, the regression should include the following terms in addition to the two main effects (of G and E), and their interaction (GxE): the main effects of the covariates—gender, general cognitive ability, and the interaction of the covariates with both G and E—gender × G, gender × E, general cognitive ability × G, and general cognitive ability × E.

Keller (2014) attributed his view on how best to adjust for confounding variables to Yzerbyt and colleagues (2004) but provided an application of this general solution to GxE models specifically. He also elaborated on the nature of related biases, and illustrated the profound gap between his expectations for adjustments to avoid confounding and the selected GxE literature he reviewed—in fact, not a single study that was featured as novel by Duncan and Keller (2011) met Keller's expectation. Although such a lack of proper statistical treatment, on its own, might not mean that the previously published GxE findings were not real, it does generate uncertainty about them (Keller, 2014). In all fairness, Keller (2014) acknowledged that the recommended treatment could be objected to, specifically, via references to model overfitting and multicollinearity. The pros and cons related to either approach are discussed in the broader epidemiological and other related literature (e.g., Chen et al., 2008; Kalil, Mattei, Florescu, Sun, & Kalil, 2010; Kim, Watkinson, & Anastassiou, 2011; Mizushima,

Tsuchida, & Yamori, 1999; Singh, Repsilber, Liebscher, Taher, & Fuellen, 2013), with no unequivocal outcome.

Scaling

There is a debate in the literature on how GxE interaction effects should be scaled. In psychology, the presence of interaction is typically detected via adding an interaction (product) term to a regression model and establishing the statistical significance of this term. In linear regression analyses, the product term's coefficient captures the degree of deviation from the additivity of main effects on the outcome (Kendler & Gardner, 2010). In logistic regression analyses, the product term's coefficient captures the degree of departure from multiplicativity in the risk of the outcome (Knol, van der Tweel, Grobbee, Numans, & Geerlings, 2007). Although it has been argued (Darroch, 1997) that the additive model of interaction is preferable, in fact, the literature is replete with examples of both types of regression analyses.

Because the field of GxE interaction, particularly as delineated in this chapter, is defined first and foremost by the statistical conceptualization of the interaction, making inferences regarding the mechanistic or biological relationships between the predictors and outcomes requires adherence to a set of conditions and assumptions (VanderWeele, Hernández-Díaz, & Hernán, 2010). One of the issues relates to the scaling of the interaction effects (Kendler & Gardner, 2010). Thus, simple scale transformations, e.g., logarithmic transformations that are commonly used for normalization purposes, can yield a statistically significant although spurious interaction, whereas *bona fide* interactions can disappear (Eaves, 2006; Kendler & Gardner, 2010; Thompson, 1991). The issue of scaling in the GxE field has been (Rothman et al., 1980) and remains (Eaves, 2006; Rothman & Greenland, 2005) disputed without an adequate resolution.

To gain a more concrete appreciation for how the concept of scaling removes interactions in a GxE study, we performed two simple simulation studies.

Simulation 1

We started by generating genotypes and environmental exposures for 500 participants. Genotypes, using the variable name geno, were sampled randomly from the set {0,1}, with 75% probability of a 1 and 25% probability of a 0. This represented a very simple case of a single gene under a dominant heritability model, in which the gene is captured by two alleles, B and b, with B being dominant over b. The genotypes BB and Bb were assigned the value 1, and the genotype bb was assigned the value 0.

TABLE 8.1 Contingency table of genotype (geno) and environmental exposure (env) in simulated dataset.

	env	
geno	0	1
0	69	60
1	172	199

We then generated an environment, with the variable name env, as a simple yes-no exposure to an environmental factor, with a 0 (no exposure) 50% of the time, and a 1 (exposure) 50% of the time.

We assumed environmental exposure to be independent of genotype as both variables were generated independently. Table 8.1 is the contingency table showing the randomly generated data.

This indicates that of the sample of 500 participants, there were 371 participants with either BB or Bb genotypes and 129 participants with the bb genotype; there were 241 unexposed and 259 exposed individuals. Of the BB and Bb participants, 172 were unexposed and 199 were exposed to the environmental factor; of the bb carriers, 69 were unexposed and 172 were exposed to the factor.

Next, we created a continuous (noncategorical) phenotype from the genotype and environmental exposure of each participant. We defined the genotype effect, g, and the environment effect, e, as the contribution of each feature to the phenotype, and assigned them values of 2 and 1, respectively. We then defined phenotype as an additive function of genotype and environment with the expected value of phenotype for each subject, given the genotype and environment, is g*geno + e*env. Table 8.2, the contingency table of means was thus.

Here we created an additive model. To do so, we added the same fixed value (in this case 2) to every column, going from the first row to the second row; and, we added the same fixed value (1) to each row, going from the first column to the second column.

The actual phenotype of each participant was the expected mean for that participant, plus some randomly generated (Gaussian) noise. As we started with a standard deviation for a noise level of 0.05, the following

TABLE 8.2 Table of expected means of the phenotype for each genotype/environment combination.

	env	
geno	0	1
0	0	1
1	2	3

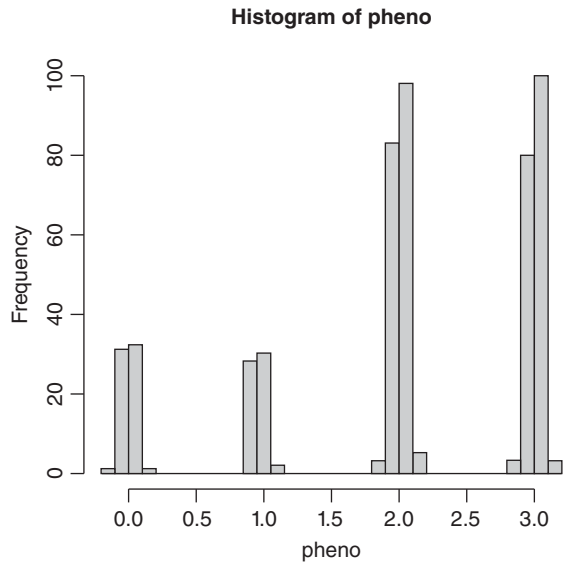


Figure 8.2 Histogram of simulated phenotypes using a standard deviation of 0.05.

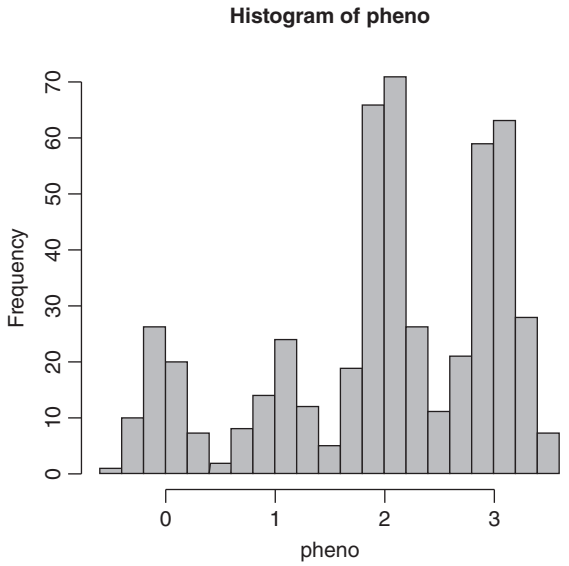


Figure 8.4 Histogram of phenotypes using a standard deviation of 0.2.

distribution of phenotype values was produced, as indicated in Figure 8.2.

In this case, with a small level of noise in relation to the magnitudes of the G and E effects (indicated here by g and e, respectively), the values of genotype and phenotype were quite obvious for each participant. In the second step of our simulation, we increased the standard deviation of the noise to 1 so that the statistical problem was not so trivial. This increase in noise changed the distribution of phenotypes, as indicated in Figure 8.3.

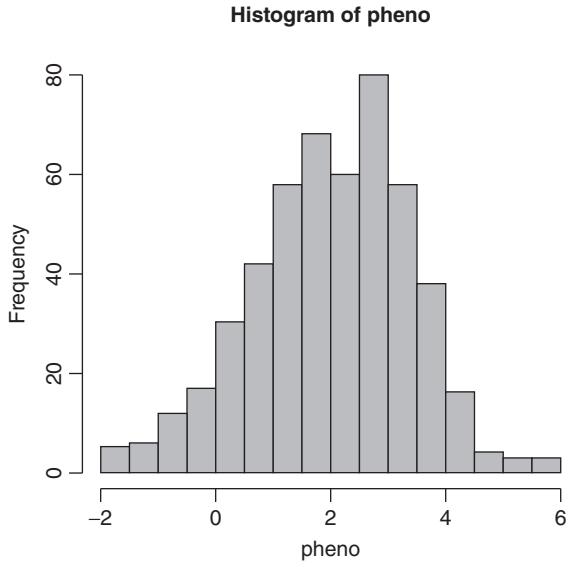


Figure 8.3 Histogram of simulated phenotypes using a standard deviation of 1.

This increase in noise relative to the effect sizes (G and E) caused the distribution of phenotype values to resemble a continuous spectrum. In contrast to the previous example, the genotype and phenotype values were no longer clear.

As a third simulation (Figure 8.4), we established a noise level somewhere in the middle, e.g., 0.2. In this scenario, the distribution of phenotypes was different enough to estimate the specific genotype and environment effects, as shown below. However, the issues related to noise were not trivial, even in this circumstance.

Consider the average value of the phenotype for each genotype–environment value (Table 8.3).

These data are consistent with the parameters used to construct the model. This model is an additive model with no interactions between gene and environment, because it was constructed that way.

However, in practice, one never knows what the true underlying model is: one might have a good idea of what it should be, based on prior evidence, but all a researcher really has is the phenotype, genotype, and environment values and a guess for the model. We then guessed that we had an additive model with a GxE interaction, and used

TABLE 8.3 Table of observed means of the phenotype for each genotype/environment combination in simulated data.

	env	
geno	0	1
0	−0.0197	1.0338
1	2.0133	3.0059

TABLE 8.4 Table of observed means of the phenotype for each genotype/environment combination in simulated data, after scaling the phenotypes by an exponential transformation.

	env	
geno	0	1
0	1.04	11.82
1	113.97	1140.07

regression to estimate the effects (Table 8.4); that is, we regressed pheno on geno, env, and geno X env. R, gives the following output:

```
Call : lm(pheno ~ geno + env + geno:env)
Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) -0.01970    0.02487  -0.792    0.429
geno         2.03303    0.02883  70.519   <2e-16 ***
env          1.05346    0.03589  29.349   <2e-16 ***
geno:env    -0.06086    0.04144  -1.469    0.143
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05
                                    '.' 0.1 ' ' 1
Call : lm(pheno ~ geno + env + geno:env)
Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) -0.01970    0.02487  -0.792    0.429
geno         2.03303    0.02883  70.519   <2e-16 ***
env          1.05346    0.03589  29.349   <2e-16 ***
geno:env    -0.06086    0.04144  -1.469    0.143
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05
                                    '.' 0.1 ' ' 1
Call : lm(pheno ~ geno + env + geno:env)
Coefficients:
            Estimate Std. Error t value Pr(>|t|)
```

There are two things to notice here. First, our estimates for geno and env (in other words, g and e) were highly significant, and very close to the true values of 2 and 1, respectively. Second, the GxE variable was not significant—there was no statistical evidence for a GxE interaction. This was no surprise to us, but it might have been if this were real data instead of simulated data.

Next, to show what would happen if we scaled the data in a different way, we took the pheno values calculated above and replaced them with 10^{pheno} (that is, the inverse of taking the logarithm, base 10) (Table 8.4). We called this new phenotype variable pheno2.

In Figure 8.5 are the histogram of pheno2 and a table of means for each GxE combination.

We transformed our additive model into a multiplicative model: the second column became 10 times the first column, and the second row 100 times the first row. (These

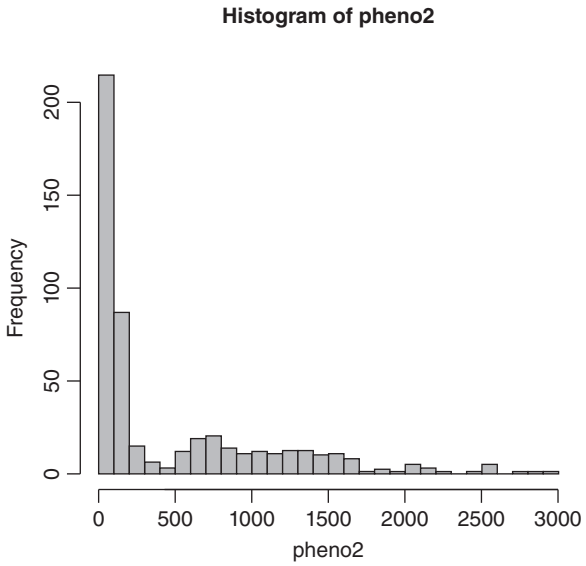


Figure 8.5 Histogram of phenotypes using a standard deviation of 0.2, after scaling the phenotypes by an exponential transformation.

multiplicative factors are not an accident—they are equal to 10^1 and 10^2, where 1 and 2 were our values of e and g.)

We then ran the same regression model—an additive equation with interaction—on these rescaled data:

```
Call: lm(pheno2 ~ geno + env + geno:env)
Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)    1.043     42.229   0.025   0.9803
geno         112.925     48.955   2.307   0.0215 *
env           10.779     60.952   0.177   0.8597
geno:env    1015.325     70.368  14.429   <2e-16 ***
Call: lm(pheno2 ~ geno + env + geno:env)
Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)    1.043     42.229   0.025   0.9803
geno         112.925     48.955   2.307   0.0215 *
env           10.779     60.952   0.177   0.8597
geno:env    1015.325     70.368  14.429   <2e-16 ***
Call: lm(pheno2 ~ geno + env + geno:env)
Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)    1.043     42.229   0.025   0.9803
geno         112.925     48.955   2.307   0.0215 *
env           10.779     60.952   0.177   0.8597
geno:env    1015.325     70.368  14.429   <2e-16 ***
```

This analysis showed an extremely highly significant interaction effect. Also, among the main effects, only genotype was significant, and to a much lesser extent than in the previous model.

What can we learn from this? Suppose the data came from a biological process that was truly multiplicative; that is, that the multiplicative model was a true reflection

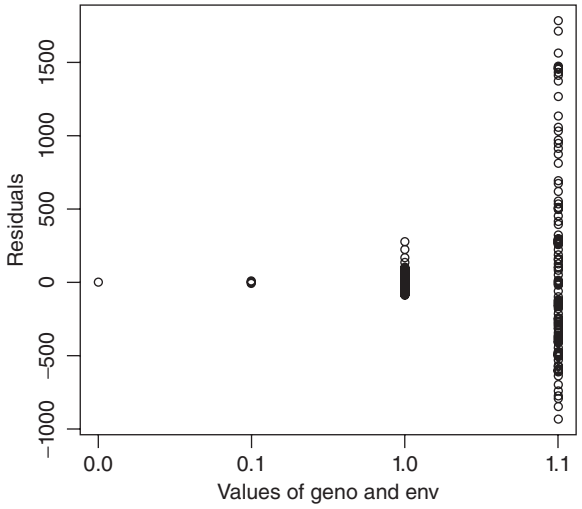


Figure 8.6 Model residuals using exponentially-transformed phenotypes, as a function of genotype and environmental exposure. Note the large difference in variance of the residuals among different combinations of genotype and environmental exposure.

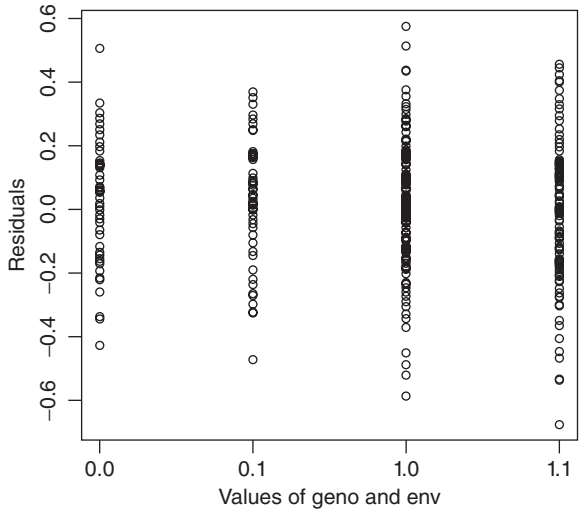


Figure 8.7 Model residuals using unscaled phenotypes, as a function of genotype and environmental exposure. Variance of residuals is approximately the same across all genotype/environment pairs.

of reality and the interaction term above always appeared using this type of additive model. We could then propose taking the logarithm of the phenotype variable—and if we do that, then we would get the first regression model with no significant interaction term (note that if we took the log with respect to a base other than 10, the estimated coefficients would change but the nonsignificance of the interaction term would not). In other words, if we have a significant interaction term in one model, it can be wiped out in another model by transforming one of the variables.

Another lesson to be learned is that the two regression models here were not equally valid. One of the assumptions of a regression model is that the variance of the error term should not depend on the explanatory variables. For our second model, when the additive model applied to pheno2, this was not the case: Figure 8.6 of the residuals against the combinations of genes and environments shows that that the residuals exhibited a huge variance for the 1–1 case, but a variance near zero for the 0–0 case.

This type of structural dependence of residuals on variables used in the model is a hint that the model is inappropriate for the data, and that transformations of the data *should* have been applied. For comparison, we looked at this plot of residuals for our first model (Figure 8.7), when pheno was on its original scale (or equivalently, after taking logs of pheno2).

This is preferred—the residuals now appear to be independent of both genotype and environment.

Simulation 2

In Figure 8.8 we give an account of an interesting example from L. Eaves (2006) of a scenario in which a standard analysis of affectedness by logistic regression is likely to show a significant GxE interaction, whereas a good case can be made that there is no such interaction in the disease etiology. The disease model assumes additive effects of a candidate gene and measured environment on a latent liability to the disease, and a person is affected if that person's liability is greater than a threshold that is constant over the population.

Before describing our second simulation, we consider the example illustrated by Figure 8.8. For simplicity we consider two possible genotypes G = 1 and G = 2; this could be a SNP locus with a dominant allele, for example. There are four possible values for the environmental variable E = 1, 2, 3, or 4. For each genotype G = 1 and G = 2, there is a baseline distribution of liability when E = 1, and each additional unit of E adds a constant increment to the liability—it is important to emphasize that these increments take a constant value (0.35 in this example) not depending on the value of G. In this sense, there is no interaction between G and E in the etiology of the disease. The two baseline liability distributions (one for G = 1 and one for G = 2) are shown as the two probability density functions in the first row (corresponding to E = 1) of the figure above. Both of these baseline liability distributions happen to be bimodal mixtures of two normal distributions. This may look a bit exotic but helps make

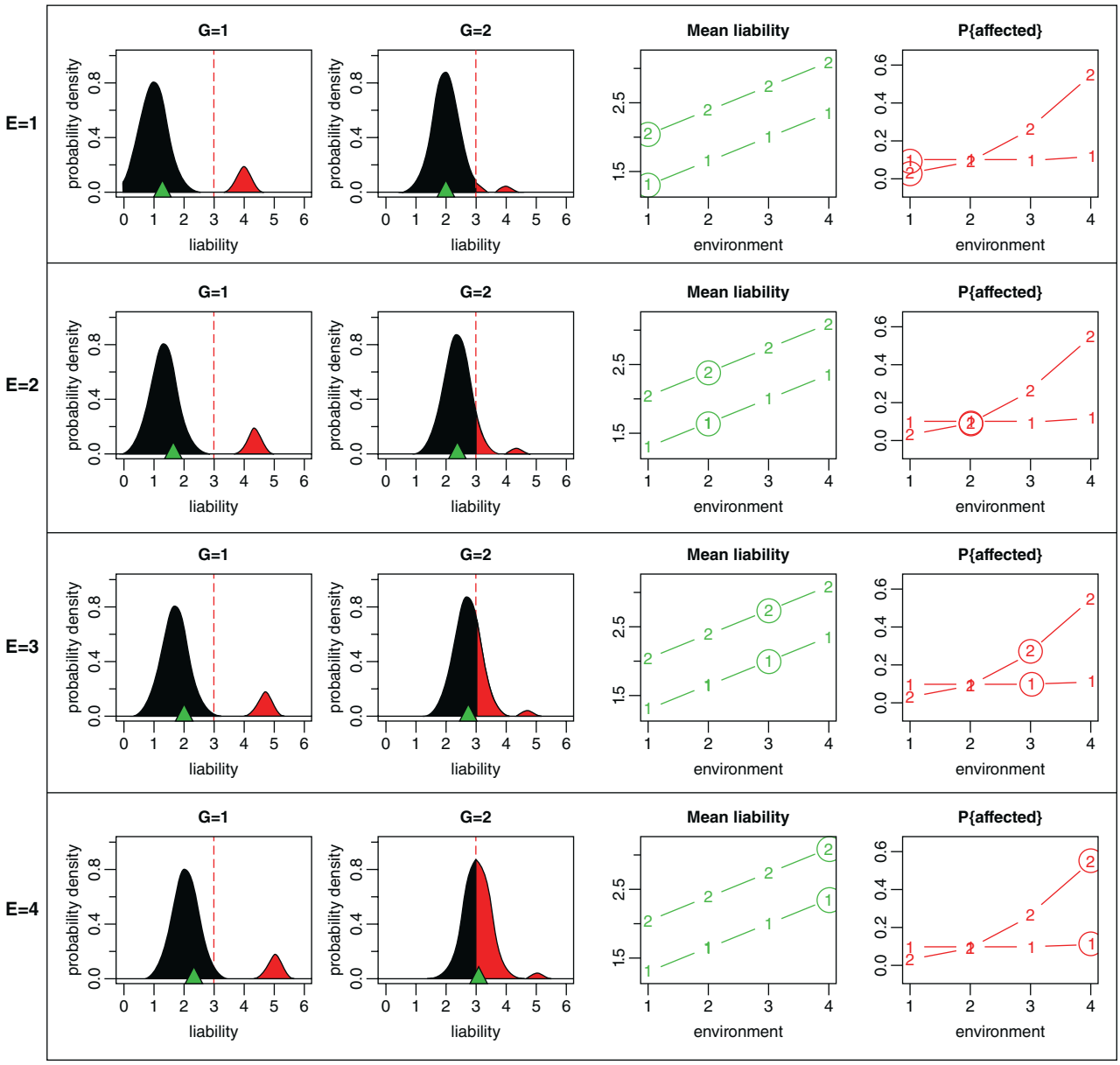


Figure 8.8 Illustrating an example of Eaves (2006) having GxE interaction in a model of affectedness but no GxE interaction in the corresponding model of liability. See footnote 1.

the phenomenon easy to generate and visualize, and, as we intend to show elsewhere, similar phenomena can also be manifested with simpler normal distributions.

Scanning down the first column of Figure 8.8 we see that when G = 1, the effect of each unit of E is to shift the liability distribution to the right by a constant amount, here 0.35. Similarly, scanning down the second column, when G = 2, the effect of each unit of E is precisely the same, adding 0.35 to the liability. The green triangles in the first two columns show the mean liabilities in the various (G,E) combinations. Notice how moving from one plot to the next in a column simply shifts the liability distributions and their means to the right by 0.35. These mean liabilities are illustrated in the green plots in the third column of Figure 8.8. In both the third and fourth columns of the figure above, the 1's and 2's in the plot indicate which genotype is being plotted, and the points corresponding to the value of E in a row are circled. So in the third column, the circled green values mark the two mean liabilities for G = 1 and G = 2 for the value of E shown in that row. Since the effect of environment on liability is the same for all genotypes, there is clearly no interaction between

genotype and environment in determining liability. This is reflected in the third column of figure above, which shows the classic configuration of parallel lines, signifying no interaction.

However the situation is very different if we look at the probability of being affected. We assume each person is affected if his or her liability is greater than 3.0. In the liability densities shown in the first two columns of Figure 8.8, the threshold at 3 is shown as a red dotted line, and the red areas under the liability density curves to the right of the threshold represent the probability of being affected in each (G, E) combination. These probabilities are plotted in the fourth column of Figure 8.8. For example, when E = 1, looking at the two liability density plots in the first row, we see the red area is larger when G = 1 than when G = 2; in the P{affected} plot in the E = 1 row, this corresponds to the circled red 1 being above the circled red 2. In contrast, when E = 4 in the bottom row, we see that the red area for G = 2 is much larger than that for G = 1; this corresponds to the circled 2 in the P{affected} plot in the fourth row being well above the circled 1. The nonparallel (indeed, crossing) nature of the curves showing the dependence of P{affected}on E for the two values of G suggests an interaction.

To investigate the kind of behavior we can expect when standard data analysis methods are applied to a scenario like this, we simulated 1000 data sets, each of which consisted of 1000 people having genotypes, environments, liabilities, and affectedness generated according to specifications following Eaves (1996). Analyzing the liabilities by ordinary least squares regression showed no evidence of GxE interaction: the P values for the interaction term were uniformly distributed between 0 and 1, with 46 of the 1000 P values (4.6%) falling below 5%, as expected when there is no interaction. On the other hand, using logistic regression to analyze the affectedness typically showed a very highly significant GxE interaction; in fact, the median P value for the interaction was only 0.0000032, and fully 99.6% of the P values for GxE fell below 0.05. Taking a look at how these two analyses came out for a very typical data set came out as follows, with the ordinary regression for liability gave output

```
Call: lm(formula = liab ~ g + e + g:e)

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  0.27959    0.13410   2.085   0.0373 *
g            0.59320    0.07854   7.553 9.62e-14 ***
e            0.41732    0.07696   5.423 7.37e-08 ***
g:e         -0.01054    0.04402  -0.239   0.8108
```

whereas the logistic regression for affectedness gave output that included an impressively significant interaction

```
Call: glm(formula = dx ~ g + e + g:e, family
                  = binomial)

Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)  -1.1273     0.6101  -1.848 0.064651 .
g            -1.4386     0.3931  -3.659 0.000253 ***
e            -0.5886     0.2946  -1.997 0.045772 *
g:e           0.7752     0.1704   4.549 5.38e-06 ***
```

So was there an interaction in these examples, or not? As we have seen, a case could conceivably be made for both answers in both examples. However, if an explanation involving interaction relies on a particular scaling of the variables, and another reasonable scaling exists in which the interaction disappears and a simple additive model fits well, one might well prefer the simple additive model. In the first simulation, a very simple, ubiquitous transformation—taking logarithms—was sufficient to transform a multiplicative process that appeared to have a strong interaction to an additive process with no interaction. In the second example, a simple binary transformation generated an appearance of GxE, even though the main effects of G and E on an underlying quantitative trait (the liability) were purely additive. So the liability provided a simple additive description of the disease process with no GxE interaction, but as the liability is a latent variable it may require more ingenuity or sophisticated methods to uncover this simple description.

These simulations raise a more general concern pertaining to the definition of GxE interaction (Flint & Munafò, 2008). Indeed, given that statistical interactions are susceptible to scaling effects, the issue is how useful this term actually is, especially if the null hypothesis, however formulated, has no discernible biological meaning.

Types of Interactions

It is assumed that only 1–2% of cancer syndromes can be explained by inherited cancer syndromes of high penetrance (Ponder, 2001). In fact, the population-attributable fractions of known environmental factors are considered to be up to 90% for cancer syndromes (Doll & Peto, 1981; Higginson, 1968). Similarly, the population-attributable fractions of known environmental factors are considered to be up to 70% for coronary heart disease, stroke, and type 2 diabetes (Willett, 2002). However, recent understanding of the related causation reflects a number of complexities. Specifically, it appears that some environmental factors

(e.g., tobacco smoking and asbestos exposure for lung cancer) interact and increase risk multiplicatively, not additively (IARC, 1990, 2004). Moreover, there appears to be a tremendous amount of individual variation in how environmental exposures are converted into cellular mechanisms and the role of genetic factors (e.g., carcinogen metabolism, DNA repair, cell-cycle control and apoptosis) in this conversion (Vogelstein & Kinzler, 2002). Thus, what were previously considered straight environmental factors might, in fact, reflect the co-action of G and E, which leads to the etiological conclusion that most diseases/disorders are interactions of G and E or multiple Gs and multiple Es (Guttmacher, Collins, & Carmona, 2004). Multiple dimensions have been discussed in the literature that allows the classification of GxE interactions. Here we exemplify some of these dimensions.

First, Ottman (1990, 1996) discussed a number of biologically plausible types of relationships between G and E with regard to their differential effects on disease risk. In the first model, exemplified by PKU, the effect of G is to generate or magnify the role of a risk factor, which can also be generated by E. In the second model, G exacerbates the effect of the risk factor but has no effect if the person is not exposed to this factor (E). This model is exemplified by the relationship between an autosomal recessive disorder, Xeroderma Pigmentosum, and ultraviolet (UV) radiation with regard to skin cancer. Although, in the general population, excessive exposure to UV radiation increases risk for skin cancer, this exposure is substantially riskier (and, thus, results in an elevated odds ratio) for individuals with this disorder, as they are deficient in an enzyme required for the repair of DNA damage induced by UV radiation. Per the third model, E exacerbates the effect of G, but not in individuals with the low-risk genotype. For example, individuals with the autosomal dominant disorder, Porphyria Variegata, develop skin problems of different severity (i.e., excessive blistering, scarring, changes in pigmentation under exposure to sunlight). Although an exposure to barbiturates is inoffensive in the general population, such individuals respond to the same exposure with acute attacks that might result in paralysis or even death. In the fourth model, both G and E risk factors are required to increase risk. To illustrate, most individuals with an X-linked recessive disorder glucose-6-phosphate dehydrogenase (G6PD) deficiency are asymptomatic; yet the consumption of fava beans (an ingredient widely used by the general population) by these individuals might result in the development of severe hemolytic anemia. Finally, in the fifth model, both G and E risk factors have some unique impact on the disease/disorder risk so that their co-occurrence either elevates or decreases the risk compared to their occurrence in isolation. An illustration of this model comes from the development of chronic obstructive pulmonary disease (COPD) in the context of a-1-antitrypsin deficiency (i.e., an inherited disorder causing dysfunction of the lungs and liver) and smoking; in fact, risk of COPD is elevated both in nonsmokers with a-1-antitrypsin deficiency and in smokers without a-1-antitrypsin deficiency, but is particularly increased in smokers with a-1-antitrypsin deficiency.

Second, as in epidemiology (Gail & Simon, 1985), two types of interactions are differentiated in GxE research. Crossover (qualitative) interactions are stated to transpire when a particular level of a factor (either G or E) is superior for some subset (or subsets) of the sample, whereas a different level of a factor is superior for other subsets. Noncrossover (quantitative) interactions are said to manifest when there is variation in the magnitude, but not the direction of the effect. The theoretical and practical values of these interactions are different, with the former being associated with higher significance and the latter with lower significance. The interactions also differ with regard to associated methodological vulnerabilities, such as sample size and power as well as high rate of false-positive effects (Bogdan, Agrawal, Gaffrey, Tillman, & Luby, 2014).

Third, another important typology pertains to the differentiation of essential and removable interactions (Wu et al., 2009). This differentiation occurred in the accrual of data from GWAS. While working with SNP × SNP interactions of different orders, these two types of interactions were defined such that an interaction is essential when the direction (and, possibly, but not critically, the magnitude) of the effect for at least one of the SNPs is changed in the presence of the other SNP (or SNPs). The interaction is removable when only the magnitude (but not the direction) of the effect of at least one SNP is changed in the presence of the other SNP (SNPs). This differentiation and systematic screening of all possible interactions is a chance to detect more interesting and stronger effects (Chen, Liu, Zhang, & Zhang, 2007; Marchini, Donnelly, & Cardon, 2005). The corresponding number of interactions, however, even limiting the scope of consideration to two-way interactions, is staggering, with a count of a million and more.

The importance of such constellations of interactions is obvious as most candidate gene studies are embedded in conceptual models featuring a specific biochemical pathway (or often multiple pathways), including more than one

gene and more than one polymorphism. To illustrate, the Southern California Children's Health Study, investigating the impact of air pollution on children's health in general and the manifestation of asthma in particular, is based on a theory engaging such etiological factors as inflammation, oxidative stress, and anti-oxidant intake (Gilliland, McConnell, Peters, & Gong, 1999). Similar reasoning is applicable to environmental or to a mixture of environmental and genetic factors; although the original study of GxE in cannabis usage (Caspi et al., 2005) tested for a direct interaction, subsequent studies tested for three-way (Henquet et al., 2009; Henquet et al., 2006) and four-way (Peerbooms et al., 2012) interactions.

The translation of this theoretical model into specific hypotheses assumed the simultaneous investigation of multiple genes representing such pathways. Indeed, polymorphisms in these genes, genes themselves, and pathways can interact; these interactions should be properly modelled and analyzed. Furthermore, these genetic interactions can be layered with interactions with specific environmental factors. There are various methods that are suitable for multivariate analysis of high-dimensional data. These methods include standard multiple regression techniques, various machine learning, and pattern recognition methods (Cordell, 2009; Hoh, Wille, & Ott, 2001; McKinney, Reif, Ritchie, & Moore, 2006; Moore & Williams, 2009; Ritchie & Motsinger, 2005).

GxE Study Designs

To explore main and interaction effects of genes and environments, studies of GxE utilize conventional epidemiological designs such as cohort, case–control, or a hybrid of the two (e.g., case–cohort; Andrieu & Goldstein, 1998; Manolio et al., 2006; Yang & Khoury, 1997). Just as in epidemiological research, the selection among designs is driven by weighing their strengths and weaknesses vis-à-vis factors such as biases and confounding variables, temporal sequences of exposure and disease, data accessibility and quality, and capacity to investigate common and rare diseases, disorders, and risk factors (Thomas, 2010a).

In addition, the literature contains a specific line of discourse pertaining to the utilization of traditional epidemiological designs specifically for the purposes of GxE studies (e.g., Collins, 2004; Manolio et al., 2006). As of today, the most present design in the GxE literature is that of case–control. In this design, a sample of carefully chosen people with (cases) and without (controls) the disease/disorder should be ascertained for a specific primary outcome so that similarities and differences between the two groups can be investigated with regard to the distributions of genetic (e.g., frequencies of specific polymorphisms) and environmental (e.g., frequencies of specific exposures) factors (Gordis, 2000). In other words, these studies aim at investigating all individuals who are cases of disease/disorder, or are a representative sample of cases compared with a representative sample of all individuals who are free of disease/disorder. The literature acknowledges many advantages of case–control studies, specifically their relative ease of administration and low costs, their suitability for studies of rare diseases/disorders, and their capacity to sample multiple exposures retrospectively, maximizing the success of identifying true risk factors.

The majority of case–control studies are retrospective; thus, although they ascertain cases after the onset of the disease/disorder, they collect information about genetic and environmental risk factors that predates the onset of the disorder and, in so doing, make a priori assumptions about causality (Doll, 2002). It follows that they are exposed to multiple sources of bias. Indeed, as the corresponding literature has accumulated, the shortcomings of case–control studies have become a limiting factor in the utilization of this design. Among many such shortcomings, the most relevant to this discussion are the following:

1. The tendency for individuals with positive family history to participate at higher odds (Bhatti et al., 2005; Wang, Fridinger, Sheedy, & Khoury, 2001), which biases sample structure in a particular way
2. The tendency for clinically diagnosed cases to represent the most severe tail of the distribution (Guo, 1998), which biases the prevalence-incidence estimates (Neyman, 1955) and overlooks specific cases such as short-episode or fatal cases (Taube, 1968)
3. The difficulty for undiagnosed controls to constitute a bias-free group (Schlesselman, 1982; Wacholder, Silverman, McLaughlin, & Mandel, 1992) and the degree of comparability (by geographic and ethnical ancestry and by predominant environmental exposures) of cases and controls (Helgason, Yngvadottir, Hrafnkelsson, Gulcher, & Stefansson, 2005; Rosenberg, Li, Ward, & Pritchard, 2003)
4. The difficulty of accurately documenting exposure, as most of these studies rely on recalled rather than evidenced exposures to environmental (Feinstein, 1985) or genetic (Silberberg, Wlodarczyk, Fryer, Ray, & Hensley) risk factors.

In realizing the magnitude of these biases and the difficulties associated with the qualification and quantification of risk at the population level (Austin, Hill, Flanders, &

Greenberg, 1994; Hill, 1965) even when specific adjustments for these biases can be applied (e.g., Ben-Shlomo, Smith, Shipley, & Marmot, 1993), it has been argued that the estimates of risk at the population level is best obtained through prospective, population-based cohort studies (Gordis, 2000).

A number of arguments are put forth when the advantages of cohort studies are discussed (e.g., Manolio et al., 2006). First, in contrast to case–control studies, prospective cohort studies utilize representative samples of the population before disease/disorder onset. The underlying idea here is to follow a representative sample from before, throughout, and after specified time points (Manolio, 2003). These time points can be defined in a number of ways, e.g., as bracketing the age at onset of a particular disease/disorder (e.g., type 1 diabetes) or as developmental stages (e.g., infancy, childhood, adolescence, adulthood). The main aim of this design is to ascertain, in the population as a whole rather than among already affected individuals, risk factors for the manifestation of the disease/disorder or biomarkers for the disease/disorder's development. Thus, reduction of many related types of bias is the chief consideration for choosing prospective cohort design over case–control design. Second, cohort studies are particularly important for understanding the etiology and course of diseases/disorders with regard to investigating risk factors that are subject to recall biases (Langholz, Rothman, Wacholder, & Thomas, 1999). Third, prospective cohort design allows a comprehensive and standardized collection of various indicators of premorbid exposure in accord with the main objectives of the study. The problem of recall bias is not relevant, as exposure information is collected prior to the onset of the disease/disorder (Colman & Jones, 2004). Fourth, all members of the cohort are recruited and followed in a systematic way, so that the resulting sample is truly representative and all types of cases of disease/disorder are marked by equal probability of detection. Thereby, the case identification bias that is so problematic in case–control studies is minimized (Manolio et al., 2006). Fifth, unlike the case with case–control studies, multiple diseases/disorders can be studied simultaneously and the time window for disease/disorder onset can be established more precisely (Manolio et al., 2006).

Prospective cohort studies impose a number of requirements (Manolio et al., 2006). First, it is assumed that individuals ascertained into the cohort are characterized by similar genetic (e.g., ancestry) and environmental (e.g., dietary preferences) factors that are distinct from those who are not included in the cohort. Second, it is assumed that participants who are excluded due to attrition are similar to the remaining participants with regard to disease/disorder risks, both genetic as well as environmental. Third, inclusion/exclusion criteria, recruitment, and definition of outcomes should be unified for all members of the cohort. In other words, to avoid biases and ensure the similarity of data collection between cohort members who are and are not exposed to risk factors, whether genetic or environmental, it is assumed that the probability of disease/disorder diagnosis is independent of the exposure to the environmental risk factors, as well as of potentially confounding factors such as age, access to care, and other critical exposures. It is particularly important to document and track changes in exposure history; thus, exposure information should be collected repeatedly (Zeger, Liang, & Albert, 1998). Fourth, it is assumed that all members of the cohort are systematically evaluated for the occurrence of diseases/disorders. The critical feature of prospective cohort studies is that all cohort members have equal probability for the detection and diagnoses of diseases/disorders, regardless of their access to medical care. Therefore, cohort studies cannot rely on the identification of outcomes in the course of everyday clinical care and must embed regular evaluations of the cohort participants into the study procedures. Such evaluations, given their time-consuming and resource-heavy implementation, are the target of criticism of cohort studies. Fifth, and most importantly, it is assumed that prospective cohort studies adequately capture both incidence and accumulation of diseases/disorders and, thus, are characterized by large sample sizes. Sixth, it is assumed that these studies provide an opportunity to comprehensively sample risk factors of interest prior to the onset of cases.

To summarize, it has been argued that prospective cohort studies (Manolio et al., 2006) are particularly suited to (1) studying the full range of disease/disorder manifestations (e.g., diseases/disorders with high mortality at onset like pancreatic cancer or with a long preclinical phase such as type 2 diabetes; Collins, 2004); (2) the identification of predictive biomarkers manifesting prior to the clinical presentation of the disease/disorder (Langholz & Goldstein, 1996); (3) the identification of risk factors that transform after the onset of disease/disorder due to treatment, change in lifestyle, or imperfect or biased recall (Colman & Jones, 2004); (4) the investigation of common complex diseases/disorders of a polygenetic nature (Foster & Sharp, 2005); (5) the simultaneous investigation of multiple outcomes (ARIC Investigators, 1989; Colditz, Manson, & Hankinson, 1997; Kolonel et al., 2000; Leibowitz et al., 1980; Lloyd-Jones, Larson, Beiser, & Levy, 1999; Newman

et al., 2006; Troyer, Mubiru, Leach, & Naylor, 2004; Tsai et al., 2002; Women's Health Initiative Study Group, 1998); (6) confirmation and extension of findings obtained by other means—i.e., via other designs, such as case–control studies (Aleksic et al., 2002; Ellenberg & Nelson, 1980; Kannel, 1995) and dispelling misconceptions (Kannel, 1995; Stamler, 1991); and (7) providing, with adequate protection, wide access to data and samples for analysis and reanalysis (Marshall, 1997).

There are multiple examples of large-scale cohort studies that contribute to the world's general understanding of the epidemiology of health and disease/disorders, including studies in the United Kingdom (Foster & Sharp, 2005; Harvey, Matthews, Collins, Cooper, & U.K. Biobank Musculoskeletal Advisory Group, 2013; Pramanik et al., 2012; Swanson, 2012; Ul-Haq et al., 2014), Iceland (Winickoff, 2001), Germany (Aleksic, Jahn, Heckenkamp, Wielckens, & Brunkwall, 2005; Wichmann, 2005; Wichmann & Gieger, 2007), Sweden (Abbott, 1999), Canada (Gibson et al., 2008; Godard, Ozdemir, Fortin, & Egalite, 2010; Kosseim et al., 2013; Webster, 2008), France (Goldberg & Zins, 2014; Spira, 2014), and Japan (Yuasa & Kishi, 2009). These samples are of considerable size. For example, the UK BioBank, with a case population of 10,000, is considered to be adequately powered to detect risks of <1.15 for G and 1.50-2.00 for GxE (G. D. Smith et al., 2005). However, the public-health significance of genetic risk below 1.50 is not apparent, although it is of etiological and general scientific interest (Terwilliger & Weiss, 2003). Moreover, there are ethical, legal, and social issues related to establishing, maintaining, and using biobanks (Gottweis, Chen, & Starkbaum, 2011; Haga & Beskow, 2008; Kaiser, 2002; Weisbrot, 2012).

Notwithstanding such concerns, it has been argued that there is no comparable study in the United States and there is a need for (at least) one (F. S. Collins, 2004). The justification for this need is that, although there are many prospective cohort studies (Kannel, 2000; Riboli & Kaaks, 1997; The Women's Health Initiative Study Group, 1998), not a single one is substantially large or comprehensive enough to address the modern dominant causes of morbidity and mortality that may occur during the life span or to cover the diverse characteristics of the general U.S. population (Manolio et al., 2006). To illustrate the magnitude of effort that is envisioned in this context, consider the following excerpt from a power calculation, conducted to set up a framework for research using prospective cohorts (Manolio et al., 2006).

> According to our estimates, a prospective cohort study of 1,000,000 subjects would have sufficient power to detect an environmental exposure odds ratio of ≥1.5 for diseases of ≥0.05% incidence per year, such as colorectal cancer, whereas a study of 200,000 people could only detect an environmental odds ratio of ≥2.3 for diseases with this incidence. The minimum detectable odds ratios for genetic factors were slightly lower (indicating the power of the study was higher), mainly because a single individual has two "chances" of carrying a dominant risk allele. For interactions, however, the minimum detectable odds ratios were much higher (that is, the power was lower), as would be expected from the much smaller number of participants exposed to both genetic and environmental risk factors. Whereas a prospective cohort study of 1,000,000 had sufficient power to detect a GxE interaction odds ratio of ≥1.4 for diseases of ≥0.5% incidence a year, a study of 200,000 could only detect this GxE interaction odds ratio for diseases of ≥3% incidence. For a disease of 0.05% incidence, the minimum detectable odds ratio was about 2.4 in the 1,000,000-person study, and as much as 7.0 in the 200,000-person study. Minimum detectable gene–gene odds ratios were slightly lower than GxE odds ratios. Genetic and environmental marginal odds ratios and interaction odds ratios of at least 1.5 are likely to be important to detect, as this is the magnitude of risk associated with genetic variants that is known to be important in complex diseases such as diabetes (Altshuler et al., 2000; Grant et al., 2006). A cohort of 200,000 will provide adequate power within 5 years for only the most common diseases, such as cataracts and hypertension, and will miss these effects for important diseases such as myocardial infarction, diabetes and all cancers. By contrast, a cohort size of 500,000—the number recommended by the NHGRI Expert Panel for a US cohort—will capture many more of these effects. For rarer diseases such as Parkinson disease or schizophrenia, GxE interactions would probably not be detectable within 5 years, even with 1,000,000 participants, but might be approached by continued follow-up and accrual of additional cases (or pooling with other cohort studies) over time. Conversely, GxE interactions for more common diseases, such as hypertension, could be examined early in follow-up and could be assessed for consistency in key subgroups. Of course, consideration of higher order interactions (gene-by-gene-by-gene, or multiple interacting genetic and environmental factors) will require larger sample sizes and might not be approachable within a single study, even for the most common outcomes. (Manolio et al., 2006, PP. 817–818)

Although the envisioned efforts are breathtaking and impressive, the value of cohort studies is not universally accepted (Barbour, 2003; Khoury, 2004). The main points of criticism are the necessity for large sample sizes and long durations, both of which are associated with high costs (Clayton & McKeigue, 2001). Other criticisms of prospective cohort studies point to their lack of flexibility and innovation, as they are locked into particular constraints by design and original hypotheses (Jamrozik, Weller, &

Heller, 2005; Kannel, 2000; Taubes, 1995). Moreover, there are concerns about a multiple testing issue (Terwilliger & Weiss, 2003), as there are a large, and perhaps infinite number of models that could fit the generated data. Arguing against forming new prospective cohorts (the anticipated cost of which is estimated at $3 billion), some (Willett et al., 2007) have suggested assembling cohorts using a combination of samples from existing studies. Although appealing from a cost-reducing standpoint, such a strategy has a number of drawbacks, specifically, lack of standardization of measures across samples, inability to take advantage of new developments in measurement (e.g., dietary intake) and exposure assessments, lack of representation of all strata of the society, uneven age bands (most if not all of existing cohorts include individuals younger than 50, yet it is important to cover a whole spectrum of life span, from birth to death), and constraints pertaining to free and open access to the data by qualified investigators (Collins & Manolio, 2007). These concerns are part of an ongoing discourse, where both sides are trying to negotiate the best possible solution that utilizes both approaches, to whatever degree possible.

In sum, given that both of the major designs used for studying GxE (i.e., case–control and cohort designs) are less than ideal and come with their own array of pros and cons, the field has been challenged with the development of methodological innovations that might overcome the limitations of both or either approaches.

One such innovation is the nested case–control design (i.e., subsamples of both controls and incidence cases from the cohort), which represents an attempt to capitalize on the strengths of both designs while compensating for their weaknesses. The case–control within a cohort or nested case–control design (Mantel, 1973; Prentice, 1986) assumes the utilization of an informative subgroup of cohort members. Although a subtype of the classic case–control design, this design is more resistant to various biases because it permits selection of incident cases and a sample of disease-free controls from an already-established prospective cohort. In other words, as various environmental indicators are collected for the cohort in an outgoing fashion, critical exposures are assumed to be measured before the onset of diseases/disorders of interest. Moreover, biological samples in cohort studies are typically collected if, at the study entry, they can provide unique preexposure information. This design allows the construction of subsamples of cohort members as grouping meets specific objectives of an investigation (e.g., examining the impact of exposure to a particular environmental toxin at a particular geographic location). The use of biobanks, then, overcomes the concern of reverse causation by relying on stored specimens and the information on exposure, both of which were obtained at enrollment.

Yet another innovative design is referred to as Mendelian randomization—a technique that permits an investigation of the causal effect of modifiable exposure to a disease/disorder while capitalizing on the availability of the measured variation in genes of known function (Gray & Wheatley, 1991; Greenland, 2000; McGrath, Mortensen, Visscher, & Wray, 2013; Relton & Smith, 2012). The logic behind this design is as follows: in an ideal genetic association study, Mendelian laws are assumed to guarantee the comparative evaluations of groups of individuals, so that groups established based on specific genotypes (e.g., AA, aa, and Aa) will be comparable to a randomized comparison. This is reasonable given that these genotype-based groups should not differ systematically, except for the effect of linkage disequilibrium (i.e., the dependency between genetic sites that extend over the locus under study due to the phenomenon of linkage disequilibrium). This design is thought to be less susceptible to reverse causation and confounding (Clayton & McKeigue, 2001; Didelez & Sheehan, 2007; Julier et al., 1991; Smith & Ebrahim, 2003) and has been used in GxE studies (Lewis et al., 2011).

In addition, there are numerous nonconventional epidemiological designs applicable to the analyses of GxE interactions. One such design is a cluster of family-based association tests (FBATs), which can be exemplified through case–parent trios (Schaid, 1999), case–sibling pairs (Gauderman, Witter, & Thomas, 1999), extended pedigrees (Laird & Lange, 2006), and other combinations of relatives (Cui et al., 2003; Guttmacher et al., 2004). The FBATs are designed to avoid bias from population stratification. In general, population stratification is of concern for studies of GxE only if there are differential relationships between gene and environmental factors in the population of the substructures (e.g., dissimilar genetic ancestries in exposed and unexposed individuals). One of the most frequently utilized designs is that of the case-parent trio design (Shin, Infante-Rivard, Graham, & McNeney, 2012). In this design, the exposure information is collected only on the cases, and the comparison carried out is that of the relative genetic risks between exposed and unexposed cases. Notably, this design assumes that the parents are also genotyped; this information is especially important for studies of early-onset diseases. Yet another oft-used design is that of discordant sibships (Dabelea et al., 2000; Hoffmann et al., 2011). In this design, the exposure information is collected on all cases and controls and the interaction is tested by means of standard

conditional logistic regression. In addition, the literature contains examples of the utilization of twin studies (Boomsma, Busjahn, & Peltonen, 2002), family segregation (Andrieu & Demenais, 1997), and linkage analyses (Gauderman & Faucett, 1997; Gauderman & Siegmund, 2001; Schaid, Olson, Gauderman, & Elston, 2003) for testing the existence of GxE with unknown genes or specific genetic regions (Yang & Khoury, 1997). Yet, although FBATs are quite powerful for testing GxE interactions, assuming that relatives' exposures are not highly correlated (Gauderman et al., 1999), these designs lack power for testing main effects. In fact, their power for testing main effects is substantially less than that of conventional case–control studies that utilize unrelated controls.

Another design that could be used only to test interactions, not main effects, is the case-case or case-only design (Piegorsch, Weinberg, & Taylor, 1994). This design was developed to overcome the poor power for the detection of multiplicative interactions attributed to small numbers of cases or controls in cells at the cross-overs of risk factors for G and E (i.e., where the risk is present for both G and E) in the standard case–control design (i.e., the counts in the cells where both G and E risk factors are manifested can be low). The key feature of this design is the assumption of GxE independence in the general (source) population; specifically, this assumption allows one to avoid estimating this association among control individuals, which, in turn, increases power for the test of interaction. If this assumption is not violated (e.g., as it is in the case of air pollution), then the case-only design will generate reasonable estimates of odds ratios for GxE. However, if this assumption is violated, the design will generate a biased estimate of the interaction and an elevated Type I error rate (Albert, Ratnasinghe, Tangrea, & Wacholder, 2001). In reasoning through the bias vs. efficiency predicament, a two-part process might be helpful, wherein first, a formal test for the adequacy of the GxE independence assumption is carried out, and, second, the results of this test are used to determine whether the more robust case–control or the more powerful case-only design should be utilized. Yet this process has its own caveats (Mukherjee et al., 2008). First, the majority of GxE studies are still carried out on samples of modest size and would therefore be underpowered to test for the independence of G and E, likely resulting in a biased process. Second, the corresponding calculations for the variance components in the underlying model can be challenging given the model's uncertainty. The field has offered ways to overcome some of these caveats. For example, a method called empirical-Bayes (EB)-type shrinkage estimator has been developed (Mukherjee & Chatterjee, 2007) to achieve a balance between bias and efficiency. In other words, this estimator can maintain optimal or close to optimal mean squared errors among all of the different estimators of interactions irrespective of the true state of the GxE relationship. Empirical interrogations of this estimator suggest that it is unbiased asymptotically. Furthermore, most violations of the assumption of G and E independence are not egregious (Liu, Fallin, & Kao, 2004). The usage of the estimator, then, in conjunction with the increase in the sample size, is thought to result in an eventual decrease in Type I errors (Mukherjee et al., 2008). This estimator appears to present an approach to detecting and estimating GxE interactions from case–control studies by maintaining a desired level of Type I error. Moreover, it does this in the context of realistic assumptions of G and E dependence while improving power compared with the traditional case–control studies that assume G and E independence.

Yet another type of nonconventional design is that of a two-phase case–control design (White, 1982). This design leverages readily available surrogate indicators of exposure (e.g., self-reported retrospective accounts of exposure, phase one) to choose individuals for more detailed assessment of exposure or genotyping (e.g., indicators of exposure based on particular biomarkers, phase two). Phase one typically capitalizes on the existence of both disease/disorder status and the surrogate indicator of exposure present in an ongoing case–control or cohort study, so that a sample for phase two can be built using independent sampling. Thus, although phase one might be relatively inexpensive, phase two can be quite expensive because information on exact doses, confounders, or modifiers requires additional data collection (Breslow & Chatterjee, 1999). Optimally, in phase two, more rare cells (typically, the exposed cases) are overrepresented. In the analyses, the information from both phases is combined so that corrections for biased sampling in phase two can be introduced. An illustration of the utilization of the two-phase case–control design comes from the Atherosclerosis Risk in Communities (ARIC) study, where the interaction between polymorphisms in *GSTM1*/*GSTT1* genes and cigarette smoking on the risk of coronary heart disease was investigated (Breslow, Lumley, Ballantyne, Chambless, & Kulich, 2009; Li et al., 2000). The literature has examples of direct (Caporaso et al., 2009; Thorgeirsson et al., 2008) and indirect associations (Thomas, 2000). A two-phase design was used in a randomized trial of estrogen plus progestin to evaluate interactions of treatment with thrombosis biomarkers (Dai, LeBlanc, & Kooperberg, 2009). According to the results of this study, estimates of the

interaction effect were much more accurate than the estimates obtained from either the case–control study or the two-phase study (and corresponding estimators) in which G and E independence was not assumed.

The two-phase design has a number of derivatives, one of which is countermatching. In this design, each case is matched to one or more controls on the basis of exposure; each matched set should contain the same number of exposed individuals. An illustration of countermatching comes from studies of breast cancer (Langholz & Goldstein, 1996). Notably, the usage of this design has been stated to increase power both for main effects and for interactions (Andrieu, Goldstein, Thomas, & Langholz, 2001).

Finally, it is important to note alterations in established designs such as those of GWAS using either microarray (Engelman et al., 2009) or sequencing (Bickeböller, Houwing-Duistermaat, Wang, & Yan, 2011) data. Now GWAS is used to carry out whole-genome analyses for environmentally responsive variants, known as Genome–Environment-Wide Interaction Study (GEWIS; Khoury & Wacholder, 2009). The expected advantages include both improvement in the targeting of interventions and treatment and the provision of more data for understanding mechanisms of complex human diseases and disorders (Caspi & Moffitt, 2006). However, as GEWIS is new, it has a number of challenges, chiefly those dealing with multiple testing (Caspi & Moffitt, 2006), handling effects of nested environments (Rodgers, Ezzati, Vander Hoorn, Lopez, & Lin, 2004), utilizing existing specimens and medical and other records (Modinos et al., 2013), and interpreting GxE findings (Zammit, Lewis, Dalman, & Allebeck, 2010). To date, there are only limited examples of GEWIS. For example, GEWIS has been utilized to examine the role of genetic moderators in the effect of coffee drinking on Parkinson's disease (Hamza et al., 2011).

As Clayton and McKeigue (2001) pointed out, "The prospects for epidemiology in the post-genome era depend on understanding how to use genetic associations to test hypotheses about causal pathways, rather than on modelling the joint effects of genotype and environment" (p. 1359).

Power

As it gains experience and wisdom, the field is able to look back and reflect on its own accomplishments and failures. Thus, it is a well-recognized problem that the majority of early candidate–gene studies recruited samples that were substantially too small (Wacholder, Chanock, Garcia-Closas, El Ghormli, & Rothman, 2004). As sample size is directly related to effect size, there is always a question of what magnitude is considered to be of enough importance and interest to justify a research effort. The current trend in the literature is to view odds ratios of 1.4 as important, interesting, and potentially significant for public health (Hemminki et al., 2006). Detecting effect sizes of this magnitude calls for large sample sizes. Furthermore, the requirements for sample size increase exponentially when whole-genome rather than candidate gene studies are considered (Wang, Barratt, Clayton, & Todd, 2005). Perhaps unsurprisingly, the cost–benefit ratio of an association study that requires a sample of 10,000 cases and 10,000 controls to identify a gene whose variant is associated with an odds ratio of 1.4 has been questioned (Wang et al., 2005).

It is a well-established observation—empirically and theoretically, in both data-based and simulation-based studies—that statistical power is lower for interactions compared to main effects. It is also widely understood that the consequences of lower power are twofold: when underpowered, true effects are more likely to be missed; while conversely, the proportion of false discoveries among all discoveries is more likely to be high. In general, the power needed to establish and evaluate the impact of any predictor is positively related to the variance of that predictor; lower power to detect interactions is chiefly due to the fact that the dispersion of the product term in nonexperimental settings tends to be low (McClelland & Judd, 1993). On the other hand, power is maximized when the sample is drawn from the extremes of the distributions of main effects. While capitalizing on extremes is possible and suitable in experimental studies, it may be impossible and even inappropriate for human research, especially in the realm of public health.

Many researchers (e.g., Boks et al., 2007; Garcia-Closas & Lubin, 1999; Hwang, Beaty, Liang, Coresh, & Khoury, 1994; Smith & Day, 1984) have specifically investigated the statistical power of GxE studies and have similarly concluded that the power to detect GxE interactions is substantially lower than the power to detect either G or E main effects. Sampling alterations (e.g., the utilization of the extremes design) are possible with environmental/exposure extremes (i.e., sampling from high and low environments at equal numbers), but are near impossible with genotypic extremes (i.e., ascertaining the two types of homozygous carriers at the same frequency). Correspondingly, the way to maximize the variance in the product term is to maximize the variance in first-order (i.e., main effects or G and E) terms (Boks et al., 2007). For example, for a single-polymorphism/single-exposure study, it would mean looking for a polymorphism in which the frequency of the

derived (i.e., minor) allele in the population of interest is as close to 50% as possible; an exposure factor observed at its extremes at approximately the same numbers (e.g., 50% are highly or severely exposed to the factor of interest and 50%—never or only slightly exposed) would also be needed. Moreover, as described already, other considerations, such as sampling strategy (Cologne et al., 2004), study design (Kraft & Hunter, 2005), measurement error in the terms (Burton et al., 2009), correlations between variables capturing G and E (McClelland & Judd, 1993), and types and distributions of outcome and exposure variables (Luan et al., 2001) also impact statistical power to qualify and quantify the GxE interaction.

When these general considerations are applied to the literature on GxE, the overwhelming conclusion is that, so far, GxE studies have been underpowered (Burton et al., 2009; Duncan & Keller, 2011; Luan et al., 2001). This consistent conclusion has been reached in a number of studies (Mukherjee, Ahn, Gruber, Ghosh, & Chatterjee, 2010) for a variety of designs and circumstances: case–control studies (Foppa & Spiegelman, 1997; Garcia-Closas & Lubin, 1999; Hwang et al., 1994; Luan et al., 2001), case-only designs (Yang, Khoury, & Flanders, 1997), and association studies for detecting genetic main effects, where the use of GxE interaction is indirect (Hein, Beckmann, & Chang-Claude, 2008; Kraft et al., 2007). It is noteworthy that the largest studies of putative GxE effects to date have largely produced null results (Surtees et al., 2006), again, raising the suspicion that findings in smaller studies may, in fact, embody false positives.

Notwithstanding the study design, there are other factors that are important to consider in the determination of sample size. These factors are allele frequency, mode of inheritance, the prevalence of exposure (or its distribution if continuous), odds ratio for the main effects of G and E and the interaction effect of GxE, significance level, and desired power (Thomas, 2010a). Moreover, power appears to be sensitive to the nature of the estimators used to qualify and quantify GxE (Mukherjee et al., 2008). There are multiple pieces of software for the relevant power calculations, most notably, QUANTO (http://hydra.usc.edu/gxe, Gauderman, 2002) and POWER (Garcia-Closas & Lubin, 1999).

It appears that the current state of affairs in the field of GxE studies is characterized by the winner's curse phenomenon (Capen, Clapp, & Campbell, 1971): when the power is low, discovery studies presenting positive findings are more likely to report substantial effect sizes (Flint & Munafò, 2008). Such an ascertainment bias leading to an overestimation of genetic effects has been discussed (Goring, Terwilliger, & Blangero, 2001), as well as illustrated in the field of genetic association studies (Lohmueller, Pearce, Pike, Lander, & Hirschhorn, 2003). Thus, in a meta-analysis of 301 association studies, out of 25 loci detected as significantly associated, for 24, the odds ratios reported in replication studies were substantially lower compared with the initial report (Lohmueller et al., 2003). It is assumed that the pattern of results for GxE studies is similar (Flint & Munafò, 2008). The genetic association studies whose results have been replicated, as well as the replication studies, have utilized samples that included thousands (Zeggini et al., 2007) and tens of thousands (Cox et al., 2007) of individuals. GxE studies, compared with these genetic association studies, use sample sizes that are smaller, despite the fact that power calculation procedures prescribe the opposite. Although there are some large samples (>4,000, Surtees et al., 2006), they represent exceptions to the rule, and the average size of GxE samples is much smaller. For example, for the 18 studies of the serotonin transporter, the average sample size was 600 (Uher & McGuffin, 2008). The general rule is that if the interaction is of the same magnitude as the main effect and the power is maintained at the same level, the sample size for a study of GxE must be increased fourfold (Brookes et al., 2001; Smith & Day, 1984). This ratio, however, changes dramatically (to 100 or greater) if subtler (<20% of the main effect) effect sizes for interactions are considered (Brookes et al., 2001). Improved (i.e., with denser marker coverage) and enhanced (i.e., with larger sample size) GWASes should also include detailed indicators of environment, so that not only G, but also E is measured (Vineis, 2004; Willett, 2002). As discussed already, in many situations, interaction terms (either GxE or GxG) can bias and overestimate heritability estimates if they are not measured and modeled properly.

Replication

In general, it has been observed that the degree of replicability in the field of GxE is low. There are many different sources of heterogeneity in GxE studies, both for G (e.g., the ancestral population allele frequency) and for E (e.g., different sizes or chemical constituents of particulate air pollution across regions), as well as for confounders (e.g., co-pollutants, ethnic distributions with differing genetic background risk) that are inevitable and par for the course (Thomas, 2010a). If explained, understood, and accounted for, these sources of heterogeneity can provide insights into the etiology of the disease/disorder (Greene et al., 2009). Yet if sources of heterogeneity are attributable to spurious

inconsistency resulting from methodological limitations, data differences, and random differences between various studies, they turn into sources of noise (Thomas, 2010a).

Moreover, even if the field has conscientiously invested in attempting to replicate a finding, there is still ambiguity with regard to understanding and interpreting the results generated by such attempts. For example, the influential study by Caspi and colleagues on the connections among variation in the promoter of the serotonin transporter gene, stress, and depression (Caspi et al., 2003) has generated numerous replication attempts that have yielded contradictory results. Meta-analytic approaches have also generated conflicting conclusions: for one meta-study that exercised an inclusive approach, the phenomenon is replicable (Karg et al., 2011), whereas for another exercising a less inclusive approach, the phenomenon is, in fact, an epiphenomenon propagated by publication bias (Duncan & Keller, 2011). It is important to mention that results of meta-analyses themselves might be biased, depending on how the specific studies to be included are selected (Egger, Smith, & Phillips, 1997).

It has been suggested that the poor track record of replicating previously reported findings of GxE interactions is partially attributable to lack of power in both the discovery and replication samples (Burton et al., 2009; Ioannidis, Trikalinos, & Khoury, 2006; Matullo, Berwick, & Vineis, 2005). It is clear that better powered studies are needed for both discovery and replication attempts. Yet, this realization triggers another concern: as discussed above, it is not clear whether the results of large-scale studies aimed at dissecting a small effect of GxE are worth the effort, as their public health significance is questionable. It has been argued that specific genes involved in interactions are more likely to be affected through marginal rather than interactive effects (Clayton & McKeigue, 2001). The counterargument is that even when marginal effects are not detectable, there could be statistically significant interaction effects, which will be missed if the focus is exclusively on marginal effects. Indeed, it has been stated that the presence of interactions in the absence of main effects is a ubiquitous phenomenon in nature (Moore, 2003; Moore & Williams, 2009). Yet most examples of such universality come from studies at the molecular and cellular rather than the epidemiological level, although there are some examples of specific G factors that appear to group only with specific E factors, and that very combination generates excessive risk (Guttmacher et al., 2004).

In summary, there is much concern about the low rates of replication in the field of GxE. Yet these concerns are not limited to this field; in fact, the field of GxE is only one of many in which concerns about replicability and effectiveness of research are profound (Macleod et al., 2014).

Publication Biases

Both scientists and scientific journals are leery of publishing so-called null results (i.e., results that do not generate new findings). Among the many reasons for this phenomenon, the main one is that null results (or nonreplications, if a study was an attempt to replicate a previous finding) cannot be viewed as definitive: the inability to reject the null hypothesis does not mean that the null hypothesis is proven. Simply put, both attention and rewards in science are given mostly for the discovery of something new rather than the negation of something old. This publication bias, although logically understood, is assumed to be quite harmful to scientific literature in general and to the GxE literature in particular (Duncan & Keller, 2011), due both to its ubiquity (Thornton & Lee, 2000) and its distortion of the true significance of discovery findings (Ioannidis, 2005). The impact of this harm is difficult to quantify precisely, although some relevant estimates suggest that it is qualitatively large (Duncan & Keller, 2011), as per the hypothesis that many negative results go unpublished, amounting to an increased field-wide Type I error rate.

Another type of bias is nested within the bias against the publication of null results. This bias is captured by the disproportional publication of attempts at replication depending on (1) the nature of the finding (positive or negative), (2) the sample size used, and (3) whether an attempt at replication was coupled with a novel finding or presented by itself. It appears that the threshold for a publication of a nonreplication is substantially higher (i.e., a much larger sample size, sixfold compared with positive studies) if required, and a broader scope of work (i.e., a positive result on an additional GxE) is anticipated (Duncan & Keller, 2011).

It is important to note that the GxE literature is not unique in terms of producing a publication pattern characterized by a small number of high-profile findings, followed by a mixture of replications and nonreplications (Flint & Munafò, 2008). Such a pattern has been seen before in the literatures on GWAS (Munafò et al., 2003; Munafò, Matheson, & Flint, 2007) and endophenotypes (Flint & Munafò, 2007; Munafò, Brown, & Hariri, 2008).

Illustrations

So far, we have reviewed the general set of considerations for conducting GxE studies and have exemplified issues and

observations that have been accumulated by the field. In this section of the chapter, we will illustrate these generalities with two scenarios: one statistical (using a variety of diverse phenotypes and exposures and a single variant of G) and the other biological (using a cluster of related phenotypes, a single type of E, and a type of G).

Understanding the Variation in the Promoter of the Serotonin Transporter Gene

In mammals, serotonin (5-HT) is a major neurotransmitter, involved in numerous highly important biological processes like food intake, sleep, reproduction, circadian rhythm, thermo-regulation, pain, learning and memory, perception, social behavior, and mood regulation (Kriegebaum, Gutknecht, Schmitt, Lesch, & Reif, 2010). Its function in the brain is to substantiate a major type of brain signaling. Multiple proteins regulate the synthesis, degradation, transport, and reception of serotonin, and the production of these proteins involves multiple genes (Duman & Canli, 2010). Specifically, the synthesis of serotonin starts from the amino acid tryptophan and is two staged: the first rate-limiting step is catalyzed by tryptophan hydroxylase (TPH, the production of whose isoforms is controlled by two genes: TPH1, expressed primarily in the periphery; and TPH2, expressed primarily in the CNS). The degradation of serotonin engages enzymes monoamine oxidase A and B, encoded by the X-linked MAOA (central to the degradation of serotonin following its reuptake from the synaptic cleft by the serotonin transporter) and MAOB (central to the degradation of dopamine) genes, respectively. Serotonin is transported into the vesicles near the presynaptic membrane of neurons by the vesicular monoamine transporter (Vmat). The reuptake of extracellular serotonin is necessary for regulating serotonergic transmission and tone. This process is accomplished by the serotonin transporter, a protein encoded by the serotonin transporter gene (referred to as 5-HTT, SERT, or SLC6A4 and located at 17q11.1-q12) that enables the reuptake of excess serotonin from the synaptic cleft. Postsynaptically, serotonin binds to multiple serotonin receptor subtypes, which are encoded by 16 different genes.

In humans (but not exclusively), the SLC6A4 gene is highly polymorphic. One of the most studied polymorphisms in this gene is a common VNTR polymorphism in the promoter region (known as 5-HTTLPR polymorphism). This polymorphism exists in the form of two alleles: a short (*s*, composed of 14 copies of 20–23 base-pair repeated units); and a long (*l*, composed of 16 copies of the repeat unit) variants. The allele *l* has an embedded SNP (rs25531), which involves an A to G substitution. The presence of the G allele is associated with an expression rate similar to the *s*-allele (Hu et al., 2006). Although the allele frequencies for both polymorphisms (VNTR and SNP) vary in different populations, neither is rare, generating a robust source of individual differences in the functional properties of the synthesized protein. Individuals homozygous for the short variant (*s*-carriers) are thought to be characterized as demonstrating lower mRNA transcription (Lesch et al., 1996), increased extracellular 5-HT levels (Mathews et al., 2004; Montañez, Owens, Gould, Murphy, & Daws, 2003), and altered 5-HT receptor densities/function (D.-K. Kim et al., 2005), although recent work has suggested a more complex mechanism, such as regional up- and down-regulation of specific 5-HT receptors (Hariri & Holmes, 2006). The VNTR polymorphism is one of the most studied for associations between structural variability in the genome (i.e., variation at this site) and a plethora of behavioral traits (emotional regulation, Hariri & Holmes, 2006; coping with stress, Homberg, 2012; social conformity, Homberg & Lesch, 2011; social behavior, Kiser, Steemers, Branchi, & Homberg, 2012; emotionality, Murrough & Charney, 2011). As investigations of this polymorphism account for a substantial portion of the behavioral GxE literature, we have undertaken a descriptive characterization of this work.

To accomplish this task, we identified, using the PubMed, PMC, and Medline databases, a set of empirical articles published between January 2000 and December 2012 (including those published electronically, even if the journal publication date was in 2013); no unpublished work (i.e., dissertations) was included. Two literature searches were performed, using selection algorithms (1) ((“alleles” OR “genotypes” OR “genes” OR “polymorphisms”) AND (“GxE” OR “G by E” OR “gene × environment” OR “gene by environment”)) AND (Humans) and (2) ((“alleles” OR “genotypes” OR “genes” OR “polymorphisms” OR “GxE” OR “G by E” OR “gene × environment” OR “gene by environment”)) AND (“serotonin transporter” OR “HTTLPR”) AND (“humans”). The resulting pool of articles ($n > 1{,}000$) was examined with the following inclusion-exclusion criteria. The publications were included if the study examined an interaction between the serotonin transporter gene promoter polymorphism and an environmental exposure indicator deemed relevant to developmental psychopathology as a predictor of a psychological/psychiatric outcome (some of these studies also examined additional variants in other genes). The articles were excluded if (1) exposure indicators were obstetric complications, environmental toxins, diet, physical exercise, medical conditions, or hormonal intervention; (2) no

exposure indicator was identified and the interaction term included G and such factors as indicators of temperament, personality factors, or other psychiatric disorders (e.g., depression, anxiety, addiction); (3) outcome variables were other (nonpsychiatric) medical diseases or disorders (e.g., Crohn's disease, obesity); (4) the sample included related individuals of any kind (twins, other sibling pairs, or any other family members); and (5) more than one variant in the *SLC6A4* gene was investigated (e.g., haplotypes were analyzed). The application of inclusion–exclusion criteria resulted in the selection of 192 articles (see Appendix).

These articles were reviewed to extrapolate answers to a number of specific questions systematically. In general, the intent of the analyses presented here was to see whether this literature contains indications of the utilization of the best practices in the field (i.e., regarding observations and recommendations discussed in this chapter) in the selected publications. Thus, both the extrapolations and interpretations are based on the descriptive analyses of these studies as a group.

The first set of questions dealt with the sample size and the design of the analyzed studies. The sample size ranged from $n = 24$ to $n = 4{,}334$. Importantly, indicators of central tendency were quite variable: mean = 594.5, median = 301, mode = 118 (sd = 769.8). Taken together, this set of studies was still quite far from what is recommended as the standard in the field in terms of sample size. The majority of the samples were characterized cross sectionally ($n = 123$, 64.1%), but a substantial number of samples ($n = 69$, 35.9%) contained longitudinal data. All studies utilized a version of the traditional case–control design, even if there were previously collected longitudinal data.

Second, the studies were diverse in terms of utilizing samples including only women ($n = 27$, 14.1%), only men ($n = 9$, 4.7%), or both genders ($n = 156$, 81.3%). The studies were also diverse in terms of including different races and ethnicities.

The third block of questions pertained to issues of measurement error, both in G and E variables, however defined. In general, details of measurement were not well explicated in this set of studies, although many contained conventional psychometric indicators of the assessments that were utilized either to measure the outcomes or the exposure (E). The presentation of the measurement approach toward G was predominantly characterized by missing information with regard to the error rate for genotyping: only 34 studies (17.7%) reported error rates. Furthermore, only a handful of studies reflected on whether these rates met the expectations established in the field and discussed possible related biases. Notably, very few publications contained information pertaining to the presence of missing data and the process by which this missing data was accounted for (n = 28, 14.6%).

Fourth, only a very small proportion of outcome variables (6.8%) were transformed.

The fifth set of questions had to do with the range of outcomes, exposures, and polymorphisms (see exclusion and inclusion criteria above) utilized in the articles. All three were observed to present considerable ranges: 1–59 for outcomes (mean = 2.7, median = 2, mode = 1, sd = 4.7), 1–35 for exposures (mean = 2.2, median = 1, mode = 1, sd = 2.9), and 1–14 for polymorphisms (mean = 1.8, median = 1, mode = 1, sd = 2.0). Importantly, only 23 studies (12%) exercised any type of correction for multiple comparisons. The most frequently used was the Bonferroni, with other methods such as false discovery rate (FDR) applied only rarely.

Sixth, among the statistical techniques utilized for testing interaction effects, preferences were given to ANOVA/ANCOVA or MANOVA/MANCOVA (~20%) or different types of regression approaches (linear or logistic, ~60%). Typically, the statistical software used was not specified. When specified, the software was not tailored for GxE analyses in the majority of cases, and, therefore, was not necessarily the best vehicle to analyze the data.

Seventh, relatively few studies ($n = 45$, 23.4%) reported the obtained effect sizes and discussed their practical meaning.

Curiously, there were journals that were particularly receptive to the GxE studies involving the serotonin transporter gene during the period of time between 2000 and 2012. Thus, *Biological Psychiatry* published 15 and *Journal of Affective Disorders* published 12 of the 192 articles commented on here.

In this section, we summarized studies utilizing the statistical concept of GxE. Clearly, this interpretation of GxE attracts a lot of attention in the field and appears to generate studies, with the rate of published studies increasing over time. Interestingly, there appears to be a delayed reaction of the field to the criticisms that have been explicated in multiple reviews and meta-analyses. As this summary of the 192 articles demonstrates, the majority of the studies are still underpowered, have not paid enough attention to the issue of multiple comparisons, may not be sensitive enough to issues of measurement error, variable transformations and tracking confounders, and, most importantly, do not discuss the robustness, meaningfulness, or practical significance of the established interactions.

Understanding the Reaction Range in the Acquisition of Academic Skills

It is impossible, in modern society, to overestimate the impact of key academic skills such as reading, mathematics, and science reasoning on subsequent life success and life outcomes. This impact is omnipresent worldwide, and the effectiveness of country-specific primary and secondary educational systems is judged, in part, by how well students score on international competitions, such as the OECD Programme for International Student Assessment (PISA). In the twenty-first century, PISA has become "the world's premier yardstick for evaluating the quality, equity and efficiency of school systems in providing young people with these skills" (http://www.oecd.org/pisa/keyfindings/pisa-2012-results-overview.pdf, p. 2). While the importance of these skills is not disputed, there are two additional considerations that are also rather axiomatic at this stage. First, it is accepted, with the exception of a few rare developmental trajectories (i.e., extreme giftedness or circumscribed skills manifested in certain types of atypical development like autism), that all academic skills are constructed by a child as he or she experiences schooling. In other words, a child acquiring these skills builds a number of new cognitive (i.e., brain-based) representations that will guide the processing of relevant information. The formation of these representations requires a functional reorganization of the brain. Second, it is also known that, within any educational system (whether it is high-scoring such as Chinese, Taiwanese, or Finnish; mid-range-scoring such as German, Spanish, Russian, or American; or low-scoring such as Mexican or Indian, as per a number of PISA cycles), a tremendous amount of individual difference scatters student performance across the continuum. The presence of individual differences has been of interest to researchers around the world. As schooling was put in place only in the first half of the last century, the research into the student-based variation in learning that occurs even when teaching is homogenized has a history of only about 50 years. Yet these 50 years of research have unequivocally established that the efficiency of mastering the key academic skills of reading, mathematics, and scientific reasoning is tightly connected to variation in both the brain (in terms of its processing of the relevant information) and the genome (both structurally and functionally). Thus, the understanding of both the acquisition of, and individual variation in, core academic skills requires the investigation of how structurally diverse genomes assume the task of reorganizing the neural connections of the brain through schooling to acquire the academic skills of reading, mathematics, and scientific reasoning under the pressure of particular educational systems. In other words, this understanding requires a differentiation of the mechanism (or mechanisms) that delivers the environment (teaching or schooling) under the skin, so that a biological machinery (i.e., within a child) that ensures both the initial acquisition of skills and their further automatization and that explains individual differences in both the acquisition and utilization of these skills may unfold. It is argued here that one such mechanism is that of epigenetic regulation in general and DNA methylation in particular.

Five bodies of literature substantiate this argument.

First, the literature substantiates a high degree of genetic control in both the acquisition and maintenance of these three academic skills (reading, mathematics, and scientific reasoning), with some variation across skills. The literature also offers evidence that, while the degree of genetic control seems to be stronger in individuals who exhibit low performance on the academic tasks that utilize these skills, there is no reason to believe that the mechanisms of genetic control for poorer performers are different from the mechanisms of genetic control for stronger performers. In fact, it appears that whatever these mechanisms are, they operate across the range of academic performance (Elliott & Grigorenko, 2014).

Second, similar to other complex phenotypes, academic skills such as reading and reading-related components are highly heritable. However the currently considered candidate genes and corresponding polymorphisms do not account for meaningful portions of the previously estimated heritability. This phenomenon, which applies to these specific phenotypes among many others, has been referred to as the missing heritability problem. Concordantly, although limited, there is growing literature on the importance of GxE for the acquisition of academic skills (Pennington et al., 2009; Rosenberg, Pennington, Willcutt, & Olson, 2012; Taylor et al., 2010).

Third, there are large literatures (Fields, 2011), although uneven for the three skills, substantiating the presence of distinct distributed brain signatures that differentiate individuals who (1) are engaged in particular tasks requiring skills of reading, mathematics, and scientific reasoning as compared to individuals who are engaged in other types of tasks (or when the same individual is engaged in different types of tasks); (2) have acquired the skills versus those who have not (i.e., either when comparing young children who have not yet begun their formal education to older children who have completed

of primary education, or adults who have corresponding functional skills against those who do not have them, for example, literate and illiterate adults, or adults who can and cannot perform operations involving quantitative or scientific reasoning); and (3) perform within the normal range (i.e., within a particular quantification, whether 1, 1.5, or 2—whatever the criterion dictates—standard deviations around the population mean) compared with those who perform outside the normal range (i.e., outside of the established criterion, as defined already).

Fourth, there is a growing body of research indicating the role of epigenetic mechanisms in general and DNA methylation mechanisms in particular in all types of learning (Levenson & Sweatt, 2005). This research, however, has been conducted predominantly on animal models. The human epigenetic literature, however, has assessed the role of this mechanism only in social learning, and there is not a single study that investigates the role of this mechanism in cognitive/academic-related learning to date.

Fifth, there is now a strengthening line of reasoning which connects the literatures on the missing heritability problem, GxE studies, and epigenetics (Slatkin, 2009).

Thus, we argue that the acquisition of academic skills, all of which are both heritable and sensitive to environmental exposure (i.e., pedagogy), exemplifies the biological concept of GxE. As was the case 100 years ago, there is substantially less research on this biological interpretation of GxE compared to its statistical interpretation, but the reasoning presented in this chapter can and certainly should be translated into testable hypotheses.

FUTURE DIRECTIONS

Three observations appear to be instrumental in summarizing the material presented in this chapter in light of future developments. First, there is a critical mass of literature, spread across multiple fields of inquiry (epidemiology, genetics, psychology, and other fields) that indicates that designing, implementing, and interpreting GxE studies require conscientious consideration of a number of methodological caveats. Future studies of GxE should be judged being both aware and proactive about these caveats. The field is too advanced now to forgive any naïveté in those who wish to practice in it. Second, methodological rigor should be expected not only of publications, but also of proposals for GxE studies. In other words, funders should be educated along with researchers on the pros and cons of GxE studies. Finally, the whole field should carefully consider the practical implementations of GxE research. Even when carried out as rigorously as possible, what can the field learn from this research and at what cost? Answers to these questions should surely frame the future of GxE research.

CONCLUSIONS

There is no question that GxE studies have made an impact on the fields of developmental psychopathology, neuropsychiatric genetics, and genetic epidemiology, among others. As is obvious from the discourse above, this impact is complex and has instigated numerous kinds of actions and reactions.

First, there are hopes. The appeal of studying GxE is in the possible applications of the most reliable findings (yet to be secured!). Given the state of the field, it is difficult to predict what findings will be deemed reliable and what applications might be derived from these findings. Specifically, such findings can form a foundation—or at least lead to a set of guidelines—for targeting interventions for individuals at high risk (Khoury & Wagener, 1995). Three types of such guidelines have been discussed. The first type of recommendation (following the established the presence of the statistical GxE interaction) involves avoiding specific exposure. For example, researchers (Vandenbroucke et al., 1994) investigated whether the occurrence of venous thrombosis in young women who use oral contraceptives might be explained by the factor V Leiden mutation (this mutation results in resistance to activated protein C and, therefore, increases susceptibility to thrombosis). The reported differential increases in risk (Vandenbroucke et al., 1994) were four-fold among users of oral contraceptives, eight-fold among carriers of the mutation,, and 30-fold among carriers who used contraceptives. Clearly, carriers should consider alternative methods of contraception. The second type of recommendation involves forming relevant public-health policies. For example, in a study in Rwanda (Kolassa et al., 2010), individuals with extremely high levels of trauma exposure were stratified based on their genotypes at the serotonin transporter gene promoter site. It was reported that the individuals with the ss genotype were marked by a higher chance of manifesting lifetime PTSD regardless of the number of traumatic experiences, whereas the individuals with the l allele (i.e., ll or sl) had an elevated chance of developing lifetime PTSD only when the number of traumatic experiences was elevated. In the Florida Hurricane Study, individuals with the s allele were characterized by (1) the elevated

risk of PTSD only when their exposure to hurricane was higher and their social support was lower, compared to the rest of the sample (Kilpatrick et al., 2007); and (2) the decreased risk of PTSD in low-risk environments, but with an increased risk in high-risk environments (Koenen et al., 2009). Assuming that the multiple inconsistencies of GxE studies may be resolved and the robust findings replicated, relevant policies can be established to diversify services for individuals in disaster zones. The third type of recommendation involves seeking and receiving particular interventions in accordance with a particular genotype. In general, it has been stated (Baird, 2001; Rose, 1992) that in the realm of public health, the predicted health gains are superior in situations when the whole population, not just the high-risk group is targeted. This superiority is justified (Wallace, 2006), in particular, by the relative unimportance of genetic mechanisms in the risk of common complex disorders/diseases (e.g., lung cancer); the complexity of various types of interactions, GxG and GxE (e.g., schizophrenia); and the simplicity of the representation of environmental exposure, as typically captured by a single environmental factor. At the present time, there is no convincing support for the idea that delivering interventions based on individual genotypes improves the desired outcome. Yet, there are hopes that such examples will appear (Benner et al., 2014; Tucker-Drob & Harden, 2012), as, at least in developmental psychopathology, it has been suggested that "differential susceptibility may ideally lead to differential intervention and thus more effective treatment" (van IJzendoorn et al., 2011, p. 50). There is also hope that the biological interpretation of GxE will help the field connect currently unconnected dots (e.g., to understand in detail the acquisition of highly heritable skills, for example, academic skills, which require a specific type of environmental exposure for each individual).

Second, there are precautions. In particular, two scientific journals, *Behavior Genetics* (Hewitt, 2012) and the *Journal of Abnormal Child Psychology* (Johnston, Lahey, & Matthys, 2013), have established requirements to be met before manuscripts presenting candidate–gene main or interaction effects can be considered for review. These requirements reflect many of the caveats of the field that we have discussed in this chapter. Thus, 15 years of GxE studies have taught the field to be particularly sensitive to the methodological aspects of research in general and the reproducibility of the results in particular.

Third, there are commentaries. This chapter was conceived as a constellation of observations from the literature on GxE, which is large and continues to grow, regardless of precautions. Although hopes for GxE remain high, so far, their realization has, in general, not risen to the level of our expectations. If anything, this discrepancy, as well as the numerous issues discussed in this chapter, "provides significant reason to pause for reflection" (Eaves, 2006, p. 1).

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APPENDIX

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CHAPTER 9

Genetics and Family Systems: Articulation and Disarticulation

DAVID REISS

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This chapter focuses on the rapprochement between genetics and the social sciences in the study of the family. This rapprochement began nearly a century ago and has accelerated in the last decade. This rapprochement has revised our concepts of family development, of how its subsystems influence one another and how the family shapes development of its child and adult members. This rapprochement extends into family-level interventions designed to treat individual and relational disorders or for preventing them. However, despite nearly a century of intellectual transaction between social and genetic approaches to the family system there remains troublesome disarticulation between the two perspectives. Moreover, there is notable disarticulation within the domain of genetic analyses between quantitative (twin and adoption methods) and molecular approaches.

GENETICS AND THE SOCIAL SCIENCES: A HISTORICAL SKETCH

The rapprochement achieved so far emerges from a long, and sometimes troubled, history of the connection between genetics and social science. It is now possible to recognize significant turning points in a century-long history of combat, truce, and alliance between these two essential approaches to the study of human development. The purpose of this review is to outline how this emerging rapprochement of social and genetic analysis has reshaped our understanding of the family and to suggest the practical significance of this revised view. We also suggest that rapprochement has helped reshape our view of genetics and, while not a primary focus of this chapter, some of these changes will be noted in order to gain a better understanding that—in the rapprochement of two lines of work—both the science of genetics and of family systems has been irreversibly altered.

As we note later, the systematic application of genetic principles to understand emotions and behavior extends back millennia. However, we lack a published history of behavioral genetics, as this field of inquiry is now termed, although there have been preliminary efforts (Gottesman, 2008; McGue, 2010). Moreover, there is no systematic effort to review the history of the transactions between

behavioral genetics and social science. In this vacuum several assumptions have arisen; among the most important of them is a view that social science is the older, softer, and less coherent discipline and that its inferences about families and human development must be significantly revised in the light of the much newer discipline of genetics. In this chapter, we will review areas where genetic studies require major revisions in thinking about the family. However, a systematic history of the interplay of genetics and social science might offer a different perspective: both the formal study of behavioral genetics and of social science have their roots in the late nineteenth century and each prodded the other to change during the ensuing decades.

The ancients had a firm practical grasp of both genetics and family systems. Darwin in *Variations in Plants and animals under domestication* (Darwin, 1920 (1868) documented the acumen of the ancients in cross breeding. He cited the thirtieth chapter of Genesis, where Jacob exacts revenge on his father-in-law by the selective breeding of Lavan's sheep (and became wealthy by keeping the best). Further, after Darwin praises the keen observations of and implicit knowledge of heredity by British animal and plant breeders, he cites Plato, Alexander the Great and Virgil for equal acumen. The Book of Genesis also provides evidence of the keenest observations of the interplay between family process and social convention. It would be hard to find in current accounts a shrewder appreciation of family social systems than the story of Tamara's successful seduction of her father-in-law, an account interleaved between two halves of the sage account of the interplay between parent–child and sibling relationships in the story of Jacob, Joseph, and his brothers.

At what point does keen observation and intuitive understanding of lawfulness of biological and social processes shade into science? While this question may give way to endless, and some might argue fruitless, philosophical debate there seems little doubt that the exacting experiments with peas by Gregor Mendel marks a starting point for scientific genetics. Mendel presented his results to the Natural History Society of Brunn in 1865. The society published his paper the following year (Mendel, 1948 (1866)) in their journal to which a large number of European scholarly libraries subscribed. Further, Mendel was said to have distributed many reprints of his paper and drew attention to it in scientific correspondence (Hunter, 2000). However, it was not until 1900 that Mendel's work was recognized and highlighted by the German botanist, Carl Correns (Correns, 1950). By this time a searching and rigorous social science was well underway as exemplified by the remarkable study of the social factors in suicide by Emil Durkheim (Durkheim, 1951 (1897)). With the same rigor that Mendel sought to illustrate the independent assortment of heritable traits of the pea plant so did Durkheim painstakingly attempt an isolation of factors of social cohesion—in religion, family life, and political stability—that prevented suicide. As we now understand the analysis of covariance, confounding, and counterfactuals, Durkheim understood that testing his thesis required accounting for the potentially confounding role of mental illness, alcoholism, heredity, season, and geographical location. Well before these historically decisive publications by Corrans and Durkheim, Francis Galton, with his strong interest in both heredity and life circumstance, published the first paper on the use of presumptively identical twins to identify sibling specific experiences in life that led to differences in their competence in adult life (Galton, 1876), a phenomenon that now goes by the awkward name *nonshared environment* and is investigated using the same strategy.

THE TWIN METHOD AND THE EQUAL ENVIRONMENTS ASSUMPTION

The current age of behavioral genetics, however, had a very clear starting point: the discovery of the twin method. As Rende, Plomin, and Vandenburg (1990) pointed out, the first use of the twin method—as we know it today—was by the Stanford graduate student Curtis Merriman. His was the first of many major advances in behavioral genetics to be developed by a graduate student. Merriman published his thesis in 1924 to argue first, that there were two types of twins: fraternal and duplicative. Then he demonstrated that the correlation on intelligence tests between twins was higher for the latter. Since there were no agreed on criteria for identifying duplicative twins he knowingly used a short cut that blunted his analysis. Opposite-sex twins must be fraternal and among same-sex twins roughly half are duplicative. Hence, a comparison of same-sex versus opposite-sex twins should provide a lower bound for estimating genetic influence on intelligence. Rende and his colleagues also underscored an even more direct use of the twin method by the German dermatologist Herman Siemens who, in 1924, directly compared concordance rates and correlations between identical (one egg as he termed them) and fraternal (two-egg) twins. Siemens understandably focused on skin conditions but also reported on children's mental capacities and school performance. His 1927 paper anticipates modern-day diagnosis of twinships

specifying physical characteristics that are likely to be identical in one-egg twins (Siemens, 1927).

In the two decades following Merriman's (1924) and Siemens' (1927) path breaking advances the twin method was applied to a broad range of human variability. Perhaps none were as controversial as those of Franz Kallman, who estimated high heritability of schizophrenia from comparing concordance rates of monozygotic (MZ) and dizygotic (DZ) twins (Kallmann, 1946). Conflict between the study of families as social systems and the study of genetics reached a fever point in the ensuing years because family systems researchers proposed an entirely alternate theory of the origins of schizophrenia as a disorder shaped by abnormal interactions in the family.

The most influential and enduring social formulation was that of Margaret Singer and Lyman Wynne, who developed a family process concept of *transactional thought disorder*. Parents' communication style, particularly their vague, amorphous, and shifting descriptions of ambiguous stimuli, could induce thought disorder and ultimately schizophrenia in their children. These parental patterns could be readily observed in the parents' responses to Rorschach blots. Singer and Wynne could, using blind coding of parental communication deviance and child's thought disturbance, successfully identify parents with a schizophrenic offspring (e.g., Singer & Wynne, 1965). Their argument for the social transmission of schizophrenia was indirectly buttressed by a stream of attacks on the twin method, mainly by family clinicians and researchers (Jackson, 1960), criticism that continues (Joseph, 1998, 2001). Critics compiled evidence that identical twins were treated much more similarly by their parents than were fraternal twins and hence differences of between-twin correlations between the two groups of twins reflected environmental rather than genetic influences. As strident as this debate became, it also set the stage for an extended process of scientific conflict resolution since both sides, the geneticists and the environmentalists, could agree that the validity of key assumptions of the twin method were not only critical but also testable. The fundamental assumption of the twin method was that the environments (social and physical) of DZ twins were as correlated as those of MZ twins: *the equal environments assumption*.

Thus, an early order of business was the resolution of debate about the equal environments assumption of the twin method, an endeavor that reflects equally the work of social scientists and geneticists. The first step towards exploring the equal environments assumption was a more precise definition of this assumption. Clearly, family researchers were correct about the special treatment of MZ twins: they were more frequently dressed alike, had names that went together such as Jane and June and were more likely to be confused by family members and strangers alike. But if estimates were of, say, the heritability of schizophrenia, could it be argued that clothes, first names, or even being confused with one's sib are plausible etiologies of schizophrenia? Moreover, MZ twins might have more correlated environments because they are genetically similar (Eaves, Foley, & Silberg, 2003). For example, babies with irritable temperaments evoke annoyance or withdrawal of their parents. If this temperament is heritable then evoked reactions of parents will be more similar for MZ than DZ twins because the former are identical. Thus, the definition of the equal environments assumption focused on the equality of correlated environments plausibly linked to the behavior under investigation that do not arise as a consequence of the twins' genotype. Stated thusly, the equal environments assumption is not easy to test by straightforward computations in traditional twins studies. Two strategies, however, have demonstrated its validity.

The first has been analysis of twin samples where twins or their parents or both have misperceived their zygosity. Usually, it is MZ twins that are misperceived as DZ though the reverse sometimes happens. Early studies made efforts to correctly diagnose zygosity through fingerprinting (Goodman & Stevenson, 1989) or blood typing (Scarr, Scarf, & Weinberg, 1980) and recent studies have added more elaborate genetic testing (Conley, Rauscher, Dawes, Magnusson, & Siegal, 2013). All studies published thus far, using this approach, have shown that twin misperception does not materially affect heritability estimates: MZ-DZ differences are the same or greater in genetically diagnosed twins as they when the distinction is made only by the parents' or the twins' perceptions.

A second strategy provides even more persuasive evidence: the analysis of twins reared apart. In two separate samples (Bouchard, Lykken, McGue, Segal, & Tellegen, 1990; Pedersen, Plomin, McClearn, & Friberg, 1988; Plomin, Pedersen, McClearn, Nesselroade, & Bergeman, 1988) correlations between MZ twins reared apart were equal to, or nearly so, for many but not all measures of temperament, personality, cognitive measures, and a range of physical measures such as height and blood pressure.

These important confirmations of the equal environments assumption should have allayed the major concerns of social scientists studying the families although it needs testing continuously as the twin method is used in new domains of study where the equal environments assumption might not hold. Moreover, other assumptions lie beneath the standard computations of the twin method

that need constant examination including the assumed absence of notable interaction of the environment with a subjects entire genotype and no genetically-based mate selection in the parents of the twins.

THE ADOPTION METHOD AND SELECTIVE PLACEMENT

There are two different designs that capitalize on the natural experiment of adoption. Both involve comparing a characteristic of the parent, or the environment shaped by the parent, with characteristics of the child. In one design, adoptive parents and their children are compared and this comparison is contrasted with identical comparisons between a second group: parents rearing their biological children. A second, more difficult design, recruits birth parents who have placed their child for adoption at birth or very soon thereafter. Comparisons between the birth parents and the child are contrasted with those between the adoptive parent and their child. While the child may be placed at birth, the biological mother cares for her child for 9 months of pregnancy so that potential effects of prenatal rearing must—where possible—be ruled out. A recent design, to be discussed later, capitalizes on the new technology of in vitro fertilization. Mother-child comparisons are made between two groups: one where the mother's own egg is fertilized and then implanted in her womb and another where a donor's egg is implanted (Rice et al., 2009).

The first use of the adoption design was published only three years after Merriman and Siemens published the first use of twin studies. In 1927, Barbara Stoddard Burks, a psychologist and student of Lewis Terman, published an elegant paper comparing adoptive parents' intelligence scores with their adopted children and contrasted that with a closely matched group of biological parents raising their own children (Burks, 1927). This remarkable report recognized that biological parents provided both environmental and genetic influences whereas adoptive parents only environmental. Where parent–child correlations for the biological group exceeded those of the adoptive group, she reasoned, the difference represented the role of genes in parent–child transmission. Moreover, she recognized that parental intelligence was a limited measure of environmental influence on children and thus included a culture index of the home that included parental education, interests, and the size of their library—a measure that anticipated current and widely used measures of the home environment (Caldwell & Bradley, 1978). Finally, Burks recognized that valid inferences drawn from the adoption design assume that the adoption process does not selectively place children in order to match characteristics of the birth parents—say intelligence, interests, or occupational background—with those of the adopting parents. The *selective placement assumption* is logically equivalent to the equal environments assumption; if it is violated results will seriously overestimate genetic effects. In presenting the results of this prescient paper, Burks exploited a special advantage of the adoption method: the capacity to directly assess the environmental effects of parental characteristics and of the home environment on child development. She found evidence that both genes and environment contributed to variation in child IQ.

Two teams independently carried out the first use of the adoption method for the study of the transmission of psychopathology from parents to children. Leonard Heston, who at the time of his study was a psychiatric resident, reported a comparison of the adopted away offspring of a group of mothers with schizophrenia, hospitalized in Oregon, and a matched control group born to mothers without major mental illness. The children were placed at or near birth in a foundling home or with a family; the latter included some who were relatives of the mother with schizophrenia (a potential confound in an otherwise remarkable effort by an investigator taking his first step in research). Heston reported a preponderance of psychiatric problems in the offspring of schizophrenic mothers (Heston, 1966). At the time Heston was tracking the offspring of psychiatric patients after their Oregon hospitalization, Seymour Kety, Paul Wender, David Rosenthal, and Fini Schulsinger were tracking adopted offspring of schizophrenic female patients in Denmark and also both the biological and adopted relatives of the adopted offspring who became schizophrenic. They reported a preponderance of psychopathology in the offspring of the schizophrenic parents (Rosenthal et al., 1968) as well as in the biological but not in the adoptive relatives of adopted offspring who developed schizophrenia (Kety, Rosenthal, Wender, & Schulsinger, 1968). These data were presented at an epochal meeting in Dorado Beach, Puerto Rico where Heston reported additional data from his study showing no effect of the rearing conditions of his adoptees—institutional care versus family care—on the psychopathology he measured (Heston & Denney, 1968). The cumulated evidence argued for an important role of genetics in the parent-to-child transmission of schizophrenia, entirely circumventing the weaknesses of the twin method. However, these investigators also concluded that that there was little evidence that rearing

played any role in schizophrenia. Heston showed no effect of the extreme variation between foundling-reared and family-reared adoptees, and the Kety group found no excess of schizophrenia and related disorders in the adoptive parents.

The impact of these presentations and their conclusions were particularly dramatic since they directly followed a summary at Dorado Beach by Lyman Wynne of his many studies showing an association of communication deviance in parents with their offspring's schizophrenia (Wynne, 1968). Although Wynne was circumspect about the etiological significance of his work, the overwhelming impact at the time was that genetics were important and the social origins of this disorder were, at the very least, unproven. However there were serious flaws—clear now after more than 40 years—in the arguments of both camps.

The Danish and Oregon teams did not recognize that institutional versus family rearing—the key comparison in the Heston report—might not be the decisive environmental contributor to schizophrenia. (The effects of institutional rearing on child development were clarified in a much later adoption study by Michael Rutter and his colleagues (Rutter & O'Connor, 2004) where the effects were not psychotic disorders but on cognitive development and on promiscuous attachment to strangers.) Similarly, the diagnosis of schizophrenia in a rearing parent—the focus of the Rosenthal group—was not necessarily an index of a home environment specifically pathogenic for schizophrenia. Both teams missed the opportunity to do a simple cross tabulation to detect the possibility that a poor rearing environment might enhance the impact of genetic liability—however crudely measured—although the small samples were vastly underpowered to test for statistical interactions.

For their part the Wynne group underestimated the importance of the genetic relatedness of the parents and children they studied. While they viewed parental Rorschach responses from an interpersonal perspective their measures might reflect only the behavioral expression of the same genes in the parents that, transmitted to their children, enhance their liability for schizophrenia. Now called *passive gene–environment correlation*, this form of parent–child transmission is a major counterfactual to all studies seeking to establish a causal link between family process and child development where parents and children are genetically related. Interestingly, the adoption design provides a uniquely direct method for estimating the importance of passive gene–environment correlation. For example, using the same adoption design as Barbara Stoddard Burks seven decades later, McGue and his colleagues reported an association between parental alcohol dependence and impulsive and delinquent behavior in their offspring. However, this association held only for biological parents rearing their own offspring and not for adoptive parents and their children. The findings suggested parental alcoholism was not an environmental risk factor for offspring behavioral problems but that genetic factors influencing alcoholism in parents were passively transmitted to children where those same genetic factors impaired the offspring's behavioral self-control (King et al., 2009).

There were important epilogues to this dramatic Dorado Beach confrontation, a confrontation that may be among the most pivotal moments in the history of developmental psychopathology. Lyman Wynne partnered with the Finnish psychiatrist Pekka Tienari to replicate and extend the Danish and Oregon studies. Tienari tirelessly tracked children of Finnish schizophrenic mothers placed for adoption at an early age and developed a closely matched control group of adoptees whose biological parents were not psychotic. The ultimate sample was almost five times larger than the Danish and Oregon studies and included measures of communication deviance as well as other direct measures of family process. Assembling the sample took years, and it was not until 30 years after the Dorado Beach conference that the first major results were published. Parental communication deviance did not have a main effect on schizophrenia, but it did have decisive moderating effect on the genetic liability for thought disorder in the adopted offspring. At high levels of communication deviance offspring with genetic liability showed *more* thought disorder than did offspring without genetic liability, but at low levels of communication deviance the offspring with genetic liability showed *less* thought disorder than controls (Wahlberg, Wynne, Oja, Keskitalo, et al., 1997). Wynne and his colleagues recognized this pattern as one formulated by Kendler and Eaves 9 years before; Kendler and Eaves (1986) termed it *genetic control of sensitivity to the environment*. Individuals with this sensitivity genotype would show greater adaptation that those without the genotype under favorable environmental conditions but do worse under unfavorable conditions. This form of gene–environment interaction was reintroduced by Jay Belsky and colleagues with the term *differential susceptibility* (Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Belsky & Pluess, 2009) apparently without recognizing either the original contribution of Kendler and Eaves or the findings of Wynne and Tienari. Perhaps because Belsky and his colleagues were better known in developmental psychology their papers became the basis for a wide range of research on differential susceptibility

gene–environment research in developmental psychology and psychopathology.

The Dorado Beach conference had a second long-term epilogue, one that led to a major disarticulation of genetic and family process studies that rivaled that of the 1960s. The data from the Danish and Oregon studies were, legitimately, very encouraging to research on the genetics of schizophrenia. After all this was an entirely different method than the twin study that was still under a cloud of methodological concern. Although a review of subsequent work on the genetics of schizophrenia is well beyond the scope of this chapter, it is important to recognize that many subsequent twin studies established that the genetic factors contributed well over half the variance for the schizophrenia diagnosis, that the search for specific genes—selected in advance of study as candidates—was unsatisfying and that a current focus is on genome-wide association studies (GWAS) using samples that exceed 30,000 individuals (for a review of the current status of this field along with a commentary on family and other environmental effects see Iyegbe, Campbell, Butler, Ajnakina, & Sham, 2014). Improved methods of genotyping have identified over 100 gene variants that are reliably associated with the schizophrenia phenotype; all these methods assume that important genes in the pathogenesis of schizophrenia enhance *liability to illness* and not, as initially suggested by Kendler and Eaves and demonstrated in the finding of Wynne and colleagues, that important genes might enhance *sensitivity to environment*. Comprehensive reviews of the etiology of schizophrenia acknowledge the large role of a broad range of prenatal and postnatal environmental social factors associated with schizophrenia. Some mention the work of Wynne (Tandon, Keshavan, & Nasrallah, 2008), and some do not (Iyegbe et al., 2014). To encompass the probability that environmental factors might additively or interactively contribute to GWAS analyses in understanding the pathogenesis of schizophrenia, GWAS researchers have proposed polygenic risk scores to summate the genetic component of such multifactorial inquiry. However, these scores reflect only genotypes identified as enhancing disease liability. The fundamental disarticulation here is that family processes researchers—beginning with Wynne and continuing with Belsky and those family researchers influenced by his work—have called attention to a functional significance of genotypic differences that, ironically, was first delineated by two behavioral geneticists, that is, the function of increasing sensitivity to environmental differences. Distressingly, this idea has been pushed to the margins in the current mammoth and hugely expensive search for vulnerability genes.

Leaving aside this very substantial disarticulation, let us summarize what the adoption design has contributed to the emerging articulation of genetic and family systems studies. First, by verifying findings on genetic influence of twin studies it has foundational status in all the more recent work on the genetics of psychopathology. Second, it has permitted more accurate estimates of the role of parenting and the family environment in the development of offspring. The original Burks study illustrates the delineation of family factors that have a substantial effect on child competence controlling for passive gene–environment correlation. The much later adoption work of McGue and colleagues illustrated the equally important weakening of a popular environmental theory positing parental alcoholism as an environmental risk factor for emerging impulsive disorders in offspring (King et al., 2009). Third, the adoption design provided a distinctive, direct way to demonstrate how the family environment moderates genetic risk for psychopathology. And finally, the adoption design provided a particularly graphic illustration of the role of genes in enhancing sensitivity to the environment; in doing so it offered an enticing and provocative challenge to mainline genetic search for liability genes to which the great majority of genetics research on psychopathology has not responded.

QUANTITATIVE GENETICS AND FAMILY THEORY: NONSHARED ENVIRONMENT, GENETIC INFLUENCES ON ENVIRONMENTAL MEASURES, AND REINTERPRETING ENVIRONMENTAL EFFECTS

We have already seen that the assumptions of the twin method were being rigorously explored by 1980, and as early as 1968, the adoption method was buttressing the conclusions of twin studies on the heritability of psychiatry's most severe disorder, schizophrenia. These two techniques, because they estimate the relative weights of all genetic influences and all environmental influences, are referred to as *quantitative genetics,* and in the 1980s the results of their use began to challenge, in some cases severely so, theories about families and their influence on child development. Three notable challenges will be reviewed here: the concepts of nonshared and shared environmental influences, genetic influences on measures of the family environment, and the role of genes in explaining the association of variables measuring the family and those measuring the psychological functioning and development of its members.

The Nonshared and Shared Environment

As early as 1932 a curious pattern of findings began to emerge in twin studies. In a remarkably well-done twin study, Harold Carter, an assistant professor in a quantitatively sophisticated department of education at Berkeley, published a twin study of personality. He found, for example, that correlation for neurotic tendencies was .62 for identical and .36 for fraternal twins after correcting for measurement unreliability (very small in his studies) and range restriction. Ordinarily, we obtain a crude estimate of heritability by subtracting these correlations and then doubling the difference (since the difference between MZ and DZ twins covers only half of the possible range of genetic differences between sibs). Here we get the value of 56% suggesting the variance attributable to not-yet-identified or anonymous genotypic differences in this and comparable samples. That leaves 46% attributable to anonymous environmental differences. Since these values are already corrected for measurement error, 1–.62 is a direct estimate of the environment that makes siblings different, the awkwardly termed *nonshared environment*. In this case the value is 38%. Since the total variance attributable to environmental causes is 42% this means that .38/.42, or 90%, of the environmental effects are those that make siblings within the same family different. Many subsequent studies found similar patterns but John Loehlin and Robert Nichols were the first to emphasize how challenging these findings were to most family theories (Loehlin & Nichols, 1976).

The major paper in the evolution of this line of reasoning was a review by Robert Plomin and Denise Daniels in 1987 (Plomin & Daniels, 1987). They emphasized that, as in the early Carter paper, evidence for the singular importance of the nonshared environment has been lying in plain sight in twin studies of personality, cognitive capabilities, and psychopathology. They also summarized the results of several adoption studies where the sample included families with two children adopted from different biological parents. If family attributes common to children in the same family influence child's temperament, personality or cognitive abilities then genetically unrelated siblings—adopted very early in childhood—should show correlations with each other at well above chance levels and these correlations should increase the longer they are exposed to these conditions. In fact, in these special samples, between-sibling correlations were small, often statistically insignificant and became even smaller the longer adopted siblings were members of the same adopting family. If measurement error is taken into account, differences between MZ twins are arguably the most direct way of assessing nonshared environmental influences. However, by definition, twins are identical in age. Thus, small differences between them—either in non-heritable physical features, temperament or environmental experiences, may be used by them and their parents to differentiate one MZ twin from the other and lead to an uncommonly high influence on their differences in their developmental trajectories. Thus, the MZ twin method may overestimate effects of the nonshared environment. Two studies using ordinary siblings support this idea: sibling correlations on several measures of adjustment tend to decrease as age differences between siblings decrease (Feinberg & Hetherington, 2000; Schachter, Gilutz, Shore, & Adler, 1978). Thus, adoption designs provide an important check here on twin findings as they did in the genetics of schizophrenia. That is, correlations among genetically unrelated siblings provides a direct measure of the shared environment; adding this to estimate of heritability derived from comparisons of MZ and DZ twins provides an alternate approach to estimating the nonshared environment. Years after the influential Plomin and Daniels review, Reiss and colleagues derived estimates of the nonshared environment on height, weight and vocabulary in adolescents using full, half and step siblings and correcting for between-sibling age differences; if anything estimates of the magnitude of nonshared effects were greater than those using just MZ and DZ twins in the same sample providing further support for the estimates by Plomin and Daniels (Reiss, Neiderhiser, Hetherington, & Plomin, 2000).

For studies of family systems there were three important sequelae of the landmark Plomin and Daniels paper. First, twin studies of individual differences in both behavioral and medical measures have been consistent, for the most part, in showing that environments that make siblings different in the same family outweigh, at a single time of observation, the importance of between family differences that would render siblings similar (see a recent summary by Plomin, 2011).

A second sequel to the Plomin review were efforts to identify specific environmental factors that might differ between siblings and be associated with outcomes for children, adolescents or adults. Researchers have frequently used the MZ twin difference measure although limitations in this design, as noted, surround these results with caution. If a difference in the environmental measure is associated with a difference in a measure of adjustment this suggest a nonshared effect. For example, Pike and her colleagues found—in a cross sectional MZ difference study—that differences in parental negativity directed at the adolescent

were associated with differences in both depression and antisocial behavior (Pike, Reiss, Hetherington, & Plomin, 1996). More convincing, of course, are longitudinal studies that ether control for measures of adjustment in the first wave or directly employ cross lag analyses. Controlling for child antisocial behavior at age 5, Caspi and colleagues reported an association between maternal expressed emotion at age 5 and child antisocial behavior at age 7 (Caspi et al., 2004). Likewise, using a longitudinal MZ twins design, with 4,508 twins, Viding and colleagues successfully predicted differences in 12-year-old children's conduct problems but not child callousness from differences in negative parental discipline 5 years previously. The associations were small, accounting for about 1% of the variance. More complex findings using the MZ twin method have been frequent. For example, Guimond and colleagues predicted differences in kindergartners, social reticence from differences in maternal and paternal over protectiveness and hostility at age 30 months (Guimond et al., 2011). The results were complex: main effects were found only for boys, and only girls showed an interaction of parenting differences scores with paternal depression. To add to the complexity, in a multipanel study Charlotte Cecil and her colleagues found reciprocal relationships between harsh parenting and self-control in children followed from age 3 to 12 (Cecil, Barker, Jaffee, & Viding, 2012). Child effects on parenting were at least as prominent as the reverse. Indeed, some studies conclude that nonshared parental environments are a consequence of sibling differences in adjustment (Vitaro et al., 2011). The MZ difference method has been used to study nonshared environments beyond the family of procreation. For example, Lichtenstein studied twins discordant for recent loss of a spouse to show that this later life differential spousal loss was associated with differentia mortality rates (Lichtenstein, Gatz, & Berg, 1998). Vitaro and colleagues showed that differential experience of aggression in friends anticipated differential aggressiveness in the MZ twins (Vitaro et al., 2011).

A second approach to exploring the role of specific nonshared experiences, *multivariate genetic modeling*, begins with an observed association between an environmental variables and a specific outcome (e.g., a contemporaneous association between maternal negative parenting and adolescent depression of .57). Multivariate genetic modeling allows a decomposition of this covariance into a portion that can be attributable to (1) the influence of the children's genotypic differences both on negative behavior of their parents toward them (a topic to which we will return) and on the child's depression; (2) the shared environment common to parent and child measures; and (3) the nonshared environment common to both. Reiss and his colleagues conducted the most comprehensive survey to date, using this method, of the role of specific nonshared factors. They used this technique to study parents, siblings, peers, and other nonfamily influences on both maladjustment and the positive development of adolescents and combined data from observer, child and parent reports (Reiss, Neiderhiser, Hetherington, & Plomin, 2000). Of the 86 contemporaneous associations examined, 29 showed a statistically significant role for the nonshared environment, mostly for maternal and paternal negative parenting and its association with both psychopathology and positive outcomes such sociability, social responsibility and self-worth. In the case of maternal negativity and adolescent depression, 10% of the covariance was attributable to the nonshared environment. Cross-lagged analyses, across three years of adolescence, showed a more diminished role for the nonshared environment almost certainly because this class of influences tends to be unstable across time in children and adolescents (Blonigen, Carlson, Hicks, Krueger, & Iacono, 2008; Ganiban, Saudino, Ulbricht, Neiderhiser, & Reiss, 2008; Larsson, Larsson, & Lichtenstein, 2004; Reiss et al., 2000). Meta-analyses of siblings from longitudinal twin and adoption studies by Tucker-Drob and Briley (Briley & Tucker-Drob; Tucker-Drob & Briley, 2014) suggest that for cognition stable genetic influences may peak or even decline in the transition to adulthood. In contrast, stable nonshared influences continue to rise across development into old age. For personality, stable genetic influences tend to decline as stable nonshared influences rise in the transition to adulthood. In general, as indivduals age stable nonshared influences become at least as important as stable genetic influences.

Subsequent to the study of Reiss and his colleagues a number of investigators used multivariate models to evaluate the role of specific nonshared environments, again with a focus on parenting and child development. Most of these have focused on negative parent–child relationships and the development of poor self-control, impulsiveness, and aggression in children (Burt, McGue, Krueger, & Iacono, 2005; Jaffee et al., 2004; Knafo & Plomin, 2006; Larsson, Viding, Rijsdijk, & Plomin, 2008). The sibling specific experience of peer relationships and its relationship has also been tested in this paradigm (Button et al., 2007). In one case with sibling-specific peer experiences playing the preeminent role (Bullock, Deater-Deckard, & Leve, 2006), general genetic factors played the predominant role in most of the reported associations but, to a lesser degree, so did nonshared environment.

Perhaps the most notable success in exploring the nonshared environment is in adult rather than child development. In 1998, an influential paper by the criminologist John Laub and colleagues reported on a 25-year longitudinal study following boys at high risk for criminal behavior. They found that a broad range of childhood characteristics could not predict continuity of or desistance from adult criminal behavior but that men's attachment to a spouse had a strong protective effect (Laub, Nagin, & Sampson, 1998). This echoed findings from 14 years before when Michael Rutter and colleagues reported the apparent salutary effects of a favorable relationship with a spouse on adult women who had been institutionalized as children (Rutter & Quinton, 1984). Each study examined only one child in a family and used standard procedures to ask whether the effects observed could be attributed to the effect of the marital relationship or whether they reflected hidden strengths of the high-risk individuals that enabled them to form these bonds. Genetically informed designs permit us to revisit this critical issue of selection versus influence from a novel perspective. For example we may follow the marriages of sibling pairs. If one twin has a happy marriage and the other does not, is there an effect of this difference on differences in their adjustment *and is this effect the same for MZ and DZ twins?* If both conditions are met findings favor an effect of marriage over an effect a heritable factor in the twins that favors a happy marriage. Erica Spotts and her colleagues reported the first cross sectional studies linking marital satisfaction to both depression and positive well-being in adult twin women an effect of marriage although, lacking longitudinal data, the effect might have been the other way around (Spotts, Neiderhiser, Ganiban, et al., 2004; Spotts, Pederson, et al., 2005). However, a prospective study reported by Burt and colleagues (2010) strengthened inference of a causal effect of marriage. Later in this chapter we will return to the significance of the nonshared environment for the study of adult development.

A third sequel to Plomin and Daniel's (1987) paper is the increasing number of reports on the importance of the shared environment. These reports have softened the blunt conclusions of the Plomin and Daniels review. These newer studies delineate environments shared by siblings that are associated with their psychological development and adaptation. These include reports on support from relatives in adult subjects (Agrawal, Jacobson, Prescott, & Kendler, 2002), types of peer groups chosen by adolescents (Tarantino et al., 2014), early substance abuse (Walden, McGue, lacono, Burt, & Elkins, 2004), adolescent delinquency (Burt, McGue, Krueger, & Iacono, 2007), conduct disorder, attention-deficit/hyperactivity disorder (ADHD), and oppositional disorder in adolescents as well as their co-occurrence (Burt, McGue, Krueger, & Iacono, 2005), cognitive performance in early childhood (Petrill & Deater-Deckard, 2004), and for measures of autonomy and sociability in adolescence (Reiss et al., 2000). An adoption study, published well after the Plomin and Daniels review, took a second look at the comparison of full biological sibling and genetically unrelated adopted adolescent siblings (Buchanan, McGue, Keyes, & Iacono, 2009). Across six measures shared environment accounted for about 20% of the total variance. In a recent publication, Alexandra Burt has clarified why this approach provides a more direct and unbiased estimate of shared environment (Burt, 2014) Results showed notable correlations for adopted adolescent siblings not only for externalizing problems, consistent with more recent twin studies cited above, but also for IQ. This contrasts with the finding from Scarr and Weinberg (Scarr & Weinberg, 1978) of near zero correlations for the same group of siblings, a finding crucial to the argument of Plomin and Daniels. The Scarr and Weinberg sample were approximately 5 years older, suggesting the possibility that the influence of environments siblings share wanes as offspring age.

Perhaps the most interesting result to date in this quest for shared environmental effects is the unheralded role of sibling relationships. Insofar as sibling relationships are reciprocal, the relationship constitutes a shared environment for each sibling. If one sibling's aggression towards a co-sibling is fully reciprocated then both share an aggressive sibling environment. If between-family differences in this shared environment are associated with measures of adjustment for each sibling, correcting for genetic effects, then we can estimate a shared environmental influence on sibling adjustment, especially with the use of longitudinal data.

Twin data provide creditable evidence for this effect but so do adoption data. For example, McGue and colleagues—in an adoption design—found that parental alcoholism problems were related to adolescent offspring alcohol use only when comparing biological parents and their offspring but was absent for adoptive parents and their adopted children; in sharp contrast sibling effects held in both groups (McGue & Sharma, 1995). Indeed, between-family shared sibling environments have regularly been associated with the development of aggression and of substance use in each sibling, controlling for genetic effects, in many twin studies (Natsuaki, Ge, Reiss, & Neiderhiser, 2009; Slomkowski, Rende, Novak, Lloyd-Richardson, & Niaura, 2005). A particularly striking set of findings comes

from the comprehensive study of adolescent twins by Reiss, Plomin, and Hetherington. To meet concurrent standards of family research they combined reports by both parents and the siblings themselves and observed ratings of videotaped sibling interaction in their own home to assess both warm and supportive relationship patterns as well those of conflict, hostility and physical abuse. They reported a total of 18 associations between these sibling measures and measures of adolescent psychiatric symptoms as well as positive attributes such as sociability, social responsibility and engagement in school and related activities. In 13 of these associations the *predominant* source of covariance was shared environment. This suggested that reciprocal relationships among siblings might constitute a shared environment crucial to the development of both of them. We will return to this finding in the next section as a prime illustration of unanticipated yield for family studies of data from a genetically informed design.

Genetic Influences on Measures of the Family Environment

In 1981 David Rowe was a young psychology assistant professor at Oberlin College. Although trained in behavioral genetics, Robert Plomin supervised his dissertation, and he became fascinated by the reports of family systems research. In particular, he was intrigued by reports that children's perceptions of how they were treated by their parents might be as predictive of their development as are observational measures of their parenting. He saw the twin method as a way of understanding this effect. If twin siblings were highly correlated in their perception of parenting, and there was little difference, between MZ and DZ twins then it might be the case that perceptions did reflect some aspect of parenting behavior as it actually occurred. Indeed, this is what Rowe found for most of his measures of perceived parenting save one: the twin perception of rejection by their fathers. Here, MZ twins perceived their father's rejection or acceptance much more similarly than did DZ twins even when their greater time spent together was accounted for. This suggested that the perception may have arisen more from heritable features of the twins themselves rather than from their parents. Rowe seemed little interested in this apparently aberrant finding (until later in his career) and family researchers even less so.

At the time Rowe published his study most family researchers were using direct observations of family interaction as a gold standard for measuring family process. For example, the meticulous work of Mishler and Waxler (1968) and Gerald Patterson (1982) and his colleagues were major influences on this standard. Thus, a report claiming genetic influence on subjective impressions of children would have carried little weight even if it had been more definitive (and had been read at all by family researchers). Thus a pivotal finding was that of Judy Dunn, the British developmental psychologist, and Robert Plomin; in their study biological parents rearing their own toddlers treated them more similarly than did adoptive parents treat their two children adopted from different birth parents (Dunn & Plomin, 1986). While there are many interpretations possible of this finding, two studies published 10 years later and in the same issue of *Developmental Psychology* and including meticulous observational coding of parent–child interaction, heavily weighted a genetic explanation. Xiaojia Ge and his colleagues (1996), in a small (45) sample of adoptive parents and their children at midadolescence, reported that the harsh parenting of both *adoptive mothers and of fathers* could be predicted by severe, hospitalizable externalizing psychopathology of the *child's birth parents* and this effect was mediated by antisocial behavior of the adolescents.

Alison Pike (1996) and her colleagues, using data from the Nonshared Environment in Adolescent Development study, used a much larger sample of twins, full sibs, half sibs, and unrelated sibs totaling 719 pairs of sibs and their families unselected for psychopathology in parents or children. They reported the same phenomenon: genetic factors that influenced negative parenting also influenced not only antisocial behavior but also depressive symptoms in a group of somewhat younger adolescents. Most importantly, these common genetic factors accounted for *most of the correlation between the measures of parenting and of adolescent adjustment*. Reiss and his colleagues (2000), using data from the same study in the most comprehensive investigation to date of the role of genes in explaining covariance between family variables and offspring development, studied the association of a range of parenting, marital, sibling variables and both psychopathology symptoms as well cognitive achievement, sociability, autonomy and self worth in a sample of 719 pairs of twins, full sibs, half sibs and unrelated sibs. Meticulous coding of observed interaction in the family's homes was combined with their self-report of relationships quality. Genetic factors common to parenting and child development and marital conflict about the child and development accounted for a substantial and often most of the covariance between the family and the offspring variable.

These data might have been regarded as uncovering one of the most astonishing and unacknowledged confounds in the history of developmental psychopathology.

Alternatively, it might simply reflect the relatively noncontroversial heritability not only of psychopathological symptoms but also of personal strengths such as self-esteem and autonomy. Thus, genetic influence on the covariance may reflect simply the reaction of parents to a child that has either developed a full-blown psychiatric syndrome or a very well developed prosocial and self-confident personality. Indeed, Richard Q. Bell (1968), in his highly influential paper on child effects on parenting, used genetic data of this kind as part of his argument. Analyses carried out by Neiderhiser and other colleagues in the Reiss group suggested a different scenario: heritable features of less well developed behaviors—perhaps temperaments—evoke parental reactions which, as a consequence of this evocative gene environment correlation, go on to accelerate the transformation of simple temperaments into syndromes of pathology or psychological health. Were that the usual case it would revive the notion of genetic *expression outside the* skin first formulated by the geneticist Kenneth Kendler (2001). That is, genetic information proceeds through the usual channels (DNA → RNA → protein → neural processes → behavior), but the next step is not simply a prodrome of a syndrome of adaptation or maladaptation. The next step it is a *social evocative behavior* and the development of an adaptive or maladaptive syndrome does not proceed unless evocation actually occurs (see Reiss & Leve, 2007, for a full exploration of this idea).

Follow-up twin studies partially confirmed the plausibility of this novel idea about genetic expression (see, e.g., Burt et al., 2005; Larsson et al., 2008; Tucker-Drob & Harden, 2012). However it has fallen to a currently ongoing prospective adoption design to delve more precisely into the precise sequencing and developmental timing of this outside-the-skin process. Data are drawn from the Early Growth and Development Study that is following, across infancy and childhood, over 500 adoption units consisting of a birth mother, two adoptive parents and a child placed for adoption at birth; birth fathers were also recruited for many of these families. In this study, for example, Harold and colleagues traced the genetic liability transmitted to four year olds by having birth mothers high on ADHD symptoms. By 4 years of age these children showed increases in impulsive behavior that evoked hostility towards the child from their adoptive mothers that appeared to amplify the impulsive behavioral style into ADHD symptoms age 6 (Harold et al., 2013). A similar sequence has been mapped from birth mother temperamental disengagement to social withdrawal by her placed child at 27 months to hostile responses by the adoptive mother to disrupted peer behavior at age 4 (Elam et al., 2014).

An intriguing conditional sequences was mapped by Fearon (2014) in this same research group: birth parent externalizing pathology to subjective feelings of maternal distress and incompetence by child age 9 months that persisted at least another 18 months at which time the sequence had led to child conduct problems. However this sequence occurred only in the presence of marital distress between the adoptive parents. To put the matter more graphically, marital satisfaction blocked this avenue of outside the skin expression of genetic influence as securely as methylation of a gene promoter site.

As we will see, molecular genetic studies are also beginning to map out similar sequences beginning with a known gene variant and extending through an evoked response from a parent and continuing with the evolution of a pattern of behavioral maladjustment. However, the unparalleled advantage of an adoption design is that these sequences start with behavioral syndromes in the parents of already established adaptive significance. For example, the Fearon report begins the sequence with variation in birth mother's externalizing problems including clinically diagnostic levels of antisocial personality disorders and substance abuse. We can then ask how are the genetic risks for these highly comorbid conditions first manifested in infancy, controlling for the effects of prenatal exposure to drugs, alcohol and smoke and the effects of birth mother's psychopathology on self care and obstetrical complications. The answer is important here: by 9 months these genetic risks are first expressed in dysphoric feelings *in the adoptive mothers* about their functioning as a mother. But these initial effects are already being offset by satisfying marriages. What heritable features in the child evoked this maternal dysphoria? Fearon and colleagues diligently searched among the usual suspects, temperamental features of the child, without success. We will return to this informative failure in a moment.

While these informative sequences of evocative gene–environment correlation are just being mapped out many studies have established the substantial effects of genetic factors on a broad range of environmental measures including peer relationships in childhood and adolescence and social support in adults (see Kendler & Baker, 2007, for a review). Many studies report substantial genetic effects on the probability of becoming married, achieving marital satisfaction, and getting divorced. (Jerskey et al., 2010; Jocklin, McGue, & Lykken, 1996; Johnson, McGue, Krueger, & Bouchard, 2004; Lykken, 2002; McGue & Lykken, 1992; Spotts, Lichtenstein, et al.,

2005; Spotts, Neiderhiser, Towers, et al., 2004; Spotts, Prescott, & Kendler, 2006; Trumbetta, Markowitz, & Gottesman, 2007). These results reflect not only genetic influences of a spouse's own behavior within a marriage but also evocative effects of one spouse's heritable qualities on the marital satisfaction of the co-spouse. In toto, many of the heritable characteristics that have evocative effects on marital and parent–child relationships can be attributed in part to heritable features of temperament and personality but across many reports these are accounting for, at best, a modest proportion of these effects (see the previously cited review, Jaffee & Price, 2007). While beyond the scope of this chapter, these data suggest a need to refine and reformulate our understanding of heritable features of children and adults that evoke responses from others. Beyond patterns of self-regulation, cognitive processing, organization of habits and sociability—encompassed in current schemes of temperament and personality—we will certainly want to consider in children genetically influenced individual differences such as differences in their subtler social cognitions, their physical appearance, their smell and their tactile sensitivity.

Returning specifically to the parent–child relationship, a recent meta-analysis by Ashlea Klahr and S. Alex Burt (2014) reviewing no fewer than 56 twin and adoption studies confirms substantial genetic effects on the parent–child relationship. Not only do they report robust evocative effects of heritable attributes of the child, but also there are notable genetic effects of the parents' genotypes on parenting behavior. David Rowe, (1981) the first to report genetic influences on how adolescents perceived their parents, might be astonished to see this extraordinary confirmation of his first, very tentative observation; regrettably his creative and penetrating work in behavioral genetics was cut short by his very untimely death.

Taken together, these findings of genetic influences on measures of the family environment constitute the starkest challenge to business as usual in both typical family studies and for most genetic studies as well. They make clear that models of family influence on offspring development are seriously misspecified without genetic information. First, despite Bell's (1968) challenge to the field over 45 years ago child effects in parent–child relationships are almost certainly underestimated. Indeed, inferences drawn from classical longitudinal studies and their consequent cross-lagged correlations between child factors such as temperament and parental factors such as hostile parenting are seriously weakened by these data. In this example, we can note that child temperament is only partial heritable; individual differences in temperament also reflect environmental influence including parenting. Child temperament at 3 months, for example, might be a proxy for variation in parenting at 1 month. In contrast, genotypically influenced behavior is tied to the child and evocative genotype environment correlation in this context is much more securely child based; children's genotypes are what they bring to human relationships and although genetic expression—within the cell nucleus and outside the skin—is sensitive to social influence, genotype is completely resistant to it.

Likewise, the effects of a parent's own genotype on his or her parenting, an inference we draw from twins who are parents, poses another challenge to traditional family research. Parents may treat children harshly in part because of their own genotype. When their genotypes are transmitted to their offspring the genotype of the child may be expressed as antisocial behavior. This *passive gene–environment correlation*, a phenomenon we have already noted in describing earlier studies of the transmission of schizophrenia, can masquerade as a direct social effect of parenting. Two genetically informed research designs directly address this possibility. The first are adoption designs that correlate a characteristic of a parent, (one that is thought to have a direct social impact on the child) with a measure of adjustment in the children and then compare these two correlation for birth parents and the children they are raising with adoptive parents and their adopted child. This is precisely the design of the first adoption study by Barbara Stoddard Burks. A second design focuses on children of twins, particularly twins who are discordant for the parental characteristic. For example, parental alcoholism is thought to have disruptive effect on parenting and on household routines and through these social mechanisms to increase the liability of impulsive behavior and alcohol use in offspring. If this were the case then the correlations between parents and children should be the same in biological and adoptive families.

To extend this example to children of twins, let us suppose we have sample of twins who are mothers and where there is a substantial number of these twin mothers who are discordant for alcoholism. In the case of MZ twins the child's aunt (the identical twin sister of the child's mother) is a genetic carbon copy of the child's mother. Thus, if the parental influence is entirely genetic then the child's liability should be the same no matter whether it his mother or his aunt who drinks; the liability for the child—in the case of the genetic transmission—should be less if his mother is a DZ twin. If the liability is social transmitted then the liability should only be among children of the drinking twin. As a recent review of children of twin studies (McAdams

et al., 2014) has shown, the pattern is quite distinct for parental depression and alcohol use. Social mechanisms are involved in the transmission of depression from parents to offspring although the reverse influence, the social effect of child psychopathology on the parent cannot be ruled out. However, the association of parental alcoholism with offspring alcohol use as well as with other forms of impulsive behavior is via genetic mechanisms with little evidence of the role of social processes. This corresponds to findings from adoption studies where parent–child associations of parental depression and offspring depressions (and other problems as well) are found almost equally in biological and adoptive families (Bauer et al., 2007; Marmorstein, Iacono, & McGue, 2012; Tully, Iacono, & McGue, 2008).

The refrain must now be familiar: the verification of an important finding in quantitative genetics by two radically different procedures: twin and adoption. As the McAdams et al. (2014) review illustrates, the children of twin design has been used for more direct measures of family process including marital conflict and parenting styles with evidence for environmental effects and passive gene–environment correlation depending on the family measure and assessment of the offspring. A more recent elaboration of the children of twins design—incorporating a second sample of children who are twins in the same analytic model—can now distinguish between three mechanisms of transmission: social, passive gene–environment correlation and evocative gene–environment correlation. Among other results these studies have confirmed the importance of evocative gene–environment correlation in the association of parental negativity and externalizing in adolescent offspring (Marceau et al., 2013; Narusyte et al., 2011).

A simple solution for controlling for passive gene–environment correlation—for estimates of parental social influence—is to study parents genetically unrelated to their children: adoptees. In this brief history of the interface of social and genetic research we encounter once again the pivotal role of adoption studies. Although excruciatingly difficult to design and execute, in comparison to twins studies, they are the most direct approach to controlling for the effects of passive gene–environment correlation.

We have reviewed an impressive body of data converging on two major ideas. In the shorter term the association between parenting and child development or between the parents' marital satisfaction and child development may be attributable to genetic factors common to both. In the longer term, the transmission of parental characteristics to children—including those that directly shape the child's social environment—may influence child development solely because the genes that influence the parentally-shaped environment also, when transmitted to the child, shape the child's behavior. Need every study of family life now require a twin or adoption design? We think not, but we will return to this topic briefly in the coda to this chapter.

Before concluding this section let us return to siblings for a final time to consider a paradox. By adolescence most genetically informed studies suggest that a great deal, if not most, of the covariance between many measures of parenting and measures of adolescent adjustment can be accounted can be accounted for by genes common to both. The reverse, several studies suggest, is true for sibling relationships. The covariance of measures of sibling adjustment with carefully measured qualities of the environment they provide for each other is attributable, in most cases, to shared environment. To put the matter another way for many family variables studied thus far, parents are important to adolescent development substantially because they amplify, as a consequence of evocative gene–environment correlation, heritable characteristics in their offspring. However, the environments created by siblings for themselves—through sustained patterns of interactional reciprocity—appear to have a main effect on adolescent adjustment independent of their genotype. Are genetic data suggesting that siblings are the tyrants of their families—for better or for worse? Not only are adolescents, by virtue of their genotype shaping their parents' behavior toward them, but also they are providing an influential world for themselves. While many parents of adolescents might agree with such a view a single report by Danielle Bussell and her colleagues on the Nonshared Environment in Adolescent Development project suggest a different scenario. She proposed that multivariate genetic modeling can be applied to covariance between measures of two family subsystems. Thus, the covariance between parent–child subsystems and the sibling subsystem can be decomposed into that attributable to common genes (the same genetic factors in the child that evoke parent–child hostility also evoke sibling hostility), to shared environment (between family differences in parenting style are associated with between family differences in sibling relationships independent of child genotype) or nonshared (the parenting hostility uniquely directed at one sibling is associated with that siblings hostility toward the co-sib independent of genotype of the child and of between-family differences in parenting). In examining both positive and negative interaction of mothers with adolescents and the sibs with each other Bussell found that it was the shared environmental components of the parenting–sibling relationship

association that was, by far, the most important (Bussell et al., 1999). Given the remarkable stability of the quality of parent–child relationships across adolescence (Reiss et al., 2000), it is reasonable to suppose that the quality of mother–child relationship measured at child age 14 reflects not only current status of that relationship but also its recent past. If that assumption is correct it might be said that the sibling relationship bears a memory of between family differences in parenting style and becomes an agency of that difference in emerging adolescence. We linger over these data because this commemorative function of sibling relationships has been little studied in classical family research but is an arresting example of possible new vistas on the family opened up by genetically informed design—new unless you count the Book of Genesis and its clear portrayals of the interleaving of parent–child and sibling relationships in the case of Rebecca, Jacob and Esau or, as noted, repeated in a second generation of the same family between Jacob, Joseph and his brothers.

MOLECULAR GENETICS AND THE FAMILY

How molecular genetics entered the field of family research. Thus far we have reviewed studies where the knowledge of genetics is inferred from correlations between individuals of known genetic relatedness. However, none of those studies identifies which of the 30,000 genes in the genome, or which noncoding regions, play a role in these effects. The lessons to be applied from this line of quantitative genetics to research on the human family are clear, challenging, and—for the most part—unheeded. The tools of quantitative genetics have been developed over decades; its inventors were psychologists, physicians and educators who wanted answers to practical problems. The assumptions behind the methods were vigorously investigated; different methods were used to arrive at comparable estimates and much of the work was conducted well under the radar of the broad reaches of biomedical science or public acclaim.

Just the reverse has been true of molecular genetics. Francis Crick, a physicist by training, and James Watson a biologist with an early interest in molecular genetics, collaborated to identify the structure of DNA in a highly competitive and conspicuous race with Linus Pauling among others seeking the same goal. Their one page publication in Nature (Watson, 1952) attracted worldwide attention as the discovery of the secret of life. Nine years later they became Nobel Laureates. Skipping quickly over the following decades of this history we come, 31 years later, to a raucous meeting of the biotechnology firm Cetus. There, Kary Mullis presented a poster describing his work, in collaboration with other Cetus scientists, on the double-probe technique that was to be the foundation of the polymerase chain reaction (PCR). Mullis, a tempestuous figure throughout his life, had to be separated from a physical brawl at that meeting. In contrast to the unpredictable temper of its prime developer, PCR emerged as a fully reliable tool for genotyping and spread rapidly throughout the biological sciences. Like his molecular genetic forebears a generation earlier, Mullis was awarded the Nobel exactly nine years after his first report of his findings. His trip to Stockholm also included a brush with the Swedish police (Rabinow, 1996) and left a continuing controversy over whether he deserved the award. PCR is fundamental to most of the molecular genetic studies published in the last decade relevant to understanding families. Subsequent phases of the story of molecular genetics hardly needs retelling but once again a monumental and widely publicized competition between the Celera Corporation and the US Federal Government led to the almost simultaneous announcement of the complete sequencing of the human genome, an accomplishment that has rapidly led to huge investments in searching the genome for both common and rare variants of genes that might be related to human disease including psychiatric disorders. These genome wide association studies, requiring mammoth samples, have been applied to social variables broadly considered (see a review and critique, Chabris et al., 2013) and even to a directly measured family variables (Butcher & Plomin, 2008). When a version of this chapter is written a decade hence, this tool may have yielded insight for the study of the family, but not yet.

Not long after it was developed, PCR was applied to the understanding of behavior. A working premise was that a single gene variant might lead to a single, well-specified disorder. Plomin, Owen, and McGuffin (1994) reviewed this work to highlight its utility in a restricted number of syndromes, mainly those of severe intellectual deficiency. They drew attention to an alternate conception of the relationship between genes and disorders, quantitative trait loci, where many genes operating in concert were necessary to influence the emergence of complex behavioral syndromes. They proposed that the severity or distinctiveness of a genetically influenced syndrome might be related to the number of these gene variants possessed by an individual, that some of the genes may not be necessary for development of a syndrome and that somewhat different gene sets may lead to the same disorder.

Several developments led to a major revision of this view. A new idea was that genetic variation might not be a necessary or contributory cause of complex human behavioral syndromes but rather that it rendered individuals

more or less sensitive to environmental variation. Quantitative genetics made the first contributions to this idea. As we have seen, this idea was formalized by Kendler and Eaves in 1986 and was demonstrated clearly in the work of Wahlberg (1997) and his colleagues on schizophrenia. Kendler and colleagues, using a population-based twin sample, showed that identical non-depressed twins of depressed women were more sensitive to stress, and subsequent depression, than were fraternal twin siblings of depressed co-twins (Kendler, Kessler, Walters, MacLean, et al., 1995). Long before, Cadoret observed that genetic liability for antisocial behavior rendered children more sensitive to adverse rearing conditions in their adoptive families (Cadoret, 1982; Cadoret & Cain, 1981; Cadoret, Cain, & Crowe, 1983). At the other end of the spectrum, animal research—often in mice—was able to deploy powerful knockout and transgenic methods to cause or identify specific genetic deficit and reverse these with highly targeted pharmaceuticals (e.g., Cases et al., 1995); these more highly controlled models suggested clearer links between single genes and more complex behavior such as aggression. Finally, variations in single genes seemed to have reproducible effects on the structure and function of the human brain as revealed by constantly improving brain-imaging techniques (Hariri et al., 2002). These lines of evidence prompted Stephen Suomi (working with rhesus macaques) and Avshalom Caspi and his colleagues (working with a large, longitudinal human study) to select particular genes for scrutiny. Suomi was the first to report on the association of a single gene variant with heightened sensitivity of infant macaques to variations in their early rearing environment. They focused on the statistical interaction of two variants of the rhesus version of the serotonin transporter gene with adverse early rearing environments, mother rearing or nursery rearing. Macaques with the inefficient gene variant showed the clearest effects of early rearing experience on early-appearing adaptive behavior, particularly activity patterns (Champoux et al., 2002). A the same time Caspi and colleagues reported children with the less efficient version of an x-linked gene, MAOA (similar to the gene well explored in animal studies), and who were exposed to maltreatment, developed significant aggressive behaviors (Caspi et al., 2002). A year later the Caspi group reported similar findings for the serotonin transporter gene; in this second report, young adults with the inefficient form of the serotonin transporter gene showed the effects of both childhood maltreatment and recent stress on the evolution of depression (Caspi et al., 2003). These findings attracted immediate and broad attention across all of biological science and in the public press as had other reports in the brief history of molecular genetics. They also attracted the attention of many behavioral scientists because these findings were drawn from the meticulous longitudinal Dunedin study, named for its place of origin on the South Island of New Zealand. The study had already yielded major findings in a group of almost 1,000 children followed from early childhood, and as this chapter is written, most of these children have been followed well into adulthood.

All three of these highly influential papers had three major features in common: the main effects of environmental adversity were very substantial; the main effects of the gene variants were tiny or non-existent; and the effects of the interaction were between the two. Strongly influenced by this paradigm, most subsequent work has examined single gene variants, analyzed singly or in very small numbers combined into polygenic risk scores, as *indices of individual differences in response to environmental variation*. That is, almost all subsequent work has focused on genetically influenced *receptive capacities* of individuals in families. In contrast the robust evidence for quantitative genetics of very substantial genetic effects on *effector capacities*, the capacities of individuals to select and influence their own environments, has received much less attention. Moreover, taken together, these papers had a persistent influence on the study of parent child relationships—to focus on individual differences in the sensitivity the *offspring* reactions to parents rather than on differences in the *parents'* sensitivity to children. The Caspi 2003 report focused on stress in adult life although it contained a generous section on child maltreatment that reinforced an underlying theme in the Suomi 2002 and Caspi 2002 papers adding weight, almost certainly inadvertently, a picture of individuals as responders to rather that creators of their own environments. To be clear, molecular gene–environment interaction studies have probed many aspects of healthy and pathological adult development but have rarely focused on adults as parents. Thus the great majority of subsequent reports relevant to this chapter on the family have, collectively, focused on genetic effects on individual differences among children that accounted for their varying response to their rearing conditions in contrast to a parallel focus on genetic differences among parents that account for differences in their response to their children although we will review some studies in this latter category. We will also review the very small number of molecular genetic studies that explored effector capacities in children.

Cautions in Interpreting Molecular Data

Despite these limits on the new paradigm, clearer in retrospect, the interest in these early reports was well founded.

All three were built on prior findings in quantitative genetics but also, and of immediate interest, on well controlled laboratory studies of animal and human neurobiology. Thus, there was a promise of bringing studies of the family into a unifying field of developmental human biology. Indeed, in retrospect, it is now clear that the introduction of molecular genetics into the study of the family has had entirely different dynamic than its older cousin, quantitative genetics. The former emerged slowly across half a century and with great resistance of researchers on social processes; many of its major lessons remain unlearned in family research. Since the Barr et al., 2003 papers, genotyping samples of families has been so rapidly included in the repertoire of family research that those from other disciplines—including geneticists—have called for caution (among many examples see Plomin, 2013). Some of these cautions seem well founded and we begin our review of selected, illustrative reports of this work with three of them in mind.

First, several reviews—using standard approaches to meta-analysis or the analysis of publication bias—have raised concerns about the reproducibility of some of these initial findings, particularly the moderation by the serotonin gene variants on the relationship of stress to depression in adults (Duncan & Keller, 2011; Karg, Burmeister, Shedden, & Sen, 2011; Munafo, Durrant, Lewis, & Flint, 2009; Risch et al., 2009). A particularly striking failure to replicate comes from the improbable circumstance that a second, large 30-year longitudinal study of children—the Christchurch Health and Development Study—is also ongoing on the South Island of New Zealand (Fergusson, Horwood, Miller, & Kennedy, 2011) whose population of just over a million seems to include an inordinate number of developmental researchers. However, using broader criteria for reproducibility several reviews find evidence for replicability of the Caspi report on the serotonin transporter gene (Karg et al., 2011; Mak, Kong, Mak, Sharma, & Ho, 2012; van IJzendoorn, Belsky, & Bakermans-Kranenburg, 2012). Caspi's 2002 paper on the interaction of the less efficient MAOA gene variant and child maltreatment on the development of aggression in boys has been confirmed by a very recent meta-analysis of 20 studies; importantly, this analysis found no difference in findings between smaller or larger samples or between earlier or later publications addressing, at least, some concerns about publication bias (Byrd & Manuck, 2014). Equally important, successful replication was limited to child maltreatment and not other childhood adversities. Included among the confirmatory finding is indeed one from the other South Island longitudinal study (Fergusson, Boden, Horwood, Miller, & Kennedy, 2011).

Kary Mullis's PCR gave social scientists a tool they never had before: a reliable, inexpensive ascertainment of differences among individuals, differences that preceded all else in their prenatal and postnatal social and physical world. Moreover, PCR can be used years after a study had concluded (if only a cheek swab or saliva sample can be obtained). This unique ascertainment has enabled an astonishing number of attempted reproductions of the original studies in little more than a decade. However, energized by these recent reports, investigators have examined many other gene variants—some of that work is reviewed here—with a broad variety of environmental variation and developmental outcomes. Many of these reports come from multivariate, multi-panel studies that genotyped subjects for many gene variants thus allowing investigators a wide latitude in associations they choose to study and report. Often these reports contain data only about one of these variants leaving skeptical readers to wonder whether null findings with other variants have gone unreported. Thus, particularly in this case, the empty file drawer procedure—usually regarded as a safeguard in meta-analysis against the findings of unpublished papers—cannot offer protection against unpublished analyses (Duncan & Keller, 2011).

Caspi and colleagues have presented a strong case for an alternate strategy to meta-analysis for reviewing evidence in this field: reviewing studies in animals and humans that are theoretically linked and may help explain, the moderation of environmental effects by specific gene variants (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). The fundamental idea here is that the foundational papers were exploring a theory of inherited sensitivity to stress rather than a specific hypothesis about the pathogenesis of depression. Thus, for example, a comprehensive review should include—as theirs did—experimental studies of the moderating effect of the gene variant on cortisol responses to standard stress stimuli in a laboratory setting. We cautiously explore this strategy in our current selective review. Our interest is to explore both possible as well as established use of molecular genetic tools to better understand family process.

Finally, we note that questions about the reproducibility of the foundational papers in this field—or of those that follow—is not unique to molecular genetic studies of the family. Nor have many, if any, studies in the recent history of behavioral sciences attracted such persistent efforts at reproducing the original findings. More generally, reproducibility of findings in all branches of science remains

a major concern. A survey by Begley and Ellis (2012) noted serious problems of replication problems in cancer treatment research and a special issue of *Psychological Science* raised concerns about replicability in psychology considered broadly (e.g., Pashler & Wagenmakers, 2012). As an ironic twist, the Begley and Ellis survey is—because of its lack of detail and precision—very likely itself not replicable.

A second problem in evaluating this rapidly emerging field is the high variability with which investigators explore genetic confounds. For example, population stratification is a threat to all gene association studies—for main effects and for interactions. Race is a crude marker of population stratification and there are examples of gene–environment interaction findings that do not generalize across race that serve as a reminder of the potential importance of this source of confounding (Widom & Brzustowicz, 2006). Within a study sample, unidentified subgroups may have different genetic ancestries. As a consequence, they may differ both in the frequency of the gene variants being investigated and in the behavioral measure of interest thus producing a spurious gene–behavior correlation. Likewise, where environmental variation is attributable to a blood relative (such as variation in parenting) passive gene–environment correlation may masquerade as a gene–environment interaction. It is a rare and commendable paper that examines these potential confounds (see, e.g., Sulik et al., 2012) for a test of population stratification and Kim-Cohen and colleagues for ascertainment of passive gene–environment correlation (Kim-Cohen et al., 2006). Further, investigators rarely specify in advance whether they are expecting the genetic effect to be additive (where the effect of the interaction increases from individuals who have neither deficient gene variant to those who have one to those who have two) or nonadditive, and if the latter, whether the effect should be dominant or recessive.

A particularly intractable problem is the possibility that two or more genes are at work completely mimicking gene–environment interaction: the measured gene, thought to be moderating an environmental effect, may be interacting with unmeasured genes that have notable influence on the same environmental variance. In their 2003 paper on the serotonin transporter gene, Caspi and colleagues addressed this problem by varying the timing of variables measured but only animals studies that experimentally vary rearing conditions, as in the Suomi studies, or human studies that experimentally vary the environment through an experiment (e.g. the laboratory induction of stress by Way, Taylor, and their colleagues (Way, & Taylor, 2010; Way & Taylor, 2011) or a randomized trial (e.g., Brody, Beach, Philibert, Chen, & Murry, 2009) fully addressed this issue. Indeed, virtually none of the papers we will review even address this concern, let alone test for it. Reviews of the literature in this area, either meta-analyses or conceptual, that we have already cited fail to examine papers for their adherence to this genetic toilette.

A final problem with evaluating this literature is its heavy dependence on statistical interaction although, unlike the three foundational papers, genetic main effects have been reported and we will survey some of these. Some prospects (Reiss, Leve, & Neiderhiser, 2013) and problems (e.g., Eaves, 2006) of interpreting statistical interactions have been reviewed elsewhere. The first set of problems is inherent in the statistics of interactions and, because of their wide coverage elsewhere, need only be mentioned here; these include statistical power, scaling of variables and testing for regions of significance. Of particular interest here is the problem of controlling for confounds in interaction testing. For example, Keller has suggested that most gene–environment interaction testing has failed to test for confound environment interactions or confounder–gene interactions and hence ruling out confounds has been insecure at best (Keller, 2014). A second problem is deriving mechanistic interpretation from patterns of interaction. For example, Widaman and colleagues presented an ingenious approach to both identifying crossing points in statistical interactions and attaching confidence intervals to these points. This rigorous approach can distinguish ordinal from disordinal interactions, with well-specified assumptions and limits. Widaman and colleagues argued that disordinal interactions, rigorously analyzed, favor a mechanistic theory termed differential susceptibility, a theory noted above in relationship to gene–environment interactions in schizophrenia. Ordinal interactions, according to this view, favor the original Caspi idea of inherited sensitivity. However, as Reiss and colleagues note (Reiss et al., 2013), disordinal interaction can also indicate a quite different mechanism of goodness of fit: some individuals benefit for environment A but do much worse in environment B whereas, in other individuals, the reverse is true.

The Early Growth and Development Study, using an adoption design, nicely illustrated this phenomenon: toddlers at risk for externalizing disorders (birth mothers had externalizing problems) develop favorably when parents structure assigned tasks in contrast to children at low risk for these disorders who do well when task are unstructured but respond poorly to high levels of parental structuring

(Leve et al., 2009). As for ordinal interactions, they may be due to effective social compensation for deficits associated with genotypic differences as well as to those genotypic effect on positive adjustment that are only manifest under favorable social environments (e.g. the heritability of intelligence is most apparent in favorable economic circumstances (Bates, Lewis, & Weiss, 2013; Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003). There is a growing consensus that experimental studies are crucial to advancing causal reasoning beyond statistical interactions however carefully the latter are accomplished.

Thus, in viewing over a decade of work following from the initial Suomi and Caspi papers we exercise both enthusiasm about the enlarging prospects for placing the study of the human family with a broader science of developmental biology but also remain cautious until a literature accumulates where genotyping is planned from the start of the adequately powered study, where well-conceived hypotheses provide substantial prior probabilities, where statistical and genetic artifacts are reasonably ruled out and detailed mechanistic explanations are sought in planned comparisons across studies, methods and species and in valid, experimental models. An exhaustive review of studies published thus far is beyond the scope of this chapter; as noted, we have selected studies more to illustrate the potential of molecular genetics techniques for studying the family, particularly in better specifying theories of individual differences in both responding to and evoking family process.

SPECIFYING THEORIES OF FAMILY PROCESS AND INDIVIDUAL DIFFERENCES

A core objective for systematic observation of families, certainly since the time of the redaction of the Book of Genesis, has been a better understanding of six processes within the family: variations in how children respond to very adverse parenting as well as its more ordinary variation; variations in how children evoke parental responses; factors inherent in parents that shape differences among them in sensitivity and style; variations inherent in adults that shape their marital relationships; difference among families in their response to stress; how family experience in one generation shapes the family lives of offspring when, as adults they constitute their own families years; and differences among families in their response to family-level therapeutic and preventive interventions to improve mental health. As noted, the great majority of molecular genetic studies address the first of these six questions. Some of the remaining questions have been addressed by no more than one or two studies.

Differences Among Children in Their Response to Parenting

Molecular genetic techniques have been applied to understanding individual variation in children in their response to parenting and, in far fewer instances, individual differences in parents in response to children. As noted, Caspi et al. (2002) reported that boys with the less variant of the MAOA, x-linked gene explain variations in response to maltreatment, much of it by their parents, as expressed in their developing their own antisocial behavior. This is the most securely replicated finding in the molecular genetic investigation of family social process.

Cicchetti and colleagues (Cicchetti, Rogosch, & Thibodeau, 2012) explored other moderating genes regulating serotonergic brain systems that might account for individual variation in children's response; they replicated the MAOA finding and found that the inefficient variant of serotonin transporter as well as the inefficient variant of tryptophan hydroxylase gene had a moderating relationship as well. In general, these findings suggested that children with less efficient genotypes inherited a sensitivity to maltreatment. This group also explored genes regulating other systems and with other outcomes. For example, they reported that a gene variant regulating corticotrophin releasing hormone receptors in the HPA system moderated the impact of maltreatment on diurnal cortisol variation with an interaction suggesting inherited sensitivity to stress (Cicchetti, Rogosch, & Oshri, 2011) and a gene variant regulating the oxytocin system moderated the association of maltreatment with diminished perceived social support from friends and family (Hostinar, Cicchetti, & Rogosch, 2014). The GG variant of this gene was associated with children's increased sensitivity to the stress of maltreatment although the literature on this variant is unclear whether it is expected to have protective or sensitizing properties. A recent paper from this group is of special interest; a gene variant regulating receptors of acetylcholine moderated the effects of maltreatment on personality, particularly neuroticism. Unlike, other studies of maltreatment these results suggested the gene variant enhanced neuroticism in maltreated children but diminished it in nonmaltreated controls (Grazioplene, Deyoung, Rogosch, & Cicchetti, 2013), an example that arguably reflects differential susceptibility

Molecular genetic techniques have also been applied to study variation among children in their response to less extreme variation of parenting than the stark distinction

between maltreatment and no maltreatment. A few examples, from a rapidly growing literature, illustrate the possibilities here. Starting during fetal development inefficient gene variants of the serotonin transporter are reported to influence individual differences in fetal response following exposure to maternal anxiety in utero as manifested in postpartum infant negative emotionality (Pluess et al., 2011) and the effects of maternal postnatal anxiety on infant irritability (Ivorra et al., 2010). The former interaction pattern suggested differential sensitivity to stress but the latter, given a main effect of the genotypic difference, suggested that nonanxious mothers could offset the apparent negative effect of the inefficient variant. Pluess and colleagues (2011) reported a similar study with a pattern suggesting inherited sensitivity to stress. Sulik and colleagues (2012) reported on variation in parenting quality and aggression and conduct problems in toddlers; the interaction in this report revolved around the *efficient* form of the serotonin transporter as marked by variation in two locations in the same gene. Surprisingly, children with the efficient form of the gene benefited from favorable parenting but suffered from unfavorable parenting; a pattern suggesting differential susceptibility. Kochanska and colleagues have followed approximately 100 children from toddlerhood to nearly school age; when the children were about 4 the deficient form of the serotonin transporter gene was sensitive to differences in security of attachment between the mother and the child. On a test battery assessing facets of self control (Kochanska, Philibert, & Barry, 2009) secure attachment offset the disadvantage associated with the deficient genotype. A similar pattern emerged a year later in the children's development. This time a responsive maternal style offset deficits in school and social competence (Kochanska, Kim, Barry, & Philibert, 2011). However, for measures of children's moral competence, children with less efficient variant showed performance that was better than those without if they had highly responsive mothers and worse if they did not, an example of differential susceptibility.

Differences Among Children in Evoking Parental Responses

As quantitative genetics has shown, genotypic variation in children not only influences variation in their receptiveness or sensitivity to parenting but also plays a major role in evoking parental response. As noted in the discussion of quantitative genetics, genetic studies add a significant dimension to the study of child effects. For example, family research has accumulated evidence that irritable children who display negative emotions frequently evoke equally negative response from parents (e.g., for infants see van den Boom & Hoeksma, 1994). Molecular genetics has taken an early, hesitant start in identifying specific genotypic difference that might account for these evocative effects.

Mills-Koonce and his colleagues (2007) appear to be the first to explore this area examining the role of an infrequent variant of a gene regulating a dopamine receptor because of its association with child temperament. Following from reports of van den Boom and Hoeksma (1994) and others, we might expect such genetically influenced temperament to be disruptive of mother–infant relationship, a finding confirmed by Mills-Koonce et al. Unfortunately, they tested the effect of this variant after ruling out the effects of child mood and temperament rather than examining their mediating role in the effect of this genotype. However, working among a research group with a primary focus on the family as a social system, Mills-Koonce et al. added an innovation: genotyping the mothers as well as children raising the possibility of studying an interpersonal gene by gene interaction. In this analysis such an interaction was not found, but the less frequent gene variant in the child was associated with less sensitive parenting, an important documentation that the genotype of one member of the family might affect the behavior of another.

Elizabeth Hayden and her colleagues (2010) reproduced this finding in a larger sample of older children. In this study, the child's negative affect was explored as a mediator of the genetic effect; it did made a marginal contribution to mediating the association of gene variant and evoked parenting. The dopamine systems in the brain, presumably those most involved in emotion regulation, were explored using another gene variant—this one regulating dopamine transport from intercellular space to intra-neuronal locations. Again, because of its association with potentially troubling child temperament, Hayden and colleagues (2013) explored its role in evoking negative parenting; they reported its apparent influence on both parental hostility and lack of guidance; in these findings child negative affect played a more distinctive mediating role.

Copeland and colleagues (2011), working in a group focusing on psychiatric epidemiology, studied a gene variant regulating the endogenous opioid system in positive parenting; in animal studies a comparable gene variant is important in influencing attachment behavior. Copeland reported that children with the variant that enhances opioid receptor efficiency elicited more positive parenting for those parents that had a history of psychiatric problems; these findings resonate with an idea about genotypic variation in children that might actively heal potentially problematic parent–child relationships.

Differences Inherent Among Parents That Shape Their Response to Children

Molecular genetics techniques have also been used to explore the role of genetic variation in parents. Much of this work has been stimulated by an extended series of animal studies on the role of the neuropeptides vasopressin and oxytocin (see Donaldson & Young, 2008, for a review). These nearly identical peptides are produced in the hypothalamus, transferred to the pituitary, and then released into the peripheral circulation where they have a number of regulatory roles. They are also transferred to brain regions where their effects on social behavior in animals have been intensely studied. Perhaps the most influential animal models have been contrasts among monogamous voles, as compared to promiscuous voles, where vasopressin plays a distinctive role not only in male pair bonding but also in male parental behavior, whereas oxytocin plays an approximately comparable role in females.

Working in the context of family process, attachment, and early intervention research group, Bakermans-Kranenburg and van IJzendoorn (2008) were the first to report the association of one of several variants of the gene controlling the oxytocin receptor and observed sensitivity of parenting. Four years later Feldman and her group reported a comparable finding but with a different variant of the same gene (Feldman et al., 2012). In another study Mileva-Seitz and colleagues (2013) reported the association of a variant in a gene regulating oxytocin synthesis to maternal vocalizations towards her infant but not in maternal sensitivity. Genes regulating the oxytocin system also are associated with an apparent buffering effect.

Using the same gene variant as in the original Bakermans-Kranenburg and van IJzendoorn study (2008), Sturge-Apple and her colleagues found that it rendered the mother more sensitive to conflict with her husband (Sturge-Apple, Cicchetti, Davies, & Suor, 2012). Those with the sensitive variant were less sensitive and less warm with their toddlers when there was high marital conflict but more so when there was low conflict. Notably in this study, as in the Mileva-Seitz 2011 study, there were no main effects on maternal parenting of this gene variant. As another example, Apter-Levy and colleagues, in the Feldman research group, reported a buffering effect for the same variant on the oxytocin receptor gene that, in their previous study, was associated with sensitive parenting (Apter-Levy, Feldman, Vakart, Ebstein, & Feldman, 2013). In the new study, they focused on the effects of sustained mothers' depression on the development of psychopathology of their school-aged offspring. The variant associated with maternal sensitive parenting in the first study here was associated with a protective effect on offspring development. Genes regulating other neural systems have also been explored both for their direct effects and buffering effects on maternal parenting. These include genes regulating dopamine (Fortuna et al., 2011; Kaitz et al., 2010; Lee et al., 2010), serotonin (Bakermans-Kranenburg & van IJzendoorn, 2008; Mileva-Seitz et al., 2011), and vasopressin (Bisceglia et al., 2012).

Individual Differences and Marital Processes

As noted, quantitative genetics has illuminated both environmental and genetic process related to marriage; for the latter there appear to be notable genetic influences on whether individuals become married and then divorced or stay single. Moreover, genetic influences have been reported for satisfaction in marital relationships with evidence for evocative effects; the genotype of one spouse is associated with the marital satisfaction of the other spouse. There has, however, been scant attention to the molecular bases of these findings. In the very first attempts investigators have used two strategies. The first approach was strongly influenced by findings in the prairie voles on the role of oxytocin and vasopressin in pair bonding. Two reports came from the same Swedish twin study. For men, the presumably more efficient variant of the gene regulating vasopressin receptors in the *husbands* were associated with their *wives*' marital satisfaction. For women, variations in their oxytocin receptor influenced, but to a lesser extent, their husbands' marital satisfaction (Walum et al., 2008, 2012). As expected, these were main effects though small in magnitude. A second strategy follows from many others we have cited: genotypic variation was explored for its association to individual's sensitivity to the marital context. In two studies, the less efficient allele of the serotonin transporter gene was associated with enhanced sensitivity of the spouse to the affect of the other marital partner (Haase et al., 2013; Schoebi, Way, Karney, & Bradbury, 2012). Finally, the mother's marital history has been studied as a varying environment in the development of ADHD in boys across a broad age range. The same gene regulating the D2 dopamine receptor, that played a role in other studies cited here had opposite effects depending on whether mothers had an adverse marital history (divorces, remarriages etc.) or not (Waldman, 2007). It is possible that this maternal history was a proxy for serious personality disturbances and the negative parenting that often accompanies them.

Individual Differences in Family Functioning in Response to External Stress

We can cite but only example here on differences among mothers in their vulnerability to postpartum depression in response to either economic adversity or advantage. Mitchell and colleagues report that two less efficient variants of the serotonin transporter gene are associated with heightened risk for postpartum depression under adverse economic circumstance—indexed by mother's educational attainment—but reduced risk under favorable circumstances (Mitchell et al., 2011).

Differences Among Adults in the Role of Childhood Experiences in Shaping Their Adult Family Roles

At least three studies have examined intergenerational effects in families: do individual offspring differ in the degree to which harsh or favorable parenting influences their behavior, years later, with a spouse or romantic partner? Initial evidence suggests that several gene variants enhance the transmission from positive parenting to subsequent positive partner relationships and also favor the transmission of negative parenting to unfavorable relationship with subsequent partners (Beaver & Belsky, 2012; Masarik et al., 2014; Simons et al., 2013).

Differences Among Families in Response to Family-Level Interventions

Finally, molecular genetic techniques have been applied to understand individual differences in response to family-oriented behavioral interventions. In doing so, these studies follow in the tradition of pharmacogenetic studies that investigate how genetic variation may forecast response to specific pharmacologic agents. In applying these techniques to behavioral intervention it is important to distinguish two questions. First, does a specified genetic variation forecast an individual's responsiveness to a therapeutic agent or, second, does it offset a current or future pathological condition associated with the genetic variation? In both cases, individuals with the predictive genotype will show a greater response to an intervention but for distinct different reasons (see Reiss et al., 2013 for a more complete explanation). This distinction in mechanism has great practical significance. If a genotypic *responsiveness mechanism* is established by repeated, adequately powered randomized trials then genotyping might become a rational basis for recommending particular treatments only to those individuals who have a responsive genotype. In contrast, where a data on a behavioral treatment clearly demonstrates a *compensatory mechanism* then that treatment could be recommended to individuals even though their syndrome has a clear association with (and is probably influenced by) their distinctive genotypic profile.

Investigators experienced in family intervention techniques have reported small-sample studies of brief parent training interventions for externalizing behavior (Bakermans-Kranenburg, van IJzendoorn, Pijlman, Mesman, & Juffer, 2008) and ADHD (van den Hoofdakker et al., 2012). The former showed evidence that a variant of a dopamine receptor gene forecast greater responsiveness of children to the intervention; in the latter graphical presentation of the data (not analyzed statistically) suggested treatment had a compensatory effect for a more severe form of ADHD associated with a dopamine transport gene variant. In both cases genotyping was completed only on a subset of subjects after the trial was completed with a consequent loss of the protection from confounding ordinarily afforded by a randomized trial; thus, both reports serve as informative proof of concept' studies. This reservation does not to apply to data from two large trials of a family-oriented program for the prevention of alcoholism in African American teenagers reported by Gene Brody and his group. The great majority of participants were genotyped and gene variants associated with several neural systems were evaluated for their capacity to predict alcohol use in teens that were not already affected. These sizable genotypic predictive effects appeared only in the control groups but not in the treatment groups providing one of the best sets of evidence we now have that behavioral interventions can offset the behavioral risks associated with genotypic differences (Brody, Chen, & Beach, 2013). Yet to be resolved in these studies are the surprisingly large main effects of single genes given very much smaller single gene effects noted in GWAS studies. Perhaps a combination of poverty and racism that face these families operate as moderator, not measurable in this study, enhancing single gene effects. Or it could be a winner's curse.

Beyond Individual Differences: The Prospects for a Developmental Biology of Families

Within an astonishingly brief period of time, the PCR technique first reported by the flamboyant and controversial Nobelist Kary Mullins has spread rapidly among researchers on family process. The foundational papers by Suomi and colleagues and Caspi and colleagues are rightly credited with making a link between a molecular technique

and the social process of the family. The reports we have reviewed here constitute only an illustrative sample of this notable spread. In introducing this work we have already outlined reasons why it should be read with caution. Nonetheless, the exuberance of this work is based on much more than the new tools it affords for specifying unheralded sources of individual differences in the responses of family members to one another. Beyond individual differences these techniques, linked with other rapidly developing tools of developmental biology, promise a more mechanistic understanding of the development of family relationships and of its constituent members. However, to reach these goals, two major steps are in order now. First is the careful testing of longitudinal process models *of family and individual development*, and second is a more strategic use of *experimental modeling* to test the assumptions and explore mechanisms behind the associations studies that we have reviewed and related reports we did not. A full account of these approaches is beyond the scope of this chapter, yet a failure to mention them unfairly narrows the scope of our appraisal of what molecular genetics may contribute to the study of the family.

Longitudinal Process Models

Process models are distinct form the individual difference models we reviewed in the last section. They are designed to investigate the specific gene–environment interplay, in mechanistic fashion, that unfolds as development proceeds through well-specified periods of time. They begin to address the question not of whether but of how genotypic variation influences family process and individual development.

The best illustrations of this approach come from the application of molecular genetic techniques to understand evocative gene–environment correlations. For example, in the same report, but using two different samples, Walum and colleagues reported that same oxytocin receptor gene variant that influenced the marital satisfaction of spouses of married women at midlife also influenced variation in the quality of the social relationships for girls at ages 8–9, as rated by their parents (Walum et al., 2012). A tempting speculation here is that the oxytocin receptor variant expressed itself earlier in positive social relations that widened and deepened the social skills of the developing woman, affording her a happy marriage years later. In the parlance of genetics relational skills of adolescent girls might be an intermediate phenotype in the causal path from genetically influenced variation in the oxytocin receptor and marital satisfaction. Or as Kendler and Neale (2010) pointed out, the genotypic influence in social relationships of young girls might simply be an early indicator of gene variant that improves the prospect of a happy marriage but has no causal role. Moreover, to sketch a longitudinal process model, we need to make a shaky assumption that the two different samples reported by Walum and his colleagues are equivalent.

In another instance, and again piecing together results from samples, two separate research teams reported the evocative effect of a gene regulating brain opioid receptors. In childhood this variant is associated with positive parent–child relationships—especially where parents have prior behavioral problems (Copeland et al., 2011). Later in development, this same variant protects against the development of substance abuse in the transition from adolescence to young adulthood in males, an effect mediated by the adolescent's participation in alcohol using peer groups (Chassin et al., 2012). Again, it is tempting speculate that the opioid receptor variation, because it evoked positive parent–child relationships under difficult circumstances protects the developing boy so that at adolescence, he avoids alcohol-using peers and thus avoids an alcohol-abusing early adulthood. Such a sequence would be consistent with the quantitative genetic study of Neiderhiser and colleagues that reported a common genetic influence on evoked parenting, delinquency of peers and substance abuse by early adulthood (Neiderhiser, Marceau, & Reiss, 2013).

However, inferences about developmental processes of this kind require longitudinal data within a single sample. An intriguing example is provided by Propper and her colleagues (Propper, Shanahan, Russo, & Mills-Koonce, 2012) who studied a gene variant controlling the D4 dopamine receptor in girls. This variant was associated with several measure of these girls' academic achievement in first grade as mediated by its apparent evocation of engaged parenting when these girls were toddlers. Although statistically challenging, process models can be explored not only for genetic main effects, as in evocative gene–environment correlation, but for gene–environment interactions. For example, Davies and Cicchetti (2014) explored a process model to explain the interaction of maternal unresponsiveness to their 2-year-olds with a variant of the serotonin transporter gene on the development of externalizing two years later. This interaction was mediated by the aggressive responses of the child towards the mother at age 3, suggesting that this reaction to mothers' negative parenting is a developmental way station on the road to maladjustment. However, the child's gene variant here that was sensitive to parental negativity was the so-called long or efficient form of the transporter gene that, in most studies, has been

shown to be the insensitive variant. As at many points in the molecular genetic literature it hard to know if this is a novel finding or a failure to support previous findings on the role of the short variant in stress sensitivity.

Longitudinal process models will be immeasurably aided by a detailed knowledge of the timing in development when gene–environment interplay occurs. For example, Daniel Choe and Daniel Shaw and their colleagues reported the interaction of the inefficient variant of the MAOA gene with harsh parenting on adult antisocial behavior in a longitudinal design that had followed these men from infancy: those with low efficiency variant were particularly vulnerable at observations made between ages 1.5 to 5 (Choe, Shaw, Hyde, & Forbes, 2014).

Experiments

Passive cross sectional and longitudinal studies, that is, those that have no planned and randomized interventions, are insufficient to understand mechanisms underlying observed main effects and interaction of gene variants including those we have already reviewed. All independent variables in these studies are subject to confounding. For example, natural variation in parenting may be a proxy for genetically influenced variation in parental personality; those personality genes when transmitted to a child may influence that child's adjustment—an instance of confounding passive gene–environment correlation. Or the natural variation in parenting may reflect the evocative effect of children's heritable characteristics that are either not measured in the study or are, as yet, unknown. Thus an apparent gene–environment interaction is here confounded by gene–gene interaction. Also, causal pathways may be too complex to unravel in passive longitudinal studies. In the example above, many variables can affect a parent's engaged response above and beyond the influence of the D4 dopamine receptor gene variant. Although never used in genetic studies, the pseudo-family design—where parents and children are randomly matched in a laboratory setting—can help to isolate the effect on a parent of a child's heritable characteristics (Reiss & Oliveri, 1983). Likewise, many processes critical to understanding the genetically influenced biology of family processes, such as functioning of the brain's cortex, cannot be visualized in the settings where most passive longitudinal studies unfold. Thus, the major objectives of experiments are effective control of independent variables free of confounds, simplification of complex causal networks, and visualization of otherwise occult biological process.

Experimental procedures have a long history in the study of family relationships (Howe & Reiss, 1993). The Strange Situation is an experiment holding constant mother–child reunions while focusing on variations in children's reactions. Experiments have sought to experimentally vary parental response through standardized instructions to parents to feign affect (Hornik, Risenhoover, & Gunnar, 1987) or hold infant temperament constant by the use of standardized simulated babies (Rutherford, Goldberg, Luyten, Bridgett, & Mayes, 2013). Where visualization of evoked potential is required to identify cortical response involved in parent–child relationships, computer simulations of reunion experience can be programmed so that the precise moment of simulated reunion can be related to the timing of cortical responses that follow just a few milliseconds afterwards (White, Wu, Borelli, Mayes, & Crowley, 2013). The ecological validity of these experimental settings are always open to questions as are the degree to which variables manipulated in experiments successfully simulate more ordinary occurring experience in families. However, experimental models involving genotyping have one advantage over other models of complex family processes: the genotyped variable is absolutely constant across settings. To a large extent this is true even when animal models are used in experimental probes of mechanisms of gene-family process interplay. While even in close human relatives, such as Rhesus macaques, there are some differences in gene structure and variation the analogies in structure and function provide high levels of security that, in these animal experiments, genetic variation effectively models that in humans.

As an example of an experiment exploring a molecular genetic influence on family process, Peltola and colleagues (2014) provided women with brief exposure to infant and adult faces and measured the evoked cortical potentials immediately following these exposures. Their results suggested that the same gene variant associated with sensitive mothering in a passive design also led to more rapid and intense cortical responses to infant but not adult faces displaying intense emotions. Mothers, in contrast to women without children, showed more rapid and intense reactions to high emotion in the infant pictures but the effect of the gene variant on cortical response held for both mothers and nonmother controls. These results, not yet replicated, suggest that the gene variant is associated with a trait of emotional responsiveness to infants independent of the substantial neuroendocrine and psychological transformations that attend pregnancy, parturition and early child rearing.

There is a broad repertoire of experimental approaches available for linking the available findings on molecular genetics to a to the emergent science of developmental

biology. Experimental studies of humans, such as those of Peltola and colleagues (2014), have been abundant; among many see the work of Baldwin Way, Shelly Taylor, and their colleagues (Moons, Way, & Taylor, 2014; Way & Taylor, 2010, 2011).

Some investigators have argued that randomized, controlled trials might also be considered as experiments (see, e.g., van IJzendoorn & Bakermans-Kranenburg, 2012) since randomized interventions that change family interaction patterns do, as in more traditional experiments, experimentally control family environment assuming the randomly assigned treatment condition is effective. However, treatments that are designed to remediate or prevent serious clinical problems are invariably complex with many components and many undetected effects that may contribute to their efficacy. Howe, Reiss, and Yuh (2002) termed these meditational confounds. While techniques for componential and meditational analyses are well developed in psychotherapy research their combined complexity renders randomized controlled clinical trials a poor way to model naturally occurring, well-specified variation in the environment as occurs in ordinary development.

Experiments designed to unravel mechanisms have a fourth objective, especially in the investigation of gene–environment interaction. As detailed elsewhere (Reiss et al., 2013), experiments seek to *uncover the genetic main effect* accounting for the interaction. Recall that in their foundational 2003 report by Caspi and colleagues found no main effect of the less efficient variant of the serotonin gene on depression but rather an interaction between stress and the variant. Caspi postulated a genetic main effect on stress sensitivity and selected the serotonin transporter gene in part because of an already published brain imaging experiment where, in a small sample, Hariri and colleagues (2002) reported that this variant had a sizable main effect on amygdale function in response to experimental manipulation of stressful images. It is tempting to place these findings into a hypothesized longitudinal process model: children born with one or two copies of the inefficient gene variant have amygdale that are excessively responsive to the stress of early maltreatment and when they become adults, the gene variant sensitizes them to a range of life stressors. This main effect of a genetic variant on amygdale function then interacts with stress during the life course to lead to depression (and perhaps other adverse outcomes). In this scenario, amygdale function would be a genetically influenced intermediate phenotype in a longitudinal process model.

Indeed, Caspi's foundational publication has stimulated well over 30 subsequent experiments where brain imaging studies of individuals with and those without the inefficient gene variant are placed in a magnet for brain imaging in ways roughly comparable to the original Hariri report. We could not identify another experiment that came close to this one for rigorous attempts at replicating a result on a main genetic effect on a process that might mediate a molecular gene–environment interaction. A recent meta-analysis of these publications suggest, however, that this "candidate" intermediate phenotype may not be able to play its proposed role in the interplay among the gene variant, stress, and development (Murphy et al., 2013). The effect size in this analysis, though replicating in direction the original Hariri study, was far smaller than the original with an excess of positive reports over those expected given the statistical power of the publications in the meta analysis (suggesting a reporting bias). Perhaps most pertinent, a major source of heterogeneity among studies was age of subject; contrary to what might be expected for an early-appearing intermediate phenotype effect size increased in direct proportion to the *increases* in subjects' age. However, the few studies of children and adolescents were not included in the review and its overall estimates included unpublished as well as published data.

Just as certain patterns of gene–environment interaction suggest an inherited sensitivity to stress so have some patterns suggested—as we noted—an inherited differential susceptibility to the environment for better or worse. Experiments able to define these mechanisms and test the putative plasticity genes for the main effects on these mechanisms. Van IJzendoorn and Bakermans-Kranenburg (2012) recently reviewed evidence of these experiments, but, small in number, they are all randomized clinical trials that, as noted, have limited probative value.

As noted, animal experiments also play an essential role in delineating developmental mechanisms. However, not to exceed the bounds of this chapter we mention them only briefly. Recall, they helped shape the hypotheses of the foundational Caspi papers. In animal experimental models, subjects can be randomly assigned to adverse environments. For example, infants of mothers likely to be abusive may be cross-fostered to mothers who are highly unlikely to be and vice versa (see Maestripieri, Lindell, & Higley, 2007). Rodent models allow for a range of experiments unthinkable in humans, and in many primates including inbreeding, transgenic, knockout, and knockdown experiments.

Finally, it is now essential to link passive human studies of gene–environment interplay to in vitro experiments of two kinds. The first of these two are continuing in vitro experiments to establish the transcriptional efficiency of

gene variants employed in human studies (Flint & Munafo, 2013). For example, among the studies we have reviewed on gene variants regulating the oxytocin receptor, no fewer than six have been reported across the different studies with investigators each pursing different variants. At the level of biological efficacy are all these gene variants equivalent in effect? Are each a separable indicator of the status of oxytocin receptors, and if so, shouldn't they all be used in future studies to test the role of this receptor in family process? A strategy of this kind may be thought of as the backward utility of in vitro experiments. However, in vitro experiments may have forward utility as well. For example, Steven Cole and his colleagues identified a variant of a gene regulating the proinflammatory interleukin 6 by determining the effects of norepinephrine on the expression of the gene that regulates interleukin 6's circulating level; norepinephrine, a reliable product of stress-induced activation of the sympathetic nervous system, served in an in vitro model of the role of stress on the interleukin gene. Bringing this model forward, Cole and colleagues tested the role of this gene variation on its role in moderating the effect of depression on mortality (Cole et al., 2010). Although this study is not, strictly speaking, relevant to family studies it an important proof of concept for the forward utility of in vitro experiments in identifying gene variants relevant to the stress of family life

HAS GENETICS ALTERED THE WAY WE THINK ABOUT THE FAMILY AS A SOCIAL SYSTEM?

The State of the Evidence

This chapter has attempted to convey both the promise of genetic methods in the study of the family but also methodological challenges and controversies that these methods have raised. There is little question that the use of these methods have changed our thinking about families but before summarizing these changes it is important to inventory the security with which we can draw major inferences from the data we have reviewed.

Quantitative genetics is built on twin and adoption methods that began their development almost 90 years ago. They became highly relevant to the study of the family, particularly on mechanisms by which psychopathology is transmitted from parent to offspring, by the 1960s when the fateful Dorado Beach conference witnessed a confrontation between social and genetic explanations. There has been a vigorous program of investigation of many but not all the assumptions behind these methods, and as our review here indicates, many of the major findings in the application of these methods to the family have been reproduced. However, uneasy lies the head that is complacent about these methods.

Model testing approaches to analyzing twin data still rest on assumptions that are probably untenable unless specifically tested each time they are applied. For example, assortative mating of the twins' parents (the selection of one another on the basis of similar, heritable traits such as alcohol use or intelligence) can underestimate heritability of traits since this pattern of mating will inflate DZ correlations but not MZ correlations. As we noted, Burt (2014) clearly showed that the twin method, particularly the model testing methods used to analyze its data, may underestimate shared environmental effects and thus underestimate the importance of between-family differences. Not to batter the twin method too severely, but we have also noted its potential problems in overestimating the nonshared environment and also have presented data to argue against that concern. The adoption method has often come to the rescue of the twin method either by providing a corrective for estimates derived from the twin method or by circumventing its assumptions. Assortative mating in adoption studies leads to overestimating heritability; moreover, the adoption method better estimates the shared environment—especially in adoption designs where siblings born to different birth parents are adopted into the same family. As we have seen, the adoption method entirely circumvents the equal environments assumption; that is why it not only had a major impact at Dorado Beach but also established beyond doubt the substantial genetic contribution to the pathogenesis of schizophrenia and thus its use by Kety, Rosenthal, Wender, Schulsinger, and Heston emerged as a foundation of biological psychiatry 1968.

However, the adoption method has its own headaches. For example, as noted, the birth mother does rear her offspring for nine months: from conception to birth. While it is relatively easy to rule out the confounding effects of her use of prescription and nonprescription drugs during pregnancy the science of fetal environment is growing rapidly. Birth's mother self care, psychological status and exposure to second had smoke and toxins may confound inferences about the role of genetics in the transmission of maternal characteristics to offspring development and these are much harder to track either prospectively or retrospectively. As noted, a new version of the adoption design includes a group of mothers who adopt a fertilized egg shortly after conception thus permitting a cleaner separation of genetic and fetal environmental influence. However, the adoption-at-conception design cannot

readily distinguish prenatal from postnatal environmental effects and the number of women who, having endured the substantial medical stress of egg implantation procedures, go on to smoke or use drugs during pregnancy is extremely small (Rice et al., 2009) reducing the power of this design to distinguish genetic from exposure effects on fetal development. Recently, the adoption-at-conception and the adoption-at-birth design have been combined (Gaysina et al., 2013) to provide a much clearer delineation of genetic, prenatal, and postnatal influences of smoking on the development of conduct problems. Criticism has also been leveled at the conventional adoption design because adoptive families are typically middle class and hence there is a restricted range of environmental adversity and, critics have argued, a diminished opportunity to estimate the effects of harsh environment on child development (Stoolmiller, 1999). However, a searching empirical test of this possibility did not support this concern (McGue et al., 2007).

Overall, the corpus of work in the field of quantitative genetics is substantial, increasingly well designed, and the major findings have been frequently reproduced. Our historical review has clarified how essential it has been to ferret out all the assumptions behind these methods, to test them rigorously and to have two entirely separate methods, each with its own improvements, to estimate both genetic and environmental influences at work in the human family.

With some notable exceptions, these claims cannot be made for molecular genetic approaches. After all, its history is barely a tenth the age of its senior partner but its use has become much more widespread. We have introduced our selective review with cautious about the findings thus far. Indeed, in some minds, these cautious are sizable leading to recommendations that this line of research is of limited value (Flint & Munafo, 2013; Plomin, 2013); further, some investigators in this domain are encountering considerable difficulty in gaining funding for their work. Work in this field needs challenge and may thrive on it. Funding continuing investigation and encouraging students to enter this field should remain a high priority.

Nonetheless, investigators in this field—and to some extent editors of journals that publish their reports—have often made matters more difficult and opened it to unnecessary criticism. For example, it is rare that papers reporting results of the interplay of specific gene variants and social variables in the family include an independent replication. Given the relative ease of genotyping (in contrast, for example, to developing a twin sample) such a practice would enhance the likelihood of reproducing results in follow on studies—particularly when a new combination of gene variant, moderating environment and outcome are reported from the first time. A recent report provides an example. Petra Zimmermann and her colleagues (2011) at the Max Planck Institute of Munich combined forces with Avshalom Caspi and Terrie Moffitt and their colleagues at Duke. They drew on two longitudinal studies to report independent and confirmatory analyses of the role of variants of a gene regulating the corticoid receptor in the HPA axis feedback system on sensitivity to stress as indexed by the development of first-episode depression.

As we noted, critical assumptions behind the methods of molecular genetics as applied to families have remained largely unexamined. We have already noted many of these and need only re-state three of these assumptions here: (1) no passive gene–environment correlation for those studies of the effects of parenting; (2) no interaction between the measured gene of interest and an unmeasured gene or genes that influence the environmental variable; and (3) no confounding population stratification.

Finally, the path between quantitative and molecular genetics needs smoothing. Quantitative genetics now has excellent tools for identifying family process variables that moderate genetic influences on developmental psychopathology. Using those moderating variables in molecular genetic studies adds explanatory power to the quantitative analyses and is an important source of heightened prior probability (and hence replicability) for molecular analysis. The work of Danielle Dick (2011) illustrates this nicely. Using a twin design, she identified parental monitoring as a moderator of genetic influences on adolescent substance use; high levels of monitoring reduced genetic influence, a finding she extended using specific gene variants (see her account of this strategy). In another domain, molecular genetic analyses seems little concerned with heritable evocative effects that quantitative genetics has illustrated repeatedly not only in children and adolescents but in the marriages of adults. These have become more compelling as recent adoption research has illustrated more clearly their probable role in pathogenesis. Moreover, molecular genetics is not digging into an enormous domain for the study of gene–environment interaction: variations in the *sensitivity of the social environment* that moderate these heritable evocative effects. Finally, it seems odd that molecular genetic tools have not been deployed to investigate the most striking findings of all in the quantitative genetics of the family, the finding that genetic influences on family variables (e.g., parent–child conflict) overlap with those on individual measures of adjustment (e.g., antisocial behavior) and in notable instances account for the majority of the observed covariance between the two. Twelve years

after Suomi and Caspi introduced molecular genetic tools to study the family we have little insight into what genes might be involved in these associations.

Thus, a fair reading of nearly a century of work applying genetic approaches to the study of the family can conclude: quantitative genetics speaks to the study of family process with the voice of authority, whereas molecular genetics speaks, at present, with the softer voice of promise. What are these voices saying?

Family Research Listening to Molecular Genetics

We turn first to molecular genetic analyses. Here we summarize three areas of family research where molecular genetics can be illuminating. These examples are offered with a clear purpose. As already indicated, the attractiveness of this approach to analysis is the promise of placing the study of the human family into a secure location in the rapidly advancing domain of developmental biology. Thus, it is more than high time for molecular genetics to move beyond the almost promiscuous search for more variants connected to more environments connected to more outcomes although continued promiscuity in the search of fresh liaison with the truth is still defensible.

Child Maltreatment

Even our selective review makes it clear that many filaments of molecular genetic analyses of family converge on this major public health problem. Molecular genetics has added a much clearer delineation of individual differences in response to this severe and sustained stress in childhood. Most literature focuses on the genetically moderated impact of maltreatment on behavioral disorders in children, adolescent, and adults. However, from a public health perspective, the long-term impact of child maltreatment on adult medical health may be its most important scourge. Precisely, what is the risk of adult mental and physical illness attributable to child maltreatment? The computation of attributable risk is a secure public health indicator because it allows a calculation of the reduction in disease incidence and prevalence that one might expect if the risk factor were eliminated or fully offset by intervention. Such estimates are just being published. For example, Kessler and colleagues estimate the risk for a broad spectrum of adolescent and adult psychiatric disorders attributable to early adversity, mostly maltreatment, is an astonishing 30% (Kessler et al., 2010). This estimate may be revised downward as future studies correct for passive gene–environment correlation and retrospective bias but estimates might be revised upward in a subset of individuals if their vulnerability genes are included in the epidemiological inquiry. We do not have gene–environment studies for adult medical illness associated with child maltreatment comparable to those for child and adolescent psychopathology. However, we do not lack fastidious longitudinal studies documenting this risk (e.g., Danese et al., 2009; Widom, Czaja, Bentley, & Johnson, 2012; Wilson & Widom, 2011). Nor do we lack studies that explore the mechanisms by which this risk persists into adulthood (e.g., see Miller, Chen, & Parker, 2011) for a review chronic inflammation occasioned by the stress of early maltreatment and (McCrory, De Brito, & Viding, 2012) for persistent effects on brain structure and function). Data thus far on molecular genetic vulnerability to child maltreatment augurs well for this vital extension to adult medical illness and a trickle of data on this domain is beginning to appear (Brummett et al., 2008; Xie et al., 2013; Zhao, Bremner, Goldberg, Quyyumi, & Vaccarino, 2013).

One might think that identifying gene variants that increased children's sensitivity to maltreatment would be the most obvious public health benefit of current research and perhaps it will lead at some point to fitting remediation to specific children by virtue of their genotype. However, it hard to imagine that current efforts to reduce the prevalence of child maltreatment or to reduce the time that children are exposed to it or to remediate its potential impact on the children would become more focused or even efficient with further molecular genetic study. Would anyone now deny a child the benefit of the nurse visitation programs or child–parent psychotherapy programs, programs that seem to have an overall beneficial effect in maltreatment (Cicchetti & Banny, 2014), on the basis of their genotype? Genotyping provides fresh insights into mechanisms that might account for the impact of maltreatment on children but has no obvious impact yet on therapeutic innovation.

The reverse is true for the long-term effects of child maltreatment on adult medical illness that may become manifest decades after the maltreatment. Even if we had a thoroughly enlightened international policy on child maltreatment and its amelioration it is likely that many adults, seriously maltreated in childhood, would reach adulthood with no obvious signs of medical illness apparent but at substantial risk of future malady. It is here where an understanding of genotypes and liability can have huge implications for selective preventive interventions.

Developmental Family Neuroscience

It is fair to say that major advances in social neuroscience rest substantially on laboratory experiments where

complex social stimuli are modeled by a broad array of auditory and visual stimuli, briefly presented to just one member per family and correlated with various cortical recordings, brain imaging and blood sampling techniques. Social neuroscience becomes more social when comparable recordings are made in simulated or actual interactional games (see Todorov, Fiske, & Prentice, 2011, for review of these approaches). Social neuroscience moves into the family when these techniques test the moderation of the presence of family members on neural responses to standard stimuli (e.g., Coan, Schaefer, & Davidson, 2006; Conner et al., 2012) and validated against the quality and durability of important intimate relationships (e.g., Eisenberger et al., 2011).

Many of the molecular genetics papers we have reviewed offer a tantalizing vision of a substantial enlargement of this field to focus on the development of the family as a system deploying the technology of social neuroscience but guided by genotyping. Genotyping can be regarded as a probe of relatively stable individual differences in the operation of neural systems although Plomin et al. (1994) cautioned against the simple notion of one gene being associated specifically with one disease. A comparable caution is warranted here: the neural systems of the brain are complex and interrelated and variations in a single gene may be imprecise indicators of stable individual differences in their function.

Bearing these caution in mind, let us imagine a sequence suggested by these papers. The sequence can start with mating and marriage here. Quantitative genetic data suggest genetic influences on becoming married (Jerskey et al., 2010); it is conceivable that specific genes may be identified that regulate this starting point in the assembly of a family; it is relevant that Walum and colleagues (2008) showed an association of very small effect of a variant of the gene regulating vasopressin receptor in men on whether couples with adolescent children were married or cohabiting. That is, where a man possessed one variant the couple remained together without the commitment of marriage and if he possessed the other variant they were married. It is conceivable that members of a couple pick each other because of similarities in genotypes although such an investigation may confound population stratification effects with choice effects. Nonetheless, once married small effects of gene variants—vasopressin for men and oxytocin receptor for women—have been reported (Walum et al., 2008, 2012). Moreover, parental gene variants may promote the parent–child relationship through its enhancement of sensitive parenting (Bakermans-Kranenburg & van IJzendoorn, 2008; Feldman et al., 2012). Children's genes may also promote this relationship through eliciting or evoking positive parenting and (Hayden et al., 2013; Hayden et al., 2010; Mills-Koonce et al., 2007; Propper et al., 2012). Moreover, there are gene variants in parents and in children that might be said to have a protective effect on parent–child relationships. For example, genotypic variants may protect mothers post partum from depression despite external difficulties (Mitchell et al., 2011); they may protect parental function from marital problems (Sturge-Apple et al., 2012) and protect the parent–child relationship from the mother's own depression (Apter-Levy et al., 2013). We have described one report of a child gene-variant regulating the endogenous opiate system that appears to protect a positive parent–child relationship when parental psychiatric problems might otherwise perturb it (Copeland et al., 2011). Finally, there appear gene variants that protect relationships in a subsequent generation in the family from the transmission of interactional difficulties in the prior generation (Beaver & Belsky, 2012; Masarik et al., 2014; Simons et al., 2013). Even from these initial fragments it is possible to sketch, with the lightest and most tentative hand, a developmental sequence of between-family difference in genetically influenced promoting and protective processes unfolding across two generations in the development of the family.

When a sequel to this chapter is written, perhaps 10 years hence, it seems likely that many of these specific findings will have evaporated as attempted replications may fail or improved genetic and statistical toilette is satisfied. Nonetheless, the framework suggested here—a focus on the developmental stages of the family—may survive as a way of integrating newer, more solid findings, framing more solid hypotheses and developing better methods. As for the last, Mills-Koonce et al. (2007) and Choe et al. (2014) provided a look at the future of the role of genetics in a developmental family neuroscience; the former used the family as the unit of genotyping with genetic data collected from at least two members in each family and the latter presages a more precise timing of when, in the development of family relationships, genetic effects have their most significant influence. The framework we propose here can keep molecular genetics focused on the family and on how these molecular techniques may enlarge our knowledge of how the family unfolds over time and across generations and how it shapes and is shaped by each of its members.

Fitting Family Interventions to the Family

The field is indebted to the early publications in this field for their perspicacity, three of them reviewed here. However, it

is time to move on to other strategies to take full advantage of the molecular genetic investigation of the family. As we noted, clinically efficacious interventions are a poor way to model naturally occurring variation in family process. Moreover, post hoc genotyping of already completed trials—even where the genotyping is nearly complete for all subjects—can produce misleading results, especially where there is a genetic main effect on the liability or pathology to which the intervention is addressed. In such an instance, the apparent sensitivity of individuals (or families) with a presumably sensitive genotype under study cannot be separated from the ceiling effect of the treatment. The apparent sensitivity of the genotype may just reflect a familiar clinical truth: sicker patients get more out of treatment than those who are less so. In fitting a specific treatment to a particular family genotype there is no substitute for a prospectively designed randomized trial, planned from the start, with blocking on the genotype in question such that those with and without the genotype are equally sick or equally likely to become so.

Since genotype is a blocking variable, all subjects must be genotyped before randomization with careful attention to whatever sampling bias such a requirement may inadvertently produce. Although contemporary techniques such as urn randomization might help it should not be necessary. The theory of differential susceptibility marshals empirical evidence buttressed by evolutionary reasoning to posit a set of genes that confer plasticity on individuals (and perhaps their families). The scientific task of fitting family interventions to family genotypes provides a test, in the most practical terms possible, of the mettle of this theory. Because of their for-better-or-for-worse quality, these genotypes should be untroubled by main effects but, if the theory is true, should predict more sizable treatment effects, which should become clearly apparent in a blocked design. During an early stage of a new branch of science inquisitive exploration, even playful exploration without rigorously derived prior probabilities, should be encouraged. The exuberance with which family researchers have embraced PCR has, in some instances, exemplified this productive vein in science. Fitting a treatment to a person or to a family with serious troubles or with liability for future troubles, on the other hand, is a serious business. Suppose genotype A proves sensitive to the treatment but genotype B does not; replicated results from well-designed clinical trials would rationally lead to recommending against the treatment for genotype B. A family-based use of molecular genetics—as we have reviewed it here—offers notable potential for this fitting process. However this evolving research paradigm should conform to well-established practices for other clinical trials. These include placing the measures including genotyping, and including expected outcomes in the lockbox of clinicaltrials.gov. It is entirely conceivable that such a study is already on the drawing board if not already under way.

Family Research Listening to Quantitative Genetics

Common Genes and Covariances

We have reviewed abundant evidence that there are substantial genetic influences on most measures of family relationships including parent–child, marital, and even sibling relationships. Equally abundant evidence suggests that many of these genetic influences are shared with those that influence such important measures of individual adjustment such as depression, antisocial behavior, social responsibility, autonomy, and cognitive motivation and achievement. These are evident in relatively short periods of developmental time where, for example, negative parenting might be assessed during early adolescence and child delinquency in later adolescence. These effects of common genes are also apparent across generations as in the case of parental alcoholism and offspring impulsive behavior. Every model of family influence prior to the use of genetically informative designs is potentially misspecified. While we have already belabored the point this circumstance is also the case for molecular gene–environment interactions where presumed environmental effect on adjustment could be attributable, in whole or in part to evocative gene–environment correlation for genes not measured in the study (or unknown and hence unmeasurable) or to passive gene–environment correlation.

We re-emphasize here that genetic studies have effectively delineated family subsystems that appear to have a decisive impact on the development of its members by dint of social, not genetic, mechanisms. In our review, marital and siblings systems stand out here but the genetically informed literature also clarifies where parent–child relationships are associated with child adjustment for environmental, not genetic, reasons.

Must every study, then, be a twin or an adoption study? No. But family researchers from here on out must think genetically (Reiss, 2010) and read the genetic literature pertinent to the problem they are studying. Further, in considering interpretations of their findings they need to include the possibility of genetic influences on covariances they report. However, genetically informed studies need to be included somewhere in an extensive program of research. We think twin and adoption studies should be accessible resources for the field of family studies and

research funding should be available for their establishment and maintenance just as government funding has helped distribute high density EEG and MRI facilities, each piece of equipment available for the use of many nearby researchers. However, genetically informed designs can be used even in the pilot phases of a family research project. Let us suppose, for example, that a researcher has a novel idea about a parent–child interaction pattern than increases the child's liability for anxiety disorders. The researcher might consider trying out this novel idea on adoptive families in the initial study. Recruiting adoptive families is much easier if they do not have to be linked to the birth parents of the adopted child. If our investigator gets a positive finding on the first go-around then the investigator has identified a potentially salient attribute of parent–child relationships and already knows, using this design, that its covariance with child symptoms cannot be attributed to passive gene–environment correlation. Another option for this investigator is to use a sibling design; it allows for an immediate distinction: are the observed effects due to differences *among* families (either genetic or shared environment) or differences within families (nonshared or genetic). There are other compelling reason for prioritizing sibling designs including the important effects of sibling socialization and for studies of adult development, a topic to which we return below.

Evocative Gene–Environment Correlation and the Pathogenesis of Heritable Disorders

We have reviewed several quantitative genetic (Burt et al., 2005; Larsson et al., 2008; Neiderhiser, Reiss, Hetherington, & Plomin, 1999; Reiss et al., 2000; Tucker-Drob & Harden, 2012) and molecular genetic studies (Propper et al., 2012) that suggest as a novel mechanism by which genetic influence is expressed in behavioral disorders. A heritable disposition in the child evokes a response from a parent that, in turn, amplifies the child's disposition that evokes an even more vigorous parental response. These reciprocal effects may cycle back and forth until a clear pathological outcome is noted in the child (such outcomes from these reciprocal processes are also possible in the parents; see Gross, Shaw, & Moilanen, 2008). All of this process can be hidden in estimates of the heritability of a disorder as determined by, for example, twin designs or even newer methods of estimating heritability based on correlated patterns of genotypic similarity between pairs of genetically unrelated individuals who are similar in any measured phenotype (Yang, Lee, Goddard, & Visscher, 2011). All these heritability estimates say to us that genotypic differences among individuals lead to phenotypic differences—somehow and some way. As noted, the way might be entirely through conventional pathways from DNA to RNA to proteins relevant for fetal, child, or adult brain function (or other organs relevant for individual differences in behavior such as the adrenal gland). Or there could be an outside-the-skin mechanisms. Here the intermediate behavioral phenotypes are heritable characteristics that *evoke distinctive social responses*. That is, these heritable characteristics are likely to induce the same reactions in other family members across families so that they are detectable as a reliable and heritable social signals.

We have cited two papers from the same adoption study that illustrate how this reciprocal process may work for the early the development of conduct problems (Fearon et al., in press) and for ADHD symptoms (Harold et al., 2013). The Fearon paper illustrated how between family differences might blunt this process: families with happy marriages somehow cancels mother's role in this reciprocal process with salutary effects on the child's development of self-control.

But within-family differences may also matter. For example, the heritable properties that elicit warmth in mothers are uncorrelated with those that evoke warmth in fathers (Reiss et al., 2000); to be detectable these differences in response—shaped by either role or gender of the parent—must generalize across families (at least in the sample studied) to be detectable. But it seems likely that families may react to a range of aversive behaviors in children—each determined by a different gene set—in comparable ways: each elicits a negative response. The gene-variants we reviewed in molecular studies of evocative processes in children suggested that effects of many different genes do converge on negative parenting. To follow the logic here it is the response of the family to a diverse set of heritable signals in the child that plays a decisive role in the outside the skin mechanism of the expression of genetic effects in behavioral syndromes. The family may make fine distinctions—as in the case of mother or father differences in warm responses to their adolescent offspring or lump many genetically distinct effects on child's characteristics together as functionally equivalent in odiousness or attractiveness.

John Loehlin presented a method for tracking how the family may lump or discriminate among these heritable genetic signals (Loehlin, Neiderhiser, & Reiss, 2005). In a reanalysis of the data from the nonshared study by Reiss and his colleagues, he used a genetically informed factor analysis to suggest that the same genetic factors that elicit warmth from parents suppress conflict negativity (or vice versa). That is, so far as the family's response is concerned

all the heritable features leading to either warmth or negativity shape a continuous dimension of family reaction with warmth on the high end and negativity on the low end and this dimension of reaction—initially influenced entirely by the child's genotype but shaped by the family's reaction—is, in turn, distinctively related to child's autonomy and negatively related to the child depression and antisocial behavior. However, the child factors that elicit monitoring and control are uncorrelated with those eliciting the continuous dimension of warmth-negativity. This dimension, with high monitoring and control at the upper end is distinctively related to sociability and cognitive achievement in the adolescents; these positive attributes are unrelated to the genetically elicited warmth-negativity dimension. While highly preliminary these data do suggest that, where families are integral to the outside the skin mechanism of gene expression, they may recode the genetic information that resides in the heritable characteristics of the child.

Siblings and Adult Development

Adult development is as important to the field of developmental psychopathology as is child development. An emerging pattern of data from quantitative genetics seems to have much to say about these processes. While specific nonshared influences have been identified in early development their magnitude has not only be less than expected from the twin and adoption studies reviewed by Plomin and Daniels (1987). Moreover, in early development these influences were transitory and their shifts, even over short periods of time, accounted for much of the instability of measures of child adjustment over time. The picture looks quite different as individuals age. The nonshared influences become stable and efforts to identify them have successfully centered on marriage although sibling differences in occupational experience, exogenously caused health problems or even residential location are also candidates for large-scale effects. A major base for this interest in nonshared environment in adult development comes from the meta-analyses of Briley and Tucker-Drob already cited (Briley & Tucker-Drob; Tucker-Drob & Briley, 2014) which clarifies the increasing importance of stable nonshared influences, across development, in two large domains of personal functioning: cognition and personality.

Currently, one of the most astonishing initiatives in behavioral science is the U.S. Health and Retirement Study that follows a large number of individuals from midlife until advanced old age or death. This seminal study has spawned many other comparable surveys in Europe, Asia, the Middle East, Africa, and Latin America. All of them are searching for ways to characterize patterns of aging and for the influences that shape those patterns over time. Quantitative genetics, though early in its exploration of this domain, provides an impudent suggestion for these very large studies. The fundamental questions about aging may not be estimates of factors accounting for *differences among individuals*. Rather the question about trajectories of aging might be reframed: what factors account for *difference and similarities between siblings* in the same family over the life course? However, the quantitative genetics literature we have reviewed suggests optimism for the discovery of the potential sources of these differences—above and beyond marriage. Except in the rare case of MZ twins (they are likely to be present in only 1 of approximately 80 cases in a random sample of aging individuals) these differences could be attributable to genetic differences among ordinary siblings. Or they could be due to critical differential experiences such as a good marriage for one or a bad marriage or no marriage for the other. We think a sibling difference in life course is a productive approach to adult development but rigorous estimates of the role of genetic differences among siblings will depend on oversampling twins. Several large-scale survey studies provide precedent (e.g., Rowe, Jacobson, & Van den Oord, 1999; South & Krueger, 2008).

There is, of course, another reason for studies of midlife and aging to sample subjects by sibling pairs. We have already reviewed data suggesting that the reciprocal environments that siblings build for themselves appears to have a sustained influence on the development of each at least through the transition to adulthood. In their reviews of sibling studies, Tucker-Drob and Briley found that stable, shared environmental influences persisted across the life span (Tucker-Drob & Briley, 2014). Do reciprocal sibling relationships play a significant role in the persistence of these stable shared environmental influences? Do these reciprocal sibling environments still bear the imprint of much earlier parent–child relationships?

SUMMARY

We have sketched a history of rapprochement between genetics and the social sciences in the study of the family. There are many domains in the study of the family that have been inalterably changed by this rapprochement: a heightened interest in differences between families in the sensitivity of members to one another, early steps in

embedding the study of family processes in a genuine transactional neuroscience, the prospect of a better fit between families and family-level interventions design to reduce problems they already have or to prevent them from occurring in the first place, a clearer recognition that genetic relatedness among family members influences observed associations between characteristics of parents and of their children, a new etiological model of developmental psychopathology focusing on the role in the expression of genetic influences on psychopathology through reciprocal relationships of genetically influenced evocative behavior in the child and the response of the parent, and finally, a perspective on sibling-based sampling and analysis in the study of adult development and aging. We hope geneticists are also listening to the results of this rapprochement to better appreciate the circumstances under which specific gene variants are expressed or not expressed and to include in their investigations the outside-the-skin mechanisms reviewed here.

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CHAPTER 10

Molecular Genetics Methods for Developmental Scientists

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INTRODUCTION

The progressive biologization of developmental science in general and the science of developmental psychopathology in particular in the past several decades has been tightly linked to technological, methodological, and statistical advances in developmental biology and genetic epidemiology. Predictably, this biologization has been accompanied by a rapid increase in the number of multidisciplinary projects conducted and published by the field. For example, at the time of the writing of this chapter, a quick SCOPUS search limited to the subject area of psychology using a combination of search terms "genes"/"molecular genetics" AND "development" returned almost 3,000 results, with 240 reports published in 2013 alone—a sixfold increase compared with the total number of publications with the same keyword 20 years ago. Even more impressive, perhaps, is that the linear relationship between year of publication and number of published reports indexed by SCOPUS over the same period can be described with a point estimate of Pearson's $r = .91$ ($p < .000001$)—a large effect size rarely seen by developmental scientists in their own data!

Whether or not this accelerating increase in the amount of generated and published data will result in a better understanding of the complex relationships between human genetics and development partly depends on the accessibility of these data (in terms of both acquisition and interpretation) to its main consumers, that is, to developmental scientists. In 2012, the US National Institutes of Health launched an online educational initiative for behavioral and social scientists called Genetics and Social Science: Expanding Transdisciplinary Research (http://www.nchpeg.org/bssr/), aimed at providing accessible coverage of the core concepts and issues in the field of genetics. Nevertheless, in their own teaching and collaboration experience, the authors of this chapter have been faced with the virtual absence of a concise, integrative, state-of-the-art overview of the basic methodological issues and advances in human genetics as applied to the study of the development and manifestation of complex traits and common disorders in general and neurodevelopmental disorders in particular. Most of the published treatments of these topics and methods are relatively isolated in

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their scope and highly technical, thereby reducing their utility for interdisciplinary researchers that frequently do not have formal training in molecular genetics, genetic epidemiology, bioinformatics, and biostatistics. Therefore, the current chapter aims to fill this gap in the literature by providing an accessible and comprehensive overview of molecular genetics methods that would hopefully aid the new generation of developmental scientists in both digesting the rapidly growing number of reports on molecular genetic studies in the field and potentially serving as a starting point for designing their own projects.

This chapter is organized as follows. First, we will provide a brief overview of the basic concepts of molecular cell biology, thus setting the necessary background for presenting molecular genetics methods. Then, we will review several types of genetic variation and corresponding genotyping methods and research designs used in genetic linkage and association studies (with an emphasis on microarray genotyping and genome-wide association studies). We will then turn to the discussion of the current state of affairs with respect to the growing appreciation of the role of the structural variation in the human genome in human development and its consequences for the debate between those who attribute complex trait variation in humans to frequent or common vs. rare genetic variants. We will then turn to DNA sequencing methods, starting with the original Sanger sequencing and following with the next-generation DNA sequencing methods. After a brief discussion of gene expression profiling methods that builds on the information presented in previous sections (i.e., microarray and sequencing platforms), we will conclude with a set of comments pertaining to current and future utilization of molecular methods in the developmental sciences.

BASIC CONCEPTS

The focus of this chapter is on the methods used for acquiring information about the genetic make up of an individual (or a group of individuals) and study designs that are aimed at gaining knowledge about the etiology of a particular trait (typical and atypical) or a syndromic trait constellation. Before describing these methods, however, we need to establish what exactly the substrate for genetic information is, where it is located, and how it is transmitted and used to build a living organism. To minimize the technicality of this overview, we therefore refer the interested reader to other sources for more in-depth treatments of the relevant issues (Alberts et al., 2002; Laird & Lange, 2011; Russell, 2009; Wu, Ma, & Casella, 2007; Ziegler, König, & Pahlke, 2010).

With the exception of red blood cells (erythrocytes) that lack cell nucleus, every human body cell contains a full set of information about the primary structure of the genetic makeup of the individual. This information is stored in thread-like structures made of *deoxyribonucleic acid* (DNA) and other proteins. DNA, the main carrier of genetic information, is a large two-stranded molecule composed of a *backbone* that is formed by an alternating repeated pattern of a sugar group (deoxyribose) and a phosphate group, and organic *nucleobases* (or, simply, bases). The primary bases of the DNA are purines (guanine [G] and adenine [A]) and pyrimidines (thymine [T] and cytosine [C]). A structural unit of a single strand of DNA consists of one sugar group, one phosphate group, and a base, and is called a *nucleotide*. Recall, however, that DNA is a double-stranded molecule. The two strands are connected by a hydrogen bond between two opposing bases on the complementary strands comprising a DNA molecule: adenine always bonds with thymine (A-T rule), and cytosine always bonds with guanine (C-G rule). The specificity of these pairings is regulated by the dimensional[1] properties of the DNA bases and is frequently referred to as *complementary base pairing* rule since one can infer the sequence of one strand if the other one is known. The resulting DNA molecule resembles a twisted ladder described as a double helix.

Human DNA is structured into 23 *chromosomes* that function in cells. Each chromosome has a centromere and two arms, a short one (p arm) and a long one (q arm), that end with telomeres. Of these, 22 are autosomes consecutively labeled from 1 to 22 roughly according to their length: chromosome 1 is the longest with a length of ~248.9 million base pairs (bp); 21 is the shortest with ~46.7 million bp (http://www.ncbi.nlm.nih.gov/projects/genome/assembly/grc/human/data/). The remaining twenty-third chromosome is either an X or a Y sex chromosome, around 156 and 57.2 million bp long, respectively. Human sex cells (gametes—egg and sperm cells) contain a single set of 23

[1]Purines have a two-ring structure and are larger (wider) than pyrimidines that only have one ring. The formation of stable hydrogen bonds between DNA bases depends on the distance between strands, the size of the bases, and their geometrical properties. Correspondingly, purine-purine, pyrimidine-pyrimidine, and noncomplementary purine-pyrimidine pairings locally disrupt the DNA structure leading to DNA instability and are disfavored.

chromosomes and are termed to be *haploid* (k = 23). Most human somatic cells, however, are *diploid* (k = 46): they contain a double set of chromosomes, with one inherited from the mother and other one—the father, for the full diploid set of 44 autosomes and 2 sex chromosomes. Thus, while a haploid set of human DNA is approximately 3 billion bp long, the complete diploid set of genetic information is twice this length.

The genetic information necessary to make an entire organism[2] is stored in the linear sequence of DNA nucleotides and is used to guide protein synthesis. Proteins consist of polypeptide chains of repeating amino acids. Twenty different amino acids found in human proteins are encoded by triplets of DNA nucleotides called *codons* (e.g., the GUU sequence codes for amino acid called valine, while CGU codes for arginine). The three-letter code can be used to generate 64 different codons, but since there are only 20 amino acids that need to be encoded, the genetic code itself is considered degenerate (i.e., more than one codon can code for a particular amino acid). According to what is frequently referred to as the central dogma of molecular biology, protein synthesis follows a particular path, the DNA → RNA[3] → protein pathway. The first step in this pathway is called *transcription*. While the DNA is located in the cell nucleus, protein synthesis takes place in the plasma. Correspondingly, the first step requires transcription of DNA into a single-stranded messenger RNA molecule (mRNA) that carries the information to the plasma. During transcription, the DNA sequence is read by RNA polymerase (RNAP), an enzyme that is used to produce mRNA[4]—a template that will be used for the actual protein synthesis during the second phase called *translation*. This second step takes place in ribosomes in the cell plasma, and includes decoding the transcription-generated RNA to produce an amino acid or polypeptide chain that is then modified (folded) into the actual active functional protein.

The full sequence of DNA is called the *genome*. For a long time, the researchers' attention was focused on the amino-acid coding regions of the genome which contain codon sequences that initiate and terminate transcription, and whose transcripts undergo translation to produce a functional protein product—*genes*. These coding genic regions are separated by stretches of non-coding intergenic DNA. A gene can be formally defined as "a locatable region of genomic sequence, corresponding to a unit of inheritance, which is associated with regulatory regions, transcribed regions, and/or other functional significance region" (Pearson, 2006, p. 401). This recent definition underscores the shift from coding regions per se to regions that have at least some functional significance. At the time of the writing of this chapter, the latest human genome build (i.e., a public release of an assembly of contiguous reference DNA sequences in a chromosomal order that is representative of the human genome; the latest build has been released in 2014 and is called the Genome Reference Consortium human genome build 38 or GRCh38; http://www.ensembl.org) included 20,389 coding genes, accounting for about 1% of the total human genome length. However, the results of the Encyclopedia of DNA Elements (ENCODE; http://www.genome.gov/10005107), a public research project focused on identifying all functional elements in the genome, suggested that ~80% of the genome might have a biochemical function (The ENCODE Project Consortium, 2012), and that the distinction between genic and intergenic DNA regions is not clear-cut, but rather complicated by such phenomena as the existence of previously ignored transcription of regulatory elements and the presence of transcribed but non-protein-coding RNAs and pseudogenes (Gerstein et al., 2007; Mattick, 2004).

The transmission of genetic information from parents to their offspring involves the transfer of the genetic information into parental gametes during meiosis, and the fusion of parental gametes during zygote formation. Since meiosis is a special form of cell division that includes only one round of the duplication of genetic material but two rounds of cell division, each diploid progenitor cell gives rise to four haploid gametes. Thus, at the beginning of this process, a diploid progenitor cell contains a double set of

[2]Note that genetic information encoded in the DNA molecule is not only sufficient to make an entire organism, but is also transmittable (from parent to offspring), replicable (in order to be transmittable), and exhibits significant variation (which can be mapped to at least some facets of phenotypic variance within species). We will turn to these points later in the chapter.

[3]The RNA (ribonucleic acid) molecule, like DNA, is composed of a chain of nucleotides. However, it is typically a less stable single-stranded molecule. Unlike DNA that contains thymine as a complementary base to adenine, the complementary base to adenine in RNA is not thymine, but rather uracil (U), an unmethylated form of thymine.

[4]mRNA is not the only kind of the RNA molecules resulting from transcription and not the only one RNA molecule that participates in translation. Other RNAs (i.e., ribosomal rRNA and transfer tRNA) also partake in protein synthesis as supporting or regulating elements.

genetic material with each of the pair homologous chromosomes coming from one of the parents. Homologous chromosomes are similar in length, centromere location, and gene composition and position but are not necessarily fully identical as one is coming from the mother, and the other one—the father. After the DNA is duplicated, the cell contains four sets of the genetic material, and homologous chromosomes form connected pairs called bivalents. At this stage, it is possible for maternal and paternal chromosomes to exchange portions of genetic material during a process known as *crossing over*. After two rounds of meiotic division, four haploid gametes are formed. Chromosomal crossing over results in the recombination of maternal and paternal *alleles* (i.e., genetic variants) on the same chromosome and increases genetic variability among gametes. Importantly, the probability of a crossing-over occurring between two genomic segments at specific locations (loci) depends on the distance between these segments (i.e., segments and genes located closer to each other have a lower probability of being separated during crossing over than segments located further apart from each other—in the extreme case, on different chromosomes). This results in the deviation of the observed frequencies of *haplotypes* (combinations of alleles) from their expected frequencies in the population, the phenomenon referred to as *linkage disequilibrium* (LD). Two loci are considered linked if they are jointly transmitted from parent to offspring more often than under independent inheritance. Generally, genetic segments and genes that are located close together on the same chromosome and undergo recombination in less than 50% of meiotic events are considered to be linked, whereas genes and segments that are located on different chromosomes or at different ends of the same chromosome with crossing over happening in approximately 50% of meiotic events are considered to be inherited independently. We will return to the importance of the idea of linkage and linkage disequilibrium for molecular genetic studies of human traits in the next section.

The possibility of inheriting different alleles on the maternal and paternal DNA strands at the same genetic locus highlights the presence of genetic variability across individuals. In general, although different individuals can be said to have the same set of genes, they usually (with the exception of monozygotic twins) do not share the same exact sequence of DNA nucleotides. In diploid cells, the combination of alleles at a particular locus defines the *genotype* at that locus (e.g., if an individual has inherited the A allele from the mother and the G allele from the father, they have an AG genotype at that locus). If the two alleles are the same on both chromosomes, an individual is said to be homozygous at this locus, whereas different alleles form a heterozygous genotype. Variation in the human genome is a consequence of different types of mutation events that alter the base sequence composition of the DNA. These include large events during cell division that lead to deletions, insertions, duplications, translocations, and inversions of relatively large chromosomal segments and smaller events that typically occur during DNA replication, such as point mutations (i.e., substitution of one nucleotide for another). Generally, a locus is considered polymorphic if the mutant (minor or less frequent) allele is present in the referent population (e.g., individuals of European ancestry) at the frequency of at least 1% while the referent wild-type (major or more frequent) allele is found with the complementary frequency. The corresponding variation in the DNA sequence at that locus is called a *polymorphism*.

The human genome contains several types of genetic variation and corresponding polymorphisms. These include the *single nucleotide polymorphisms* mentioned above (SNPs; the most prevalent type of genetic variation, with 97,535,033 validated SNPs reported in the most recent build of the public SNP database dbSNP 144. (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_summary.cgi), *short tandem repeats* (repetitions of a pattern of one or more nucleotides adjacent to one another otherwise known as micro- and mini-satellites), short insertions and deletions of genetic material (so-called *indels* that generally range in size from 1 bp to 1,000 bp or 1 kilobase pair, kb), and *copy number variants* (deletions, duplications, translocations, inversions, and insertions of genetic material that are typically over 1 kb long). Prior to the technological advances in molecular genetics, only large (generally over 3 million bp or 3 megabases, Mb, in size) and rare types of structural variations that affected quantity or structure of chromosomes were identified, as they were detectable using microscopic techniques. Over the course of the past two decades, however, a large number of smaller, frequent, or common (>1% frequency) variants has been discovered and described. We will now turn to the most commonly employed study designs in molecular genetics of human traits, methods used to genotype the main types of variants described already, and inferential (including statistical) procedures that underlie the inference about the involvement of a particular genetic variant or a gene in the etiology of human traits.

MOLECULAR GENETIC STUDY DESIGNS AND GENOTYPING

Linkage Studies and Short-Tandem Repeat Polymorphisms (STRPs)

The vast majority of complex human traits, from height (Silventoinen et al., 2003) and insomnia-related symptoms (Hublin, Partinen, Koskenvuo, & Kaprio, 2011) to child language development and literacy-related skills (Grigorenko, Ngorosho, Jukes, & Bundy, 2006; Kovas et al., 2005) to adolescent psychopathy (Tuvblad, Bezdjian, Raine, & Baker, 2014) to patterns of resting EEG connectivity (Schutte et al., 2013), exhibit significant heritability, with the contribution of genetic factors estimated in behavioral studies to generally range from 30% to 80% with a median estimate around 50%. Establishing familiality and heritability[5] using behavioral genetics methods and designs such as twin studies, the analysis of familial trait aggregation (i.e., the extent to which the trait is overrepresented in families where there is at least one affected proband), and segregation (i.e., the establishment of the mode of inheritance or genetic model of the trait) are important steps in the discovery of the genetic architecture of a trait. These steps are typically followed by the application of molecular genetics methods to locate genomic regions and identify genetic variants contributing to the trait, with the goal of revealing main genetic factors that play a role in its development and manifestation. For so-called simple, *Mendelian traits* characterized by relatively low prevalence, Mendelian patterns of inheritance (autosomal dominant, autosomal recessive, and X-linked), and high penetrance (i.e., probability of observing the phenotype given the presence of the mutation) of single-locus genetic variants, the past three decades of research have been extremely fruitful with respect to the discovery of genes underlying these traits and accompanying disorders (Botstein & Risch, 2003). The molecular bases of more than 3,500 such rare disorders have been identified to date, accounting for approximately 50% of the estimated 7,000 monogenic diseases (Boycott, Vanstone, Bulman, & MacKenzie, 2013). Among them are such somatic disorders as cystic fibrosis (Online Mendelian Inheritance in Man, http://www.omim.org; MIM#219700; caused by mutations in the *CFTR* gene located on chromosome 7q31[6]) and developmental disorders such as DiGeorge syndrome (MIM#188400; caused by a deletion of 1.5–3 Mb region of chromosome 22q11.2 that contains, among others, the *TBX1* gene) or Charcot-Marie-Tooth syndrome (MIM#606482; caused by mutations in the *DNM2* gene located on chromosome 19p13.2).

The success of Mendelian gene discovery is largely dependent on the methodological advances that transformed statistical linkage analysis as a behavioral analysis tool to investigate familial segregation of traits into a molecular analysis tool (that involves positional cloning with molecular techniques) used to establish the location of the segments of the DNA shared by related and phenotypically similar individuals. This revolutionary change has been brought on by the technological advances that made the genotyping (i.e., evaluating the exact state) of polymorphic genetic markers (i.e., DNA sequences with known physical/chromosomal locations) accessible to researchers. Initially, these markers were *restriction fragment length polymorphisms* (RFLPs; highly locus-specific markers with alternative alleles associated with restriction fragments[7] that differ in size), followed by short *tandem repeat polymorphisms* (STRPs). STRPs are represented

[5]Familiality refers to the familial aggregation (clustering) of the trait. For example, developmental disorders of language are considered to be familial since prevalence of these disorders is higher in first-degree relatives of probands affected with the disorder than in families of unaffected children (Tallal et al., 2001; Tomblin, 1989). Heritability, on the other hand, refers to the proportion of the total trait variance attributable to genetic factors. In most cases, heritability is estimated as narrow-sense heritability that reflects "the degree to which the genes transmitted from parents determine the phenotype of their children" (Tenesa & Haley, 2013, p. 141). For example, heritability estimates from twin studies suggest that childhood depression symptoms are 30–80% heritable (i.e., 30–80% of the variance in these symptoms could be attributed to additive shared genetic effects). Every heritable trait is also familial, but not every familial trait is heritable.

[6]Each arm of a chromosome is divided into regions called cytogenetic bands. These regions correspond to the patterns of staining (light and dark areas) of chromosomal regions that can be detected under a microscope and are labeled consecutively starting from the centromere out toward the telomeres. Cytogenetic bands (e.g., 22q11) can be further subdivided into subbands (e.g., 22q11.1).

[7]Restriction enzymes can recognize specific nucleotide sequences and cut DNA at specific locations called restriction sites. An RFLP probe *hybridizes* with (i.e., attaches itself to) one or more fragments of the cut (or digested) DNA samples separated by gel electrophoresis based on their size, producing a blotting pattern (e.g., visualized on an x-ray film) specific to a genotype at a particular locus. Mutations in the genome (e.g., SNPs, indels) change the relative positions of restriction sites and the length of DNA segments between them, making them amenable to genotyping through this method.

by repeating sequences[8] of typically 1–6 nucleotides that are abundant in the human genome and, due to their elevated mutation rate, are highly polymorphic (e.g., with an average of 6–8 alleles estimated for European populations; Calafell, Shuster, Speed, Kidd, & Kidd, 1998). By themselves these polymorphisms mostly do not have functional significance as they are biased away from the protein-coding regions of DNA (Metzgar, Bytof, & Wills, 2000) due to potentially high disruptiveness of non-triplet (tri- and hexanucleotide, i.e., STRPs in multiples of three) STRPs that cause frameshift mutations (i.e., changes in the grouping of codons that affect which amino acids are coded for by the codons that occur after the mutation) and result in the alteration of protein structure and function. However, STRPs have been invaluable with respect to their utility in locating genomic regions affecting a variety of traits and remain the most frequently employed markers in linkage studies.

Recall that linked genetic loci are transmitted together from parent to offspring more often than expected under independent inheritance. In so-called parametric[9] or model-based linkage analysis used to study Mendelian traits, the investigator is interested in the recombination fraction between multiple loci genotyped in familial samples. The analysis of the segregation of these markers in pedigrees reveals their relative position on the genome and is used to map trait loci. Given the highly polymorphic nature of STRP markers and their relatively low genotyping error rate, it is possible to efficiently trace the transmission of DNA segments through the pedigrees. The co-inheritance of the same haplotype by individuals affected with a Mendelian disorder but not by the unaffected individuals (i.e., co-segregation of the phenotype and the haplotype) in extended pedigrees and nuclear families serves as primary evidence for the involvement of the particular genomic location in that phenotype. Parametric linkage studies specify several parameters to calculate the primary linkage statistic, logarithm of the odds (LOD) score, such as disease allele frequency and mode of inheritance, marker allele frequencies, and marker maps. The parametric linkage analysis itself is based on the maximization the LOD score[10] function to provide an estimate of the recombination fraction between STRP markers and the disease locus (and, correspondingly, an estimate of the position of the disease locus).

Linkage studies frequently follow a two-staged approach where the first scan is performed using multiple markers spaced 5–10 centimorgans (cM[11]) apart followed by a higher-density scan that is focused on the region for which initial evidence for linkage has been obtained. Given that the resolution of linkage studies is relatively low (1–10 cM), they might identify from a few to a few hundred genes predicted to be relevant for the trait and located within about 1 cM (or approximately 1 Mb) from the linkage site, depending on the pattern of the cross-overs in the region (Botstein & Risch, 2003). This two-staged approach, for example, has been successfully used to establish the linkage of a severe speech and language disorder to the locus labeled SPCH1 and located on chromosome 7q31, followed by the identification of *FOXP2* as the causal gene for the autosomal-dominant Mendelian speech and language disorder in a single three-generational UK pedigree (Fisher, Vargha-Khadem, Watkins, Monaco, & Pembrey, 1998; Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001). Although there are several examples of successful linkage mapping of Mendelian disorders using single extended

[8]Genotyping STRPs typically requires the polymerase chain reaction (PCR) amplification of the STRP region using primers that flank a particular STRP. The size of the amplified region depends on the number of repeats and, as in the case of RFLPs, gel electrophoresis can be used to separate DNA fragments of different size and establish the STRP genotype. Multiplexing (i.e., co-amplification of multiple STRPs in a single PCR reaction) facilitates genotyping of multiple STRPs at the same time, and in this case genotyping relies on using automated laser-induced fluorescence detection methods that label alleles with fluorescent dyes (fluorophores, same or different, depending on the overlap in allele size) attached to one of the primers for each of the STRP markers (for an overview of the current methods, see Guichoux et al., 2011).

[9]Parametric linkage assumes that the models describing the trait and the genetic marker are known. Nonparametric linkage relies on fewer assumptions about these models and their precise specifications.

[10]The LOD score is based on the comparison of the likelihood of the null hypothesis (no linkage) to the likelihood of the alternative hypothesis of linkage given certain model parameters. Positive and large LOD scores provide evidence for linkage. An LOD score of 3 is equivalent to $p = .0001$ or the odds of linkage of a thousand to one that the two loci (or a marker and the disease) are linked and inherited together. Although this value has been used as the cut-off for a long time in linkage studies, more recent work points to the LOD value of 3.3 as being more appropriate for controlling type I error rates in genome-wide linkage studies with multiple markers distributed across the whole genome at a certain density level.

[11]Centimorgan are units of genetic distance between chromosomal positions that are based on the evaluation of the frequency of crossing over (recombination) events between them (i.e., 1 cM equal 1% recombination, or, in physical distance, ~1 Mb).

pedigrees such as the KE family mentioned above (e.g., Asher, Morell, & Friedman, 1991; Sobreira et al., 2010), most linkage studies employ samples of multiple families to increase power to detect linkage. The statistical power of linkage (both parametric and non-parametric—see below) studies depends on several factors such as locus heterogeneity (i.e., more families are needed to detect signals that are coming from more than one locus involved in the etiology of the trait), recombination fraction between the trait and the marker locus (the further apart they are, the more families are required), correctness of the specification of allele frequency (and, for parametric linkage, other model parameters), diagnostic classification accuracy, presence of phenocopy (i.e., when a phenotype caused by nonhereditary factors matches or is very similar to a phenotype caused by genetic mutations), and genetic marker heterozygosity (or informativeness).

Note that parametric linkage analyses that specify modes of inheritance are best suited for locating loci involved in single-gene Mendelian disorders, especially in cases when there are few ungenotyped individuals in a family and the specification of the phenotype is unambiguous. When the trait is polygenic, common, *complex*, or quantitative in nature, however, it typically does not conform to a specific mode of inheritance, and parametric LOD score analyses are ill suited for establishing linkage in this situation. Correspondingly, nonparametric linkage analyses methods have been developed to account for this uncertainty in model parameters, relax them, or even remove the necessity to specify them unambiguously (e.g., remove the mode of inheritance assumption and decrease variant penetrance since complex traits and disorders are commonly thought to involve multiple genes and variants of small(er) effect sizes). This approach assumes that affected related individuals should show an increased sharing of haplotypes that are Identical by Descent (IBD[12]) in regions close to the involved genes independent of the specific mode of inheritance; that is, phenotypically similar related individuals should have similar alleles for a marker located close to the genes contributing to the trait.

A common design for a nonparametric linkage study is to evaluate allele sharing in sibships, in particular, affected sib pairs (for binary traits). When the IBD status for alleles for a marker can be determined (i.e., parents were genotyped and their genotypes at a particular locus can distinguish between children's IBS and IBD alleles), the observed proportion of sib pairs sharing 0, 1, or 2 IBD alleles can be compared with the expected proportions (see footnote 6) using a chi-square test or one-sided tests that compare proportion of sib pairs who share 2 alleles IBD with the expected proportion of 25% or compare average IBD sharing with the expected proportion of 50%. However, in the majority of cases, the IBD status cannot be determined unambiguously for either part of the sample or the whole sample (e.g., if the markers are not sufficiently polymorphic or the parents have not been genotyped). Several methods have been developed to allow for this uncertainty in linkage analysis. Among these are methods that take into account partially informative[13] matings from extended families (Sandkuijl, 1989), and multipoint methods utilizing information from multiple genetic markers at the same time to estimate the IBD distribution at each marker (Kruglyak & Lander, 1995). The pairwise sib-pair method can be extended to include larger sibships, and alternative pairwise IBD sharing analysis methods were developed to perform linkage analyses with multiple affected relatives of different degrees of relatedness (Gudbjartsson, Jonasson, Frigge, & Kong, 2000; Kruglyak, Daly, Reeve-Daly, & Lander, 1996).

So far we have mostly been discussing linkage in the context of binary traits such as disease status (affected vs. unaffected). However, many (if not most) traits of interest to developmental scientists are fundamentally continuous or quantitative in nature. These traits can be analyzed in quantitative trait linkage paradigms, and loci identified in studies that are based on these paradigms are frequently referred to as *quantitative trait loci* (QTLs). For sib-pair designs, early methods included regressing the squared difference between quantitative trait values of siblings on the estimated proportion of IBD alleles with the expectation that trait similarity in the presence of the linkage of this trait to a particular gene should be related to higher proportion of IBD alleles shared by siblings at the marker close to that gene (Haseman & Elston, 1972).

[12] Alleles are considered Identical By State (IBS) if they are represented by the same variant of a polymorphic locus. Alleles are considered IBD if they are not only IBS but also if they are inherited from a common ancestor. Two individuals (related or not) can share 0, 1, or 2 alleles IBS. While two unrelated individuals by definition share no alleles IBD, the expected proportion of shared IBD alleles in pairs of related individuals depends on the type of the relationship based on the principle of random segregation of gametes combined with the number of meiosis events that separate the two relatives in a pair (e.g., MZ twins are expected to share 2 alleles IBD at a given locus, while siblings are expected to show a distribution of 0 (25%), 1 (50%), and 2 (25%) alleles IBD).

[13] That is, when the parental genotype is not known but genotypes available for other family members can be used to calculate the probability distribution of the missing genotype.

More recent methods include extensions of the regression method that also incorporate additional information contained in mean-corrected cross-product of trait values (i.e., sibling covariance; Xu, Weiss, Xu, & Wei, 2000) and variance component methods that partition trait covariance between different relatives into the estimated IBD sharing component and the kinship component (Almasy & Blangero, 1998; Sham, Purcell, Cherny, & Abecasis, 2002). Keeping the sample size constant, variance component methods have the highest power when the number of pairs of relatives is maximized by studying fewer but larger families as opposed to more but smaller families (Williams & Blangero, 1999).

Cost-efficient whole-genome linkage studies that employ 400–800 STRP markers (sufficient to cover the whole genome) replaced early linkage studies that used numbers of markers an order of magnitude smaller in 1990s. Since then, a multitude of positive findings for simple Mendelian disorders have been reported. More recently, less polymorphic but extremely high density markers, single nucleotide polymorphisms (SNPs; see next section), have also been proposed for linkage studies. Yet the utility of linkage analyses for complex traits remains severely limited by their low genomic resolution, power constraints due to large sample size requirements (Risch, 2000), and cost and validity considerations specific to family-based designs, especially in the context of complex developmental traits. Although several approaches to increase the power of linkage studies of complex traits have been suggested, such as multivariate analyses that capitalize on the simultaneous interrogation of related phenotypes typical of complex cognitive traits (Marlow et al., 2003), developmental phenotypes that limit the age band where a particular phenotyping method is efficient remain a problem for these designs. Moreover, traditional mapping methods that focus on single time-point quantitative phenotype measures neglect the developmental nature of these traits and the dynamic pattern of their genetic control (Wu & Lin, 2006). We mention this developmental limitation here but would like to note that it is not specific to linkage studies and can be extended to genetic association studies in general (see next section). In addition, it is worth noting that sample ascertainment for linkage studies is rarely population-based and, correspondingly, traits that are characterized by locus heterogeneity (i.e., when a trait is influenced by multiple mutations at different unrelated chromosomal loci) might produce family-specific linkage signals that complicate the interpretation of linkage findings with respect to the general population (Teare & Barrett, 2005).

Candidate Gene Association Studies and Single Nucleotide Polymorphisms (SNPs)

In contrast to linkage studies, the goal of genetic association studies is to establish an association between the genotype at a particular locus and a particular trait. Although the distinction between linkage and association is subtle, it is crucial for understanding the differences between the two approaches for identifying the genetic bases of human traits. Genetic association studies assume that the *same allele* is associated with the trait in a similar fashion in the population, while linkage studies allow different alleles to be linked with the disorder or trait in different families, as long as the location of the genomic segment harboring these alleles shows evidence for linkage. Most genetic association studies are performed using DNA samples collected from unrelated individuals genotyped using markers that provide a much finer resolution than the RFLP or STRP markers traditionally used in linkage studies—single nucleotide polymorphisms (SNPs).

SNPs are single base-pair substitution polymorphisms that are typically less polymorphic than STRPs (i.e., most SNPs only have two alleles; see the NCBI database of SNPs called dbSNP, http://www.ncbi.nlm.nih.gov/SNP/). They represent around 90% of the variation in DNA and are found at the frequency of approximately 1 SNP per 1 kb of the human genome. They are found at a slightly higher frequency in intergenic compared with genic DNA, and among those that occur within coding genome segments, slightly less than half are synonymous (i.e., the base pair substitution does not change the coded amino acid) with the rest being nonsynonymous (i.e., missense, resulting in identifiable alterations of protein structure or nonsense, when the protein is rendered nonfunctional due to truncation introduced by a premature stop codon). SNPs that are located outside of the coding regions might also have regulatory and transcription-altering functions, although for the majority of these markers their functional impact and regulatory potential is unknown.

SNP genotyping and association analysis has become the leading tool for trait gene discovery due to their abundance in the human genome, low mutation rates, and simplicity of methods for SNP genotyping. We already briefly covered one such method: the RFLP genotyping touched upon in the previous section can actually be used for SNP genotyping when the restriction cut occurs for one allele but not the other, resulting in different segment lengths corresponding to each allele. The utility of this method is limited by its inapplicability to the majority of SNPs and the low degree of automatization of the process. There are several

alternatives available to researchers, and the choice of the genotyping platform largely depends on the scale of the study (i.e., ranging from platforms that genotype one to several thousand to several million SNPs). Below we will first describe two genotyping platforms used to interrogate several to several thousand SNPs to set the stage for the further discussion of SNP genotyping platforms in the later sections of the chapter in the context of genome-wide association studies.

One of the most frequently used methods for SNP genotyping in human association studies is allele-specific oligonucleotide hybridization (ASO). This method discriminates between SNP alleles by hybridizing complementary synthetic oligonucleotides (i.e., short single-stranded DNA molecules) to the target DNA segment. Allele discrimination in ASO genotyping relies on the labeling of allele-specific products with different fluorescent dye labels that are then read using fluorescent readout systems. For example, the TaqMan® assay (Life Technologies, Applied Biosystems) is based on the ASO method coupled with 5' nuclease activity of Taq polymerase during the PCR reaction (Shen, Abdullah, & Wang, 2009). TaqMan probes are labeled with a fluorescent reporter dye on one end (5') and a common nonfluorescent quencher on the other end (3') that eliminates background fluorescence of the intact probe. Each TaqMan assay uses two allele-specific probes and a pair of PCR primers. The hybridization of the probe during PCR results in the separation of the dye and the quencher, promoting fluorescence. Allele detection in this case is based on the Forster resonance energy transfer (FRET) analysis. FRET technique measures changes in fluorescence during dye excitation due to the transfer of energy in the donor-acceptor complex. In the absence of the quencher, the fluorophore dye, excited at a particular wavelength, emits light while returning to its ground state, while the presence of the quencher permits the transfer of energy from the excited fluorophore to the quencher without the emission of light. SNP genotyping typically uses cyanine dyes Cy3 (dark pink) and Cy5 (blue) for allele discrimination. The simplicity of TaqMan Assay chemistry lends it to automation and millions of assays have been developed, but low SNP multiplexing (i.e., genotyping of more than one SNP in parallel in the same assay/reaction) and high cost of dual-labeled probes limits the application of this genotyping method to projects that recruit large samples that are then genotyped using a large number of markers.

In contrast, Illumina GoldenGate Assay (Illumina, Inc), a highly multiplexing (i.e., simultaneously interrogating 96 to 3,072 SNPs) microarray platform, is based on the allele-specific primer extension (ASPE) and ligation method (Fan et al., 2006; Shen et al., 2005). In broad strokes, the increasingly popular microarray technology relies on using a small solid support surface with attached immobilized target DNA sequences (probes) to which the complementary amplified and labeled sample DNA (i.e., the DNA that is being genotyped) hybridizes. The hybridization signal is then read and interpreted with respect to evidence for a particular genotype. Illumina's microarray genotyping platforms are designed so that three oligonucleotides are synthesized for each SNP: two allele-specific oligonucleotides (ASOs) that are used to distinguish the SNP alleles, and a locus-specific oligonucleotide (LSO) that hybridizes 1 to 20 bases downstream from the ASO site. ASOs and LSOs contain target sequences for a set of universal PCR primers, and the LSOs also contain SNP-unique address sequences complementary to capture sequences attached to ultra-small silica beads. These silica beads are placed in microwells etched out of optical fibers or a silicon wafer. After the oligonucleotides have hybridized to the sample DNA, the ASO with a 3' end base complementary to the base at the SNP site is extended by polymerase and ligated to the corresponding LSO, forming a PCR template. The templates are amplified using the set of primers common to all SNPs, of which two are labeled with either Cy3 or Cy5 fluorescent dyes (but each anneals to only one of the two ASO sequences), and the third one anneals to a LSO common sequence. These reactions generate allele-specific PCR products that hybridize (using LSO to recognize a particular SNP site) to the beads carrying LSO-complementary oligonucleotides. The resulting hybridization signal is composed of the ratio of Cy3 and Cy5 fluorescence and is used to determine the genotype at each SNP site (i.e., equal intensity corresponds to the heterozygote, while the ratios of 1:0 and 0:1 correspond to the two alternative homozygote states). Note that genotyping based on indirect fluorescent signals is essentially a bioinformatic inference problem, and, although generally robust, is not immune to errors and depends on such parameters as the quality of the DNA sample, technical errors during sample and library preparation and handling, the specifics of SNPs selected for genotyping, and the accuracy of the algorithms used for SNP calling.

Both of the platforms described above are aimed at establishing the genotype (or allelic state) for each of the person in the study sample at each of the interrogated SNPs. These genotypes are represented by combinations of alleles that are labeled according to their frequency (typically the more frequent allele is considered the major

allele, and the less frequent one is labeled as the minor allele) in the current or the referent sample. Commercial genotyping platforms rely on prior knowledge about the sequence of the human genome and interrogate known sites of variation. Recall that a locus is considered polymorphic if the frequency of the minor allele (MAF) is at or above 1% in a particular population. However, it is certainly possible for an individual to carry private (i.e., found only in a particular family) or rare mutations that are missed by commercial platforms due to their low frequency (and novel mutations that have never been described and, correspondingly, could not have made it to the commercial SNP genotyping platforms). We will return to this point later in the chapter when talking about structural variants and rare variants identified using next-generation sequencing approaches. For now, we would like to concentrate on the main design considerations for candidate gene association studies.

Case–Control Designs, Single SNP, and Haplotype Association Testing Strategies

When the researcher is interested in the association between one (or several) SNPs and a binary or a quantitative trait, the simplest design strategy is to recruit either two ascertained groups of individuals that differ with respect to the binary trait (affected cases and unaffected controls) or a sample of individuals that exhibit significant variation in the quantitative trait. When the DNA from cases and controls is genotyped for a set of SNP markers of interest, straightforward association analyses can be employed to detect association signals separately for each marker. These include methods familiar to most behavioral scientists such as logistic regression that models log odds of disease as a linear function of the genotype/allele status and chi-square tests of association that test for the independence of disease status and genotype/allele frequencies with a standard 2 (cases + controls) × 3 (two homozygotes and the heterozygote) contingency table.

It is now widely accepted that the contributions of genetic factors to disease risk for complex disorders are roughly additive with the heterozygotes' risk estimated to be in-between that for the two homozygotes. Special statistical procedures have been developed to account for this additivity and improve statistical power compared with the general class of tests mentioned above. For example, the Cochrane-Armitage test (Armitage, 1955), also known as the proportion trend test, evaluates the hypothesis of zero slope for the line fitted to the three genotypic risk estimates—in this case the risk is estimated as the proportion of cases to the total sample of cases of controls harboring 0, 1, or 2 risk alleles. The choice of the particular association testing strategy, however, is not straightforward, as for some associations the nature of the relationship deviates from assumptions behind the employed statistical tests—for example, if the relationship significantly deviates from the additivity assumption (as in the case of overdominance when the two homozygotes have similar risk estimates that are also different from that for a heterozygote), the Cochrane-Armitage test will have low to null power to detect the true association. There are several strategies for overcoming this limitation, including calculating test statistics for all possible models (i.e., additive, dominant, and recessive effects) and choosing the maximum test statistic, or using Bayesian procedures (Balding, 2006).

For quantitative traits, association methods based on the extension of generalized linear model (GLM) approaches such as linear regression or analysis of variance (ANOVA) are frequently used to test for association under the assumption of additive genetic effects. These association tests typically require the distribution of the trait values to approximate normality for each genotype, and for each genotype group to have similar trait variances. In situations when the assumption of normality is violated, mathematical transformations of trait data such as log-transformation or quantile normalization can be used to approximate normal distribution. Score tests for binary outcomes like the Cochrane-Armitage test and linear regression approaches for quantitative traits can also incorporate covariates in the analysis, for example, to adjust for participants' gender and age.

One of the important concerns in genetic association studies is the presence of *population stratification*. Allele frequencies for a multitude of genetic variants vary both within and between different populations. Correspondingly, the detection of an association signal can be influenced (in both directions—by producing spurious associations and masking true association signals due to loss of statistical power) by the presence of differences in baseline allele frequencies between the populations from which cases and controls are sampled that have nothing to do with the trait of interest but rather with systematic differences in these populations' ancestry. In fact, population stratification is one of the most widely acknowledged reasons for nonreplication of genetic associations (Cardon & Palmer, 2003). In the ideal case, population stratification should be controlled by careful sample matching between cases and controls, and several methods (e.g., matching on such variables as geographic proximity, physical characteristics, self-reported family ancestry) have

been proposed to address this issue at the level of study design planning. Most frequently, however, the researchers supplement these procedures with statistical analyses of background genetic differences between cases and controls. These methods range from simply detecting background differences in genetic makeup between the populations by evaluating an independent set of multiple SNP markers that are unrelated to the markers of interest (Pritchard & Rosenberg, 1999) to more advanced methods such as *structured association* methods that assign individuals to population subclusters and perform association analyses within these clusters or use cluster membership as a covariate in the analyses (Pritchard, Stephens, & Donnelly, 2000), and *genomic control* methods that control for the inflation of test statistic caused by stratification (Devlin, Roeder, & Wasserman, 2001). When properly applied (e.g., by genotyping a recommended set of at least 25 additional SNPs) in situations when population stratification is not extreme, genomic control efficiently corrects for population stratification with minimal loss of statistical power (Dadd, Weale, & Lewis, 2009).

Note that the methods mentioned in the previous paragraph require genotyping multiple SNPs at unlinked or independent loci. So far we have been discussing association testing for single SNPs. However, in the vast majority of cases, the researchers genotype more than one SNP (e.g., multiple SNPs within a single candidate gene or in a candidate region). Independent testing of multiple SNPs in the same study introduces two problems. First, testing multiple SNPs separately leads to the statistical problem of multiple testing, well known to behavioral scientists as inflating Type I error rate. Standard multiple comparisons correction procedures such as the Bonferroni correction are overly conservative given that SNPs are frequently not fully independent from each other (i.e., are in linkage disequilibrium) and other methods that adjust for multiple comparisons in association studies have been developed. We will discuss these methods in the later paragraphs in the context of the extreme version of this problem specific to genome-wide association studies.

Second, such independent testing ignores the wealth of information conveyed by the combinations of SNPs reflected in haplotypes—specific combinations (or sequences) of alleles that occur together more frequently than expected by chance in regions of highly correlated genetic material with limited recombination. These regions are called linkage disequilibrium blocks and contain haplotypes consisting of SNPs that are in the high degree of linkage disequilibrium with each other due to shared ancestry (The International HapMap Consortium, 2005, 2007). Haplotype analyses reduce the burden of multiple testing by reducing the actual number of statistical tests performed. However, haplotype analyses can also capture complex interaction effects, such as when mutations that occur at different sites within the same gene on the same chromosome (in *cis* position as a haplotype) interact to create super alleles that have large multiplicative effects on the trait and disease risk (Drysdale, 2000; Tavtigian et al., 2001).

When haplotype phase (i.e., whether and which alleles observed for adjacent SNPs for a given individual are located on the same chromosome because they were inherited together as a haplotype from the same parent) is known, haplotype association testing is relatively straightforward and relies on extensions of methods used for SNP allele testing (e.g., by comparing haplotype frequencies in cases vs. controls). In case–control studies, however, the information about haplotype phase is typically unavailable as genotyping platforms produce unphased observed genotypes for individuals in the sample, and their parental genotypes are also typically unknown. Correspondingly, haplotype analysis in case–control studies requires statistical haplotype inference and reconstruction using likelihood-based or Bayesian methods followed by haplotype association testing (Schaid, Rowland, Tines, Jacobson, & Poland, 2002; Stephens & Donnelly, 2003; Sun, Greenwood, & Neal, 2007). For example, in an iterative two-staged approach of Schaid and colleagues (2002), haplotypes are inferred by computing estimates of probabilities of all possible haplotype pairs consistent with each individual's genotypes; these estimates are used as weights to update regression coefficients in association analysis in the GLM-based score testing framework that evaluates the presence of global (omnibus) haplotype effects and effects of specific haplotypes on binary, as well as quantitative traits.

Family-based Designs

Genetic association testing strategies described in the previous section rely on recruiting and genotyping samples of unrelated individuals. These case–control and case-cohort designs became the de facto standard in the field of complex trait genetics after linkage mapping fell out of favor. That does not mean, however, that studies of genetic underpinnings of complex traits exclusively use samples of unrelated individuals. A complementary class of study designs, called *family-based designs*, relies on using sets of genotyped relatives of various familial configurations to test for genetic associations between a trait and a set of SNP markers. These designs offer important advantages

over case–control studies: i.e., they are very robust against population stratification, simultaneously test for linkage and association, and offer unique strategies for battling the issues of multiple testing and genotyping quality control (Laird & Lange, 2006).

One of the simplest family-based designs is that of family trios which requires genotyping an affected proband and both of their parents. A specific non-parametric analytic strategy, called the transmission disequilibrium test (TDT), has been developed for these designs and tests the null hypothesis of no linkage and no association by evaluating the observed and the expected (under Mendelian laws) number of transmitted alleles (Spielman, McGinnis, & Ewens, 1993). For each marker, the TDT only utilizes data from informative families with at least one heterozygous parent and evaluates whether a particular allele is excessively transmitted to affected offspring (i.e., by comparing the numbers of transmitted vs. nontransmitted alleles), thus providing evidence for both linkage and association of that allele and the trait. Given that TDT is nonparametric, it does not require the specification of the genetic model or even the distribution of the trait. It is, however, inapplicable when parental genotypes are missing or when the analysis is focused on larger (so-called general) pedigrees.

The generalization of the trio-based TDT analytic strategy is realized in the widely used family-based association testing (FBAT) approach that permits using different configurations of relatives and missing data (e.g., nuclear or extended families with multiple affected and unaffected siblings that provide within-family controls), while preserving the nonparametric nature and robustness of the association testing found in TDT. FBAT represents a general class of family-based association tests that evaluate test statistics expressed as the covariance between an arbitrary function of offspring's genotype (genotype transmissions) and an arbitrary function of offspring's phenotype (a residual-trait deviation measure such as residuals from the sample mean offspring trait values); the details about the complex statistics underlying this method are presented elsewhere (Horvath, Xu, & Laird, 2001). Importantly, the FBAT approach and its extensions can not only handle different configurations of familial structures, but also work with covariates, are efficient with quantitative and time-to-onset traits, and permit multi-phenotype and multi-marker association testing (Lange, DeMeo, & Laird, 2002; Lange, DeMeo, Silverman, Weiss, & Laird, 2004; Lange, Silverman, Xu, Weiss, & Laird, 2003).

Other extensions of the TDT test include the affected-family-based controls (AFBAC; Thomson, 1995) method that uses data from all rather than just heterozygous parents (although it loses its immunity to population stratification) and the recently developed generalized family-based association test for dichotomous traits (GDT) that utilizes data from all possible discordant pairs of relatives in the family with resulting statistical power being higher than for other frequently employed tests of association (Chen, Manichaikul, & Rich, 2009).

As noted above, one of the main advantages of family-based designs is their robustness to population stratification. Genotyping parents also facilitates establishing haplotype phase, crucial for haplotype analyses, and the analysis of imprinting or parent-of-origin and mother–child genotype interaction effects (Cordell, Barratt, & Clayton, 2004; Weinberg, 1999). Another advantage of these designs is specific to childhood disorders where recruiting appropriately matched controls is more difficult than the affected child's parents (Laird & Lange, 2006). However, these designs have an important limitation. Although family-based designs are particularly efficient in establishing linkage and association for rare Mendelian disorders, for common disorders and complex traits their power is generally lower than that of case–control designs, while genotyping cost and recruitment time requirements are generally higher than that for case–control studies (McGinnis, Shifman, & Darvasi, 2002). Nevertheless, family-based designs might still experience a rise in popularity in the context of the analysis of next-generation sequencing data, and recent advances in analytic techniques (albeit parametric) permit using hybrid designs that utilize both population-based and family-based samples simultaneously (Zheng, Heagerty, Hsu, & Newcomb, 2010).

Candidate Gene and SNP Selection Strategies

So far we have been discussing genetic association studies in general, without reference to the specific genes or polymorphisms within them. However, candidate gene association studies typically focus on a more or less well-defined set of genes and SNPs within those genes that interest researchers. Several factors influence the selection of candidate genes and SNPs for a genetic association study, ranging from the number and nature of tested hypotheses to sample size to expected effect sizes (these issues will be covered in later sections). Multiple strategies are available for candidate gene selection, although assessing the candidacy potential of a particular gene with respect to a complex trait is an inherently imprecise and difficult task (Hattersley & McCarthy, 2005). When evidence for significant linkage to a particular genomic region

has been obtained, the researchers can select a set of SNPs and genes that are located under the linkage signal peak. This *positional* strategy thus focuses on candidate susceptibility genes that account for linkage peaks obtained in prior genetic linkage scans. Although intuitively appealing, this strategy has significant limitations as identified and replicated linkage regions are frequently relatively large and, given the general power and resolution limitations of linkage studies, are likely to miss multiple candidate genes located in other regions. The positional strategy for candidate gene selection can be used in isolation or in conjunction with other strategies, including the statistical strategy that prioritizes genes implicated in the trait or the disorder (or a related trait and disorder) in previous association studies or meta-analytical investigations (see later sections of the chapter).

Candidate genes might also be selected for association analysis using prior knowledge about the *biological function* of the protein encoded by the gene and the information about the *expression* of that gene in tissues relevant for the trait (e.g., in specific brain regions) at appropriate developmental periods. The utilization of the biological function information about the gene is an efficient strategy for candidate gene selection if and when the pathophysiology of the disease/disorder or the pathways involved in the development of the trait is known. This strategy can be augmented by using information from *pharmacological* studies that identify proteins implicated in the action of the disease- or trait-modifying drug or *animal model* studies that identify candidate genes that influence a phenotype similar to the human phenotype of interest in the model animal.

The subjectivity of candidate gene selection procedures, coupled with high non-replication rates of candidate gene association studies (Ioannidis, Ntzani, Trikalinos, & Contopoulos-Ioannidis, 2001), led to the development of a variety of computational tools that attempt to address or at least minimize problems caused by the lack of the background knowledge about the molecular underpinnings of complex traits (Zhu & Zhao, 2007). These in silico tools augment and integrate several of the identified strategies of candidate gene selection (sometimes also called candidate gene prioritization) with the goal of arriving at a multivariate strategy that would more likely result in an accurate candidate gene identification than an isolated use of just one strategy. These computational prioritization tools rely on the extraction, filtration, and complex statistical analysis and integration of heterogeneous data sets and resources available in a variety of public databases that are typically organized according to the principles of biological ontology (anatomical, cell/tissue, developmental, gene, and phenotype ontology). Many of the existing gene prioritization methods rely on two sources of input: 1) a list of candidate genes for prioritization (from a single locus, multiple loci, or even the whole genome), and 2) prioritization criteria (e.g., involvement in a disease or a certain pathway) in the form of biological keywords or seed genes that have already been linked to the trait or related traits (Brunner & Oti, 2007). These tools and computational strategies generally produce lists of candidate genes by *filtering* the initial lists into smaller subsets (e.g., based on the combination of the information about gene function, association data from genome-wide association studies, protein–protein and pathway interactions) or by *ranking* the input genes (Moreau & Tranchevent, 2012). The limitation of the filtering approach is the relatively strict nature of the filtration strategies that sometimes lead to false negative results when the true candidate gene is filtered out as failing one or more of the filtration criteria. An alternative strategy is to rank the candidate genes from least to most likely to be involved in the etiology of the trait without the application of strict filters. These methods include text mining of publicly available sources (e.g., publication abstracts in MEDLINE), similarity profiling that identifies candidate genes based on their similarity to the known genes relevant to the trait or respective biological processes, and *network analytic* methods that rely on the application of methods such as random walks or diffusion kernel to networks (e.g., a true protein–protein interaction network or an integrated functional linkage network) to identify trait-relevant nodes in preestablished networks through which information is propagated. There are multiple recently published excellent reviews of these (and other) methods available to researchers, with several accessible tutorials on web-based tools the interested reader is welcome to consult (Moreau & Tranchevent, 2012; Patnala, Clements, & Batra, 2013; Tranchevent et al., 2011). However, the application of these methods in a situation when little or no prior knowledge about the etiology of the trait and the pathways involved in related developmental processes is available remains challenging, and only a subset of human genes have been sufficiently annotated to be informative in such analyses.

Once the candidate gene or a set of candidate genes have been selected, the researchers typically face the issue of choosing polymorphisms within these genes. SNP selection for candidate gene studies, like the selection of candidate genes, can rely on the evaluation of the functional effects of SNPs. Recall that SNPs can be classified according to their functional class. A natural strategy is to select those SNPs within a gene that have identifiable consequences for the

structure and, correspondingly, the function of the protein products of that gene. In this case the evaluation of the association is performed in the context of the functional impact of the SNP on the biological pathway relevant for the trait. When there are multiple relatively frequent non-synonymous SNPs per gene, it is common to include several or all of these SNPs in the pool of candidate SNPs. The evaluation of the functional effects of SNPs might promote SNP selection by providing information regarding the degree to which a particular SNP is damaging obtained in experimental studies and analytically. Similarly to candidate gene prioritization frameworks, multiple in silico SNP effect analysis tools have been proposed, generally falling into two classes of sequence evaluation vs. structure evaluation algorithms (Mah, Low, & Lee, 2011). Sequence evaluation algorithms are more frequently used than structural algorithms since dimensional structural information is currently unavailable for most proteins, and evaluate the effects of SNPs on the function of the protein based on such parameters as the extent of change in amino acid residues (sequence homology) in evolutionarily conserved (and, therefore, assumed to have important functions) loci and their physiochemical similarity. Structural analyses, on the other hand, predict the functional effects of SNPs based on their impact on the three-dimensional protein structure, for example, by focusing on protein stability. Recently developed tools integrate sequence and structure information, as well as other prioritization-related data (such as network, pathway, and association information).

Researchers might also want to include SNPs in the *regulatory* gene elements (e.g., promoters and TF[14] binding sites), regions that can have long-distance effects on gene function (e.g., enhancer regions), and regions coding for microRNAs—small (~22 nucleotides long) noncoding RNAs that are extensively involved in post-transcriptional gene expression regulation (Ameres & Zamore, 2013). All of these elements are involved in multiple mechanisms that govern gene expression (Ameres & Zamore, 2013; Riethoven, 2010). Therefore, SNPs can disrupt or alter gene expression by influencing these elements, sometimes in a cell-type and tissue-specific manner (Dimas et al., 2009). Recently, a class of elements called *expression quantitative trait loci* (eQTL) has been discovered by establishing associations between variants located in these elements that can either be proximal (*cis*) or distal (*trans*) with respect to the location of the gene with the actual levels of that gene's expression (Dixon et al., 2007; Goring et al., 2007). Emerging evidence points to the pivotal role of eQTLs in complex traits—e.g., it has been found that SNPs associated with complex traits are much more likely to be located in eQTLs compared with SNPs located in other regions (Nicolae et al., 2010), and, correspondingly, point to the regulatory (rather than, for example, disruptive) nature of the variants associated with complex traits and common disorders.

Note, however, that commercial SNP genotyping platforms rely on using known SNP sites with a certain frequency threshold (i.e., >1% MAF in the population) that also satisfy several additional constraints necessary for high-quality genotyping (e.g., the unambiguity of the surrounding sequence is pivotal for successful target hybridization), and genotyping the full set of all discovered SNPs within a gene is impractical both from a statistical viewpoint and for cost reasons (it is, however, becoming increasingly possible with the application of next-generation sequencing methods; see further chapter sections). Given that the human genome has a linkage disequilibrium-laden correlated structure candidate gene association studies frequently employ the *tag SNP* selection strategy. Thus, loci demonstrating significant levels of linkage disequilibrium can be evaluated for association with a trait using so-called common tag SNPs that are correlated with other SNPs in the region because of the shared history and therefore tag common SNP haplotypes, removing the necessity to genotype SNPs at all possible loci. The presence of linkage disequilibrium and the availability of common tag SNPs for genetic association studies implies that it is possible to detect an association between a tag SNP and a trait without the tag SNP having any direct functional relationship with the trait and without directly genotyping the causal variant. Therefore, an important distinction for genetic association studies is that between a *direct association* and an *indirect association* that arises due to the correlated structure of the genome and the corresponding redundancy in the information provided by closely located SNPs. Differentiating between the two classes of association phenomena is an important issue for genetic association studies and frequently relies on the extensive characterization of the functional impact of the SNP on a trait or further fine-mapping (e.g., by using next-generation DNA sequencing) of the region around the SNP for which association has been demonstrated.

The selection of tag SNPs is possible in situations when the patterns of linkage disequilibrium between common variants at a particular locus are known for a given population. Fortunately, large-scale genome research

[14]Transcription factors (TF) are proteins that initiate and regulate transcription (and, therefore, gene expression) by binding to specific DNA sequences.

projects such as the International HapMap Project that focuses on discovering common patterns in the variation of the DNA sequence in the human genome (The International HapMap Consortium, 2005, 2007) provide such high-resolution genome-wide data for samples of varying ancestries: e.g., over 90% of the common (MAF > 5%) SNPs in non-African populations and around 80% of the common SNPs in Yoruba populations are highly correlated with at least one SNP in HapMap-produced data set of over 3.7 million SNPs with an oversampling of nonsynonymous SNPs.

Researchers are typically interested in obtaining the smallest possible set of tag SNPs with minimal loss of information based on pairwise correlations between SNPs or correlations of multiple SNPs indexing haplotypes. Some studies show that the reduction in the number of genotypes required to capture the common variation using tag SNPs is around 46–65% when the SNPs are chosen to capture all of the SNPs in the reference set, with a further reduction of 36–55% when the selection criteria are relaxed and without noticeable decreases in statistical power to detect true association signals, with even greater efficiency for multimarker methods (de Bakker et al., 2005). Correspondingly, several computational tools have been developed to optimize the process of tag SNP selection for candidate gene association studies using data produced by the International HapMap as well as other projects (Xu, Kaplan, & Taylor, 2007) for single as well as multiple populations simultaneously (Liu, Wang, & Wong, 2010; Patnala et al., 2013; Sicotte, Rider, Poland, Dhiman, & Kocher, 2011). However, although common tag SNPs can efficiently capture common variation in the human genome, they are much less efficient at predicting rare variants with MAF below 5% (Zeggini et al., 2005), and researchers should be aware of this limitation while designing candidate gene association studies.

An example of a successful implementation of a candidate association strategy can be found in a recent report on the genetic bases of adolescent substance abuse by Trucco, Villafuerte, Heitzeg, Burmeister, and Zucker (2014). Trucco and colleagues examined the associations between *GABRA2*, a gene previously implicated in substance abuse and conduct disorder in adults, and rule breaking as a potential mechanism mediating the effects *GABRA2* on substance and alcohol abuse risk in the developmental context. *GABRA2* is characterized by a strong LD structure, resulting in two common haplotypes specific to this gene. These haplotypes have been tagged in the study by three SNPs genotyped using the TaqMan platform for each of the 518 participants. The results were consistent across three SNPs and indicated that variation in *GABRA2* was more strongly associated with rule breaking in mid–late but not early adolescence, with over 70% of the total effect of *GABRA2* on substance abuse attributable to mediating rule breaking (which prospectively predicted substance abuse in the sample). This study represents not only a successful candidate association study that interrogated the candidate gene identified for a complex trait in adult samples but also, notably, explicitly modeled cascading developmental processes and their genetic regulation (i.e., using path modeling).

Genome-Wide Association Studies and High-Density SNP Microarray panels

The ability of common SNPs to tag genetic variants in linkage disequilibrium with them lies at the heart of the principle of *genome-wide association studies* (GWAS). In contrast to candidate gene association studies, GWAS studies are hypothesis-free in the sense that instead of depending on hit-or-miss candidate gene and variant selection, they are aimed at interrogating the whole genome. GWAS studies were made possible by the combination of advances in human genetics such as the completion of the Human Genome Project[15] (International Human Genome Sequencing Consortium, 2001, 2004), the deposition of a large number of SNPs to public databases, the initiation of the HapMap projects, and the rapid development of commercially-available high-throughput microarray genotyping platforms by Illumina and Affymetrix in the mid 2000s. Initially, these platforms aimed at using the microarray approach (described in previous sections) to genotype approximately 100,000 SNPs with MAF > 5% per sample spread across the whole genome and tagging other variants in linkage disequilibrium with them.

Current instantiations of Illumina's and Affymetrix's GWAS microarray panels include 10–50 times more SNPs than the number of SNPs used in the first published GWAS that evaluated associations between 116,204 SNPs and age-related macular degeneration in 96 cases in 50 controls (Klein et al., 2005). For example, Illumina currently offers a family of BeadChip-based microarray panels that evaluate from 715,000 SNPs per sample

[15]Coordinated by the National Institutes of Health and the U.S. Department of Energy, the Human Genome Project was the international consortium-based research program aimed at establishing the precise genomic location and DNA sequence of human genes. Its completion in 2003, 13 years after the start of the project, marked the key milestone in the science of human genetics.

(HumanOmniExpress-24) to over 4.5 million SNPs per sample (HumanOmni5Exome). In addition to including more SNPs, some of these arrays also (1) capitalize on information obtained in the 1000 Genomes Project[16] and large-scale sequencing projects, permitting genotyping of rare SNPs with MAF between 1% and 5% as opposed to only common SNPs with MAF >5% in previous generations of panels, (2) oversample exonic SNPs, boosting the power and resolution of GWAS studies to detect associations with SNPs located in coding gene regions, (3) include markers for other types of genetic variation (e.g., indels and CNVs; see later sections), and (4) allow for panel customization with the option of adding up to thousands of custom markers that specifically interest the researchers in specific studies.

Recent studies comparing the efficiency, coverage, and cost–benefit ratios (Ha, Freytag, & Bickeboeller, 2014) for different genotyping platforms suggest that while genome coverage for these platforms is slightly lower than advertised by the manufacturers and varies by study population, their tagging efficiency is still relatively high, and techniques like the imputation of unobserved genotypes based on the markers genotyped on the microarray are likely to prove advantageous for GWAS studies. Several overviews on the design of GWAS studies focusing on the evaluation of the prospective sample size and power as related to researchers' budgetary constraints, research questions and hypotheses, and choice of genotyping platform have been published and can be used as practical guides for choosing a particular genotyping platform (Ha et al., 2014; Nelson et al., 2013; Spencer, Su, Donnelly, & Marchini, 2009). Given the availability of these resources, we would like to instead focus on a set of design (and interpretation) issues beyond the choice of genotyping platform that are relatively specific to GWAS studies.

Most GWAS studies adopt a *case–control* approach, while recruiting large samples of cases and controls that are genotyped using high-throughput platforms mentioned above. Since GWAS studies typically evaluate hundreds of thousands to millions of SNP markers, they are faced with the necessity to perform the corresponding large number of statistical tests that dramatically increases the Type I error rate. Traditionally, researchers have used a relatively arbitrary cutoff of $p < 5 \times 10–^{7}$ put forward by the Wellcome Trust GWAS publications (The Wellcome Trust Case Control Consortium, 2007) or standard Bonferroni adjustments (α / number of genotyped SNPs) to declare an association statistically significant. However, Bonferroni adjustments are overly conservative in the context of the correlated structure of the human genome, and several alternatives that correct for non-independence between tested SNPs have been proposed. These include techniques that correct *p*-values based on the direct genotype-based calculation of the effective number of independent tests (Duggal, Gillanders, Holmes, & Bailey-Wilson, 2008; Gao, Becker, Becker, Starmer, & Province, 2010) and permutation testing (Han, Kang, & Eskin, 2009; Johnson et al., 2010).

Performing and correcting for multiple comparisons in the GWAS context means a dramatic power reduction for detecting associations, especially when the signal to noise ratio is high. This issue is especially pronounced when searching for indirect genetic associations with complex, polygenic traits that exhibit significant allelic (i.e., when multiple different polymorphisms in the same gene are associated with the trait) and locus (i.e., when multiple genes and genomic loci are implicated) heterogeneity, and when phenotyping is imprecise. Although the aforementioned first published GWAS study included ~150 individuals, currently performed GWAS studies generally employ much larger samples. For highly heritable polygenic traits with a strong genetic component such as height or Crohn's disease susceptibility, effect sizes for common SNPs are generally small and vary in the range of .07% to 1.96% of explained phenotypic variance (Park et al., 2010). A recent analysis of published disease- and trait-associated SNP associations corroborates these estimates with an observed range of odds ratios (ORs) from 1.04 to 29.4 and a median of 1.33 (Hindorff et al., 2009). Such small effect sizes require inordinately large samples to be detected, especially for variants with low MAF: for example, over 10,000 cases and 10,000 controls would be required to detect an association between a dichotomous trait and a disease variant with an OR of 1.3 at MAF < 10% with 80% power at $p < 10^{-6}$ (Wang, Barratt, Clayton, & Todd, 2005). While power increases with larger effect sizes and variant MAF for binary traits, GWAS studies still typically require samples on the order of 2,000 to 3,000 cases and controls to detect significant associations using currently available genotyping platforms (Spencer et al., 2009). It is worth noting that statistical power is slightly higher for detecting GWAS associations with quantitative rather than binary traits under some conditions (Yang, Wray, &

[16]The 1000 Genomes Project launched in 2008 with the goal of arriving at a refined, detailed catalog and map of human genetic variation by discovering >95% of genetic variants of up to 1% MAF across the genome, estimating their population frequencies and linkage disequilibrium patterns by performing DNA sequencing of 1,000 human genomes.

Visscher, 2010). Other factors such as the heritability of the trait, disease prevalence, the number of causal variants, the presence of epistatic (gene by gene or GxG) interactions, the degree of LD between the typed marker and the causal variant, the case/control proportion in the study sample, and the presence of covariates also all influence statistical power, and extreme care must be exercised at the stage of GWAS study design to address these issues.

Over 2,000 GWAS studies have been published since 2005, and curated catalogues have been constructed to facilitate dissemination of GWAS findings (Welter et al., 2014). Although GWAS studies have produced an array of results for a variety of traits, several issues have become apparent once these vast amounts of data have been accumulated. First, although multiple susceptibility loci have been identified for many complex traits, many were likely missed due to power limitations mentioned previously and characteristics of individual GWAS studies. Second, nonreplication and false association issues of genetic association studies, when extended to large-scale GWASes, are severe (Ioannidis, 2007; Lazzeroni, Lu, & Belitskaya-Levy, 2014), thus requiring extensive and careful validation in carefully designed replication studies, transforming a GWAS study into a two-stage design where association signals detected in the *discovery* cohort are validated in the *replication* cohort. This strategy can be augmented by GWAS association results prioritization strategies (Cantor, Lange, & Sinsheimer, 2010; Hou & Zhao, 2013) that optimize further gene, SNP, and sample selection. Third, when pooled together, disease- and trait-associated SNPs typically explain well under 10% of the phenotypic variance of complex traits (Visscher, Brown, McCarthy, & Yang, 2012). When compared with heritability estimates from behavioral genetic studies, these results suggest that trait-associated SNPs explain only a minor fraction of the heritability estimated in behavioral genetic studies. The remaining, unexplained portion has been correspondingly called *missing heritability* (Manolio et al., 2009), and this issue has received a lot of attention in the literature in the recent years. Several factors have been proposed to account for the missing heritability of complex traits, ranging from the acknowledgment of the important role of rare and structural variants (see following sections of this chapter) to the suggestions that missing heritability does not imply the presence of missing/undetected genetic variants but rather an overestimation of heritability in studies that ignore interactions among genes, their variants, and corresponding etiological pathways (Zuk, Hechter, Sunyaev, & Lander, 2012).

One interesting approach to increasing statistical power in genetic association studies, put forward in the psychiatric genetics literature, is to shift attention from direct behavioral phenotypes (e.g., disease status or performance levels) to intermediate phenotypes that are more proximal to the etiology of the trait than syndromic phenotypes. These so-called *endophenotypes* can be, for example, metabolic (e.g., peripheral hormone levels), neurophysiological (e.g., resting state EEG power), neuroanatomic (e.g., volumetric measures), or neurocognitive if the latter are proximal to the trait (e.g., phonological working memory measures in studies of developmental language disorders). Componential, quantitative endophenotypes reduce the complexity of end-point behavioral phenotypes and provide an intermediate link between biological and behavioral-syndromic levels of analysis (Cannon & Keller, 2006). The evident increase of interest in endophenotypes of complex disorders and traits was accompanied by both theoretical and methodological changes in the approaches to these traits that emphasized multivariate, dimensional and continuous investigations of multiple elements or facets of complex traits (Insel et al., 2010), in particular neurodevelopmental traits and disorders (Grigorenko et al., 1997; Smith et al., 2010).

Until now we have been describing ideal situations where, aside from design, power and interpretation issues, genetic association studies (including GWAS studies) have been otherwise properly conducted. Yet, there is an additional layer of complexity to such studies related to the technical aspects of DNA sample type, collection and handling, genotyping errors and quality control procedures. Although behavioral scientists undoubtedly recognize the complexity of the application of genetic methods, we would like to bring the attention of the reader to these issues to further facilitate their recognition and appreciation of the multi-layered uncertainty that is fundamental to modern molecular genetics methods.

High-throughput genotyping platforms have specific requirements for the volume, concentration, and quality of DNA samples submitted for genotyping. Correspondingly, in many studies, genomic DNA isolated from whole (venous) blood samples has been used as the preferred sample type. Collecting blood samples from development populations, however, might be challenging due to the complexities and potential complications of phlebotomy procedures. Inexpensive and easy to use saliva collection kits such as Oragene DNA Saliva kits (DNA Genotek, Inc) have been proposed as a viable alternative to standard procedures that typically yield ~8 ml of

anticoagulant-preserved whole blood per sample. DNA yields from saliva samples are typically lower than those from blood samples, and protein contamination rates are higher (Abraham et al., 2012). However, several studies have demonstrated that despite a slight drop in genotyping quality for saliva samples, concordance rates between blood and saliva samples are very high, and saliva samples perform well both in small-scale and large-scale genotyping projects (Abraham et al., 2012; Bahlo et al., 2010; Philibert, Zadorozhnyaya, Beach, & Brody, 2008).

Once the sample type has been selected, sample collection for large-scale projects typically takes place at multiple data collection sites. Multiple confounding issues can arise at this stage if cases and controls are overrepresented at different sites, genotyping for them is performed using different genotyping platforms and/or on separate sets of sample plates. Analyses of existing data sets demonstrated the presence of significant batch effects during genotyping that led to spurious associations due to confounding case–control status with such variables as experimental order, sample type, and confounding of family member status in family trios with plate sets that masked true genetic differences between families (Lambert & Black, 2012). Such effects are far from trivial and sometimes lead to the retraction of potentially high-impact publications, as has been the case with the New England Centenarian Study of human longevity GWAS published in and subsequently retracted from *Science* (Sebastiani et al., 2010) due to spurious associations attributable to combining data from multiple genotyping platforms. These issues are directly related to the principles of experimental design, and corresponding precautions can be taken to prevent confounding by using such procedures familiar to most scientists as blocked randomization.

Most current GWAS studies, however, rely not only on careful study design and procedures for *quality assurance* but also on the application of a complex set of procedures for *quality control* (Weale, 2010). Although the rationale behind each of these procedures is beyond the scope of this chapter, it is worth mentioning that it is common to assess the quality of genotyping per sample and per genetic marker (typically filtering out markers and samples with a genotype call rate below 95%), evaluate concordance between reported gender and gender inferred from genotypic data (i.e., based on the X chromosome heterozygosity) and between technical replicates, remove markers with low MAF (i.e., below 5%) and markers that show evidence for Mendelian segregation errors (one of the benefits of adopting a family-based design), assess population stratification using methods such as principal components analysis (PCA), and evaluate genetic markers for their deviations from Hardy-Weinberg equilibrium.[17] Given the complexity of genetic association study (including GWAS) design, execution, analysis, and interpretation, a special set of reporting guidelines called STREGA (Strengthening the Reporting of Genetic Association Studies) has been developed to facilitate reporting transparency and ease of interpretation (Little et al., 2009). In our view, these guidelines can also be used to facilitate optimal study design by bringing all of the above issues (and more) to the attention of researchers, funding agencies, and reviewers.

GWAS studies of developmental psychopathology traits are relatively scarce (Addington & Rapoport, 2012) and findings from these studies have been mixed. For example, although eight GWAS studies of ADHD have been performed, none have identified variants that would survive corrections for multiple testing. However, a recently published study used a two-stage GWAS approach with 607 adult ADHD cases and 584 controls in the discovery and 2104 ADHD cases and 1901 controls in replication samples, obtained suggestive evidence for the involvement of *FBX033* in ADHD and frontal gray matter volume (Sanchez-Mora et al., 2015).

Augmenting Genetic Association Studies Using Recent Statistical Developments: Mixed Models, Chip Heritabilities, Gene-Based Associations, and Meta-analytic Approaches

Some of the quality control procedures and adjustments can be performed in a GWAS setting simultaneously with statistical analysis. A particularly efficient method for adjusting for population structure confounders such as population stratification and familial relatedness (including so-called cryptic relatedness which arises when related samples are included in a population-based genetic association study) is the application of a set of analytical procedures known as *linear mixed models* (Kang et al., 2010; Listgarten et al., 2012; Zhou & Stephens, 2012). These models generally treat a genetic effect (e.g., number of minor alleles for a SNP) as a fixed effect in a regression model that also includes an additional random effect that models genetic relatedness (genetic covariance)

[17]Hardy-Weinberg equilibrium (HWE) describes the relationship between genotype and allele frequencies where there are no selection forces (such as mutation, selective survival or genetic drift) influencing a particular locus in a stable population. In the context of GWAS, departures from HWE can indicate genotyping errors.

between individuals in the study sample. In the GWAS context, available SNPs are used to calculate measures of genome-wide similarity between pairs of individuals (e.g., a kinship matrix) that capture the probabilities that these pairs share causal alleles and estimate their contribution to the phenotype. Developed explicitly for the application to complex quantitative traits, these methods are generally computationally intensive but are extremely efficient at controlling for a variety of confounding factors, sometimes in an SNP-specific (rather than sample-specific) manner, thereby reducing both Type I and Type II error rates.

Although these methods present a viable alternative to standard association testing approaches, they do not solve other GWAS issues such as missing heritability. Several recently developed methods that are gaining popularity in the complex trait genetics literature are aimed at addressing the missing heritability issue by estimating the proportion of phenotypic variance captured by all of the information provided by high-throughput genotyping technologies, rather than relying on single-SNP testing. This estimated proportion is called *genetic heritability* or *chip heritability*. For example, genome-wide complex trait analysis (GCTA) has been proposed as method for the polygenic modeling of complex traits (Yang, Lee, Goddard, & Visscher, 2011). Under the assumption that individuals who are more genetically similar should also be more phenotypically similar, GCTA utilizes genome-wide SNP data to estimate genetic relatedness between pairs of individuals in the sample. It estimates chip heritability by using the extension of linear mixed models to partition phenotypic variance into additive genetic variance explained by all SNPs, additive–environment interaction effects, and residual variance. However, this approach is not applicable when gene-gene interactions or dominance effects are at play, and effectively assumes that every genetic variant affects the trait and effect sizes are normally distributed. For some traits, however, it might be more realistic to assume that a proportion (but not all) of SNPs affect the trait of interest, and methods based on sparse regression models (e.g., Bayesian variable selection regression models) have been developed for such situations. Given that for the majority of traits the true genetic architecture is unknown, hybrid *polygenic modeling* approaches that combine the linear mixed modeling and Bayesian sparse regression modeling have been developed (Zhou, Carbonetto, & Stephens, 2013). Hybrid polygenic models allow for both a small number of large effects and a large number of small genetic effects to be estimated simultaneously, with the balance between the two inferred directly from the data. They are not only efficient at estimating chip heritabilities when combinations of larger and smaller effect size SNPs are at play, but also can be used to predict disease risk and quantitative trait values. Of note is that these methods are new, and few empirical reports have been published to date.

Two other classes of analytical procedures have been proposed to increase the yield of GWAS and candidate gene association studies. While polygenic modeling approaches are aimed at estimating the contribution of all of the (genome-wide distributed) genotyped SNPs to the trait, *gene-based tests* are aimed at evaluating the association between a trait and all markers within a particular gene (Li, Gui, Kwan, & Sham, 2011; Liu et al., 2010). This approach is especially powerful when a gene contains more than one causal variant, each of which is only marginally associated with the trait. Gene-based tests effectively combine the effects of all of typed SNPs in a gene and estimating a test statistics that is adjusted for non-independence between these SNPs. While genetic variants can exhibit different allele frequencies, LD structure, and heterogeneity in different populations, gene-based analyses might produce more consistent and replicable findings across populations than single-marker analyses. Gene-based tests are not only efficient in candidate gene studies, but also in the GWAS context, particularly by reducing the multiple comparisons burden as tens of thousands (number of evaluated genes) rather than hundreds of thousands or millions of statistical tests are performed. Extensions of gene-based testing procedures include the incorporation of functional information on SNPs that are assigned a prior weight based on their involvement in specific pathways and protein-protein interaction networks.

Another approach to evaluating the robustness and increasing the power for detecting genetic associations is to perform a genetic association *meta-analysis*. Even with relatively large samples, for the majority of complex traits the yield of reported and replicated genetic associations has been relatively modest. While GWAS studies typically employ a two-staged design where each of the stages is analyzed individually, there is a growing appreciation of the utility of directly combining statistical evidence for associations from multiple samples both within the same GWAS study and across published GWAS data sets (Begum, Ghosh, Tseng, & Feingold, 2012). Meta-analytic procedures, familiar to most behavioral scientists, offer an important toolset for detecting small effects that are consistent across multiple studies and cohorts, and revealing heterogeneity between studies and samples. They are especially relevant for so-called mega-analyses of association studies that are based on multitudes of individual studies performed within research consortia formed specifically to

increase statistical power. Genetic meta-analyses typically use straightforward statistical methods for combining (weighted or unweighted; e.g., using Fisher's method or a weighted Z-score method) *p*-values or effect sizes within either fixed or random effects models (Nakaoka & Inoue, 2009). Although powerful, meta-analytic techniques require special care with respect to ensuring the validity and robustness of the application of study exclusion and inclusion criteria, similarity of phenotype definition, interchangeability of SNP coding, consistent application of data cleaning procedures across data sets, and genotype imputation when studies differ with respect to the genotyping platform, as well as meta-analysis model selection.

The development of the approaches covered in this section of the chapter is reflective of the maturation of genetic association research in general and GWAS research in particular as a field that has moved beyond simple association testing, and has already contributed to disease- and trait-related gene and variant discovery. For example, Kornilov et al. (2015) performed a GWAS study of developmental language disorder in a small sample ($n = 359$) from an isolated population with an increased prevalence of the disorder using a mixed linear modeling approach. Although no individual SNP reached genome-wide significance, a gene-based analysis identified a gene statistically significantly (after correction for the number of genes for which the tests have been performed) associated with a part of the quantitative multivariate language phenotype in the population, *SETBP1*. Although the functional significance of this gene is currently unknown, several independent case study reports also indicated that *SETBP1* haploinsufficiency (i.e., when only one copy of the gene is functional) is associated with expressive language deficits in children. Yet the methods described in this section have only rarely been applied to developmental traits, and although for other complex traits (mostly a variety of somatic disorders) the accumulation of data led to a certain level of awareness of both benefits and limitations of common variant genetic association testing, psychological, psychiatric, and developmental genetics still lives in the pre-GWAS era or, optimistically, the GWAS era, compared with the post-GWAS era status for other traits.

STRUCTURAL VARIATION IN THE HUMAN GENOME AND COPY NUMBER VARIANT (CNV) ASSOCIATION STUDIES

Although SNPs represent most of the interindividual variation in the human genome, other types of variants have been receiving increasing attention in the last decade. These include structural genetic variants such as insertions, deletions, duplications, inversions, and translocations of genomic segments and segmental duplications. The field of human genetics has been extensively characterizing genetic variants at the nucleotide (e.g., SNPs) and karyotype levels (e.g., by studying aneuploidies), but structural variants that are smaller than ~3 Mb have generally been poorly characterized with respect to their number, distribution, size, allele frequencies, and functional impact.

The human genome contains several types of structural genetic variants that are frequently (albeit relatively arbitrarily) classified according to their size. Small insertions and deletions called *indels* represent the smallest class of structural genetic variants and generally range in size from 1 bp to 1 kb. Although initial estimates of the number of indels in the human genome were around 400,000 indels (Mills et al., 2006), with an average density of one indel per ~7 kb of genome, more recent data from the 1000 Genomes Project indicated that the human genome might contain over 1,000,000 indels combined over different populations (1000 Genomes Project Consortium, 2010). Indel density in the human genome is correlated with SNP density, and approximately a third of indels are found in the coding regions of the genome, thus potentially having important functional effects on the affected genes.

Structural variants that involve duplication or deletion of DNA segments over 1 kb long are called *copy number variants* (CNVs), and when structural variants of this size do not involve changes in the amount of genetic material (e.g., as in the case of inversions where the DNA sequence is flipped around with no actual gain or loss of genetic material), they are called *structural variants* (SVs). The distribution of CNVs and SVs across the human genome is not uniform: for example, as deletions are frequently associated with loss of protein function, they tend to be evolutionarily biased away from genes, and CNVs in general are biased away from ultraconserved genomic regions that are known to be under strong selection (Cooper, Nickerson, & Eichler, 2007). Structural variant frequency declines with variant length, with most (Shen et al., 2013; Wong et al., 2007; Zogopoulos et al., 2007) of the structural variants being classified as low-frequency (.50% to 1–5% MAF) or rare (< .50% MAF), and variants found at higher frequencies are called copy number polymorphisms (CNP); correspondingly, the human genome is estimated to have fewer CNVs and CNPs (e.g., ~20,000 estimated by the 1000 Genomes Project) than indels or SNPs. Note that, although SNPs vastly outnumber structural variants, given the size of the latter, the cumulative sum of base pairs that can be affected by them can actually be larger than the sum of base pairs affected by SNPs, thus

representing the second major source of genetic variation among individuals.

Like SNPs, structural variants can be benign or damaging with respect to their impact, and functional effects of this type of genetic variation are diverse. Gene expression association analyses revealed that CNVs account for 17.7% of the total genetic variation in gene expression levels (Stranger et al., 2007), and CNVs that directly lead to the increase or decrease of number of copies of a particular gene can affect that gene's transcript abundance (i.e., the amount of gene transcription product) and gene dosage. SVs, on the other hand, can disrupt transcription by creating breakpoints within transcripts, and large SVs can result in the alteration of the spatial distribution of chromosomes in the nucleus, thereby affecting important regulatory genetic interactions. CNVs, indels, and SVs located in regulatory regions might also disrupt gene expression, and these effects have been observed for loci that are sometimes millions of bp away from the target gene. The specifics of these effects partly depend on the location of the variant and the type of the regulatory element affected by it (i.e., activator or repressor). Likewise, structural variants located in noncoding regions can modulate transcription and even produce more severe effects like chromosomal fragility.

Our understanding of the landscape of structural variation in the human genome and its role in human traits has been limited in part due to the technological challenges specific to methods used for structural variant discovery (i.e., identification of the variant in a population, its validation, and characterization at the sequence level) and genotyping. CNV discovery and genotyping has relied greatly on the development of microarray approaches, primarily array *comparative genomic hybridization* (array CGH) and SNP microarrays, and in both cases the evaluation of the copy number state is done by comparing probe signal intensities to those of the reference sample. Array CGH relies on comparative and competitive hybridization of two samples labeled with different fluorophores to a set of targets, typically represented by long oligos or bacterial artificial chromosome (BAC) clones (Oostlander, Meijer, & Yistra, 2004). The fluorescence intensity signal ratio (Cy3:Cy5) between the two samples is normalized, converted to a $\log_2$ ratio, and the latter serves as the main source of information for copy number inference: increase in this ratio is indicative of the increase (or gain) in a copy number relative to the reference, while a decrease is indicative of a copy number decrease (or loss). The initial resolution of CGH studies was low and allowed for the evaluation of copy number states for variants larger than 1 kb. Commercially available whole-genome CGH arrays manufactured by Roche NimbleGen and Agilent Technologies rely on evaluating signals from multiple (i.e., 3 and more) consecutive probes to infer copy number state for each region and can genotype structural variants that are ~500 bp long. Although the CGH method is not sensitive to structural variants that do not alter the amount of genomic materials (i.e., SVs such as transversions), it is currently the leading method for CNV detection in clinical settings that previously relied on karyotyping, especially in the contexts of searching for the potential causes of unexplained neurodevelopmental disorders (Miller et al., 2010).

SNP microarray panels discussed in the previous sections have also been suggested as a method for structural variant genotyping (Cooper, Zerr, Kidd, Eichler, & Nickerson, 2008). Unlike for CGH, in this case hybridization is performed using one sample rather than two, and total normalized intensity as well as allelic intensity ratios are used for CNV inference to compare the copy number state of the tested sample with the aggregated intensity estimates of another individual or, more typically, a group of individuals (e.g., all of the genotyped individuals in a study sample). Although recent instantiations of these microarray panels include (nonpolymorphic) probes that specifically tag common CNVs and indels (especially in regions with low SNP density or coverage), in general the signal to noise ratio for CNV detection is lower for SNP panels compared to that of CGH panels (Alkan, Coe, & Eichler, 2011; Greshock et al., 2007), frequently leading to false positives (i.e., a discovery of the CNV that is not further validated using methods such as quantitative PCR). Microarrays have important limitations with respect to structural variant detection. For instance, copy number differences are evaluated with respect to the reference used to design the probes, and no information is available with respect to the actual location of duplicated or deleted regions or the position of structural breakpoints; in addition, single-copy gains are harder to detect than losses, and, as mentioned above, SVs that do not affect copy numbers are undetected by microarray panels. Furthermore, analysis of copy number states in and around repeat-rich and duplicated regions of the human genome is challenging given that microarray platforms rely on the assumption that each location is diploid in the reference, which might or might not be true, and is important given that CNVs actually correlate with segmental duplications in the human genome (Itsara et al., 2009). In addition, microarray CNV genotyping and discovery rely on the application of computational copy number detection

algorithms (Colella et al., 2007; Wang et al., 2007), which, while performing well with large CNVs, are not as accurate in detecting small structural variants, and multiple algorithms have been shown to differ with respect to identified variants with concordance rates between different algorithms sometimes falling below 50% and validation rates below 70% (Pinto et al., 2011).

Alternative methods for structural variant genotyping that overcome some of the aforementioned limitations of microarrays are single-molecule methods and next-generation sequencing. The former include cytogenetic methods like fluorescence in situ hybridization (FISH), fiber-FISH, and spectral karyotyping. These methods provide visualization of alterations of genomic structure at the single molecule level and have been used for structural variant discovery in the past. However, the fact that these methods are low throughput and have low resolution limits their application to several individuals and large structural aberrations (generally 500 kb to 5 Mb). Recently developed visualization techniques such as optical mapping and nanochannel visualization provide a more fine-grained analysis of genome structure and detect multiple types of structural variants (including complex rearrangements) and their locations but their application is also highly limited by a low throughput; these methods are reviewed elsewhere (Alkan et al., 2011; Das et al., 2010; Levy-Sakin & Ebenstein, 2013; Yamada et al., 2011).

Structural variant association study designs and analytical approaches are generally very similar to those described in this chapter for SNP-based studies. They rely on the recruitment of samples of cases and controls (less frequently—population-based samples to study associations with quantitative traits) and testing for association between the structural variant (typically a CNV) alleles (e.g., the number of copies) and the trait, either in a candidate–gene or whole-genome fashion. Given their high potential for being functionally damaging, CNVs are important vehicles for both studying candidate genes and identifying new trait-related genes.

Recall, however, that although they are collectively common and account for a significant proportion of human genetic variation, most structural variants are individually rare. In fact, structural variants in disease association studies have become synonymous with *rare variants*. In the previous sections we called GWAS studies hypothesis-free. This is not entirely correct given that GWAS study design, technologies used for genotyping, and statistical considerations guiding the analysis of GWAS studies are rooted in the common disease/common variant (CDCV) hypothesis. CDCV assumes that complex traits are primarily influenced by small to moderate effect size and low penetrance variants that are common in the population (Reich & Lander, 2001). Although initially promising, this approach has faced serious criticism in light of the landscape of findings from GWAS studies published in the last decade, most importantly the failure of common variants identified as disease susceptibility loci or QTLs to account for the major portion of genetic variance in the corresponding trait or provide evidence for their functional involvement in that trait's etiology. Correspondingly, the common disease/rare variant (CDRV) predicts that multiple rare variations in the DNA with high penetrance are the major (or at least complementary to common variants) contributors to complex trait variance and manifestation (Schork, Murray, Frazer, & Topol, 2009). Several arguments have been put forward to support CDRV. For example, it has been argued that population-level processes such as purifying selection and random genetic drift regulate the frequency of deleterious genetic variants, and rare genetic variants with recent (i.e., past 2 centuries) mutational history are more likely to contribute to common disease etiology than older common variants (Pritchard, 2001).

Much like the way recent GWAS polygenic modeling studies provide some support for the CDCV hypothesis, structural variant and DNA sequencing studies published in recent years have been pivotal in providing evidence for CDRV. The debate between the two has not been resolved, and the authors of this chapter would like to emphasize that recent attempts to reconcile the two are more likely to result in advances in our understanding of the genetic architecture of complex traits (Gibson, 2012; Schork et al., 2009). One approach is to evaluate the relative contributions of the two types of variants to the trait. A complementary approach would also seek to provide a theoretical and mechanistic account of how common and rare variants operate together, for example, by extending the well-known threshold-dependent response model to incorporate both types of variants. In this case, complex traits are regulated by a large number of polymorphisms that modulate biochemical traits contributing to the overall phenotypic trait, and individuals at the extremes of the continuous liability conferred by these polymorphisms exhibit disease states when additional risk is conferred by rare variants, the variable effects of which are conditional on the background liability (Gibson, 2012).

The digression in the previous two paragraphs and the distinction between the two classes of genetic variants is important for understanding the most commonly used structural variant association designs and problems

specific to this class of genetic association studies. CNPs with relatively high MAF can be analyzed in a relatively straightforward fashion in case–control association studies by comparing CNP frequencies in cases and controls, and the usual association study validity (e.g., as related to population stratification) considerations also apply in this case. If the analysis is performed using SNP microarray-derived data, quality control procedures developed for SNP data (e.g., call rate thresholding) are supplemented by strict quality control procedures that attempt to account for the high signal-to noise ratio of microarray-based intensity data and imprecisions in CNV detection (e.g., by adjusting probe data for batch effects and so-called genomic waves that affect probe signal intensities, and evaluating consensus between CNV calling algorithms; Diskin et al., 2008).

Another concern in CNV association studies is related to the difficulties in locating structural breakpoints specific to a particular structural variant: both true heterogeneity (i.e., presence of overlapping but not fully identical CNV segments associated with the trait) and genotyping/inference errors (i.e., when the same CNV is identified as having somewhat different start–end points for several samples) confound CNV association studies. Several strategies have been proposed to account for this issue by integrating CNVs in a study sample in a way that evaluates the boundaries between different CNVs and, for example, treats all common and unique CNV segments in the study sample as separate copy number variant regions (CNVRs). Since CNV association studies are relatively new in the field, comprehensive tools that perform CNVR detection and association analyses in an integrated fashion have only appeared recently (Forer et al., 2010; Kim et al., 2012). These tools also incorporate CNV association testing strategies for quantitative traits, most of which are based on familiar GLM techniques such as linear regression.

CNV association studies can also be performed in a family-based setting using designs similar to the ones used by SNP association studies, e.g., by using family trios or extended pedigrees. These data can be analyzed by recoding CNV data as pseudo-SNPs (and assigning minor allele counts to each sample based on the deviation from reference copy number) and using corresponding analytic techniques such as TDT. However, this two-step procedure (copy-number assignment and association testing), common to case–control CNV GWAS studies, has been criticized for artificial discretization of distributed intensity values and loss of power. Correspondingly, the FBAT approach that has been extended to CNV data in the GWAS context uses normalized probe signal intensities instead of assigned copy numbers to test for association between the trait (binary, quantitative, time-to-onset, and multivariate) and each marker (Ionita-Laza et al., 2008). Other association testing techniques for family-based designs based on variance component analysis for quantitative traits (Eleftherohorinou et al., 2011) or the further refining of the FBAT approach (Murphy et al., 2010) have also been proposed.

Family-based designs offer an important advantage over case–control CNV association designs as they permit evaluating the de novo (noninherited) status of CNVs when parental CNV genotypes are available. Determining the de novo status of a structural variant can be performed both after and during CNV calling (Chu et al., 2013). The popularity of the de novo or spontaneous/sporadic framework for CNV analysis is illustrative of the recent attention to the high per-generation genetic mutation rate in humans. For example, on average a newborn is expected to have ~70 new single nucleotide mutations in their genome with most of these mutations seemingly being of paternal origin (Keightley, 2012; Lynch, 2010). Although structural variants have not been precisely evaluated for their mutational properties yet, some estimates suggest that their mutational rate is lower than that of single nucleotide variants, and decreases with size. For example, new large CNVs over 100 kb long are estimated to occur once every 42 births (Itsara et al., 2010). However, de novo CNVs affect a significantly higher number of base pairs (16–50 kb) overall than single nucleotide variants (61 bp) per birth (Campbell & Eichler, 2013), and their deleterious potential is very high. As we mentioned above, CNVs became nearly synonymous with rare variants in genetic association studies, and in some cases the researchers' attention is exclusively focused on the role of rare de novo structural variants in the etiology of complex traits and disorders.

Although structural variant association studies are subject to the same statistical concerns and limitations as SNP studies, some of the issues are extremely pronounced in GWAS CNV investigations. Given the significant overlap in analytical approaches used for SNP and CNV association testing in the case/control setting, statistical power for CNV association tests can be evaluated using general power calculation tools. Recall that power is in part related to the frequency of the minor allele. Given their overall low frequency and genotyping issues that decrease power to detect CNVs described earlier, structural variants in general and CNVs in particular become difficult to detect in smaller-*n* studies (Wineinger & Tiwari, 2012). For example,

for single-marker tests, sample sizes above $n = 4{,}000$ might be required to detect an association even with higher MAF CNPs (Barnes et al., 2008).

Evaluating the impact of CNVs on a trait can be boosted by employing different collapsing methods, for example, by using CNV burden testing that evaluates the differences in estimated overall CNV frequencies or cumulative CNV length (burden) across different length bands between cases and controls. This powerful strategy can be augmented in a candidate–gene fashion by evaluating burden estimates for specific gene sets, such as for genes implicated in the candidate (or related) pathways and networks. In recent years, CNV burden has been linked to a host of developmental outcomes. For example, in one study individuals with intellectual disability and combined intellectual disability and multiple congenital anomalies have been found to harbor more large (>1 Mb) CNVs than control individuals or individuals with autism or dyslexia (Girirajan et al., 2011), and similar findings have been recently reported for ADHD (Yang et al., 2013).

DNA SEQUENCING: FROM SANGER SEQUENCING TO HIGH-THROUGHPUT NEXT-GENERATION SEQUENCING TECHNOLOGIES

So far we have been discussing genotyping methods and study designs that largely rely on the availability of genetic markers with known genomic locations and allele frequencies estimated for populations of different ancestries. In the case of linkage studies and in most cases of GWAS investigations, the statistical (linkage/association) signal is indicative of the location of the potentially causal variant which by itself is neither known precisely nor genotyped. Under these conditions, the causal mutation can be identified if the precise order of nucleotides in the DNA sequence is established for the candidate region. The Human Genome Project, the largest public scientific collaboration project in biology that took 13 years and $3 billion to complete, resulted in the publication of the working draft of the full sequence (also called the *reference sequence* or *human genome build*) of human genome (International Human Genome Sequencing Consortium, 2001, 2004), which revolutionized genetic science in terms of our knowledge about evolution, the number, location, and structure of human genes, the proteins they code for, and noncoding elements, led to the emergence of new fields such as proteomics (concerned with the identification and quantification of protein content in different organs and even cellular organelles) and directly or indirectly led to the development of technological, computational, and analytical tools that form the basis of the modern genetic science (Hood & Rowen, 2013).

The Human Genome Project relied on a combination of DNA sequencing technologies, most importantly the golden standard method of DNA sequencing based on Sanger's chemistry, developed in the 1970s (Sanger & Coulson, 1975; Sanger, Nicklen, & Coulson, 1977). Modern implementations of Sanger or first-generation DNA sequencing methods (e.g., methods that combine Sanger sequencing with capillary electrophoresis), albeit being faster, cheaper, and more automated these days, rely on the same sequencing approach. Sanger sequencing begins with the amplification of the target region of an unknown DNA sequence (called a *template*). A synthetic primer that is complementary to a region of the template is then hybridized to the single-stranded template, forming a double-stranded region that serves as a starting point for DNA chain extension by a DNA polymerase. The latter extends the sequence beyond the primer using complementary base pairing. A key element of Sanger sequencing is the addition of a small amount of dideoxynucleotide triphosphates (ddNTPs) to the reaction mix that also includes normal deoxynucleoside triphosphates (dNTPs). dNTPs (nucleotides) are standard building blocks of the DNA molecule, while ddNTPs lack a hydroxil group at the 3' position of the sugar that forms a phosphodiester bond between two nucleotides. The incorporation of a ddNTP into the growing DNA chain effectively leads to the termination of chain extension. In the solution where the same DNA chain is continuously synthesized, chain termination due to ddNTPs occurs randomly at all positions where the ddNTP nucleotide can be added to the chain. Thus, one reaction produces a set of synthetic products (*sequencing ladders*) of varying lengths, which can be separated according to their molecular weight. Four separate reactions are performed—one for each type of the nucleotide (A, T, C, and G). Originally, determining the actual genotype at each locus using the Sanger method relied on radioactive labeling of ddNTPs read via autoradiography of the sequencing gel that contained four adjacent lanes (one per nucleotide type). Radioactive labels were replaced with fluorescent labels and automated laser-induced fluorescence detection methods in the 1980s and 1990s. Current Sanger capillary sequencing methods use four different fluorophores in a single reaction; the sorting of DNA fragments by their molecular weight is performed using capillary electrophoresis, and less DNA is required for sequencing reactions due to multiple rounds of primer extensions coupled with the development of more sensitive detection

systems. Although Sanger sequencing remains the gold standard for targeted DNA sequencing, the application of this method in large-scale human projects (i.e., with a large number of individuals or multiple long DNA fragments) is limited by its relatively high cost and low throughput.

Modern sequencing platforms outperform Sanger sequencing by a factor of 100–1,000 in terms of daily bp throughput while reducing the cost of sequencing to .10–4% of Sanger sequencing costs when sequencing long (over 1 Mb) regions (Kircher & Kelso, 2010). These methods are typically referred to as *next-generation DNA sequencing* to reflect the paradigmatic change associated with the advent of commercially available high-throughput sequencing solutions in mid 2000s. For example, the 454 sequencing platform (Roche, Base) was the first non-Sanger technology to sequence an individual human genome (Wheeler et al., 2008). Unlike Sanger sequencing, this approach relies on pyrosequencing (Rothberg & Leamon, 2008) and can be used to sequence the whole genome or target regions of the genome. During DNA library preparation for pyrosequencing, the DNA that has been cut into short (1–1.2 kb) fragments is separated into single strands, and ligated to universal adapter primers. These adapter-ligated fragments are joined with microscopic beads (about 1 micron in diameter, with ~1 fragment per bead), which are then captured within droplets of oil–water emulsion, amplified using a PCR reaction (so that each droplet contains millions of copies of the original DNA fragment immobilized on the bead surface), and deposited into the picotiter plate (i.e., a plate that contains multiple wells that act as small test tubes) that contains fixed-location wells that can hold up to 1 bead each. Pyrosequencing reactions are then performed by sequentially washing single-nucleotide reagents and reaction enzymes over the plate (separately for each nucleotide). The actual sequencing relies on the detection of primer extension DNA polymerase activity using the so-called enzymatic cascade that generates light through the release of inorganic pyrophosphate when a specific (to the reaction) nucleotide is incorporated in a growing DNA strand. The pyrophosphate is converted to ATP by the enzyme sulfurylase, and a chemiluminescent enzyme, luciferase, then converts luciferin to oxyluciferin using ATP as a substrate. Light emission is monitored using cameras with fiber-optic bundles glued to a charge-coupled device (CCD). The emission is recorded at each step of the reaction and processed offline to infer the genotype at each nucleotide position.

Illumina's Genome Analyzer (also refer to as Solexa sequencing technology) is based on the four-color sequencing-by-synthesis approach that uses reversible terminator-based chemistry similar to that of Sanger sequencing (Bentley et al., 2008). For this platform, the DNA library also consists of adaptor-flanked fragments that are nevertheless shorter than those used with the 454 platform (generally up to several hundred bp). The DNA template is amplified using a bridge PCR method. In bridge PCR, both forward and reverse primers complementary to the adaptors' sequences are hybridized to a solid surface (*flow cell*) that contains eight independent channels. The immobilized DNA is then amplified to form spatially condensed clusters that contain multiple (~1,000) copies of the original template fragment in the form of arched single-stranded molecules. The resulting molecules are used as templates for DNA polymerase-based extension reactions that incorporate fluorophore-dyed terminator dNTPs into the synthesized DNA strand. Once a terminator dNTP has been incorporated, a CCD camera captures the fluorescent signal produced by laser excitation to identify the terminator nucleotide. The terminator group and the fluorophore are then removed for the next synthesis cycle (i.e., to determine the identity of the next base pair).

Both 454 sequencing and Genome Analyzer platforms can be used to sequence the whole genome by cutting it into smaller fragments and sequencing each of the fragments in parallel in the same reaction (*massively parallel sequencing*). This approach, called next-generation whole-genome sequencing (WGS), can be used effectively in three different applications: mutation discovery for Mendelian diseases that involve studying multiple affected individuals, discovery of the genetic architecture of complex traits and disorders, and clinical diagnostics of childhood disorders (Goldstein et al., 2013). The first two cases generally utilize designs familiar to the reader from the linkage and association sections of this chapter. Thus, DNA sequencing can be performed using samples of unrelated individuals that represent cases–controls or extremes of the quantitative phenotype variation continuum; allele frequencies can then be compared between the two cohorts at all genotyped loci that exhibit variation. In family-based designs, samples of related individuals are used to both detect mutations within the shared regions of the genome in extended pedigrees and reveal de novo mutations in family trios. Given the high cost of DNA sequencing, some studies only sequence affected individuals. Although causal mutations (i.e., for certain Mendelian disorders) can be identified based on their functional annotation and sharing among only the affected individuals, such studies sometimes utilize borrow controls from public repositories of sequencing data that have become available recently.

In this case, causal variant identification relies on multistep variant annotation (e.g., by obtaining information on the functional class and predicted effects of the variant) and filtration (e.g., by excluding common variants and mutations found in populations reportedly unaffected by the disorder in question). Note that DNA sequencing methods not only detect single nucleotide variants but also are capable of discovering small structural variants (indels), although the latter represent a certain bioinformatic challenge.

While Sanger sequencing is primarily used for targeted region sequencing (i.e., to sequence genes and regions under the linkage peaks or around significant association signals), WGS studies are similar to GWAS studies in the sense that they adopt a hypothesis-free approach by interrogating the whole genome. Given the high cost of next-generation sequencing in the context of association studies, however, targeted rather than whole-genome applications of next-generation sequencing have become popular in recent years. These applications and designs use DNA sequence capture chemistry to isolate regions of interest that are then subjected to sequencing. One of the most popular applications of targeted next-generation sequencing is whole-exome sequencing (WES) that is aimed at sequencing only the coding regions of the DNA by performing exome capture reactions prior to sequencing. Given the cumulative abundance of rare coding variants of potentially high functional impact in the human genome and the coding nature of most mutations underlying Mendelian disorders, WES has recently become the state-of-the-art tool for Mendelian disorder gene discovery (Bamshad et al., 2011).

Next-generation sequencing studies rely not only on an impressive set of recent technological but also on computational developments that permit analysis of extremely large data sets. Recall that massively parallel sequencing means that a multitude of genomic fragments are sequenced in parallel. For example, Illumina's HiSeq 2000 systems that are frequently used for WGS/WES applications are based on the Solexa method described above and generate 600 Gb of data in 12 days; these data include 3 billion ~100 bp reads per run. The generation of raw sequencing reads is only the first step in what became one of the most computationally intensive bionformatic paradigms in biological science. After extensive data preprocessing aimed at removal of low-quality reads, read trimming and removal of adapter sequences, the reads needs to be aligned to the reference genome. Since the reference sequence of the human genome is available, millions of short reads of unknown location generated by DNA sequencing platforms can be aligned (or mapped) to the reference genome. A variety of tools have been developed (Li & Homer, 2010), and their use typically requires both a certain expertise in bioinformatics and the availability of computational resources (e.g., a computing cluster). Most alignment algorithms construct reference genome indexes, read sequence indexes, or both. These indexes are then used in conjunction with statistical inference algorithms that find the part of the genome that corresponds to each read. Additional quality control procedures are typically employed after the reads have been aligned and sorted according their location, and are aimed, for example, at increasing the quality of indel detection by performing local realignment (or de novo assembly) for regions that contain indels. The third essential step is called variant calling and is performed on multiple overlapping aligned reads (e.g., typically with a goal of obtaining ~20x coverage at each genomic location). At the time of the writing of this chapter, a comprehensive bioinformatics pipeline developed by the Broad Institute at MIT has become the gold standard in WGS/WES variant calling. This pipeline uses a freely available Genome Analysis Toolkit (McKenna et al., 2010) to perform variant calling using HaplotypeCaller, an algorithm that uses a combination of de novo assembly and a Hidden Markov Model to identify possible haplotypes in the data and assign sample genotypes. GATK has been shown to outperform other variant calling tools in the majority of current human applications of next-generation sequencing methodologies (Ghoneim, Myers, Tuttle, & Paciorkowski, 2014; Liu, Han, Wang, Gelernter, & Yang, 2013).

Once the genotypes have been assigned to samples, the data produced by DNA sequencing can be analyzed using statistics similar to those developed for single nucleotide and structural variants described in the section on association studies. Given the large amount of data produced by WGS/WES studies (e.g., an individual genome is expected to have ~20,000 departures from the reference sequence), next-generation sequencing studies heavily rely on variant filtration, annotation, and prioritization to reduce the search space for the causal variant. Some of these methods use algorithms we referred to before when describing the evaluation of the functional impact of SNPs in association studies; these and other algorithms are frequently used in combination with each other to integrate data on the predicted effects of the genetic variant (e.g., using amino-acid substitution and phylogenetic conservation analysis; Hu et al., 2013) with other data such as the similarity between the phenotype in question with that of genetically modified model organisms (e.g., mouse; Robinson et al., 2014), or the presence of the variant in public databases or linkage

data (Zhang et al., 2013). Over 200 tools have been developed in the past decade for the analysis of WGS/WES data. A comprehensive overview of these tools is available elsewhere (Pabinger et al., 2014).

The statistical power of classic single-marker association tests is low for rare genetic variants, and while large samples (similar and exceeding those for GWAS studies) are required for studies of complex traits and common disorders, they are currently unattainable given the high cost[18] of next-generation sequencing. A new generation of statistical tests for rare-variant association testing has been developed to address the needs of next-generation sequencing studies. These methods include region- and gene-based multimarker tests that collapse rare variants into genetic scores (burden tests) and are useful when many rare variants are causal and produce effects in the same direction, and variance-component or random-effects methods that evaluate distributions of (weighted) aggregated score statistics of individual variants instead of collapsing them. These are more useful in case the region contains multiple non-causal variants and variants have different directions of association (Lee, Abecasis, Boehnke, & Lin, 2014; Moutsianas & Morris, 2014). Specific association methods have been developed for family-based sequencing studies, and these methods have been shown to outperform population-based association methods in case of dichotomous traits, while population-based tests offer higher power for continuous traits (Ionita-Laza, Lee, Makarov, Buxbaum, & Lin, 2013).

While low statistical power remains the main limitation of next-generation sequencing studies of human traits and disorders, the reader should in general be cautious when interpreting results from WGS/WES studies. First, technical errors can dramatically affect the false positive rate of next-generation sequencing studies. For example, one of the biggest technical challenges of next-generation sequencing is the presence of multiple repetitive DNA segments in the human genome that lead to ambiguities in read mapping and variant detection (Treangen & Salzberg, 2012). Second, variant filtration typically requires some sort of decision criteria to be imposed on the data set, and the researcher risks excluding the causal variant from the search set. Third, certain types of genetic variants of particular interest to researchers such as loss of function variants or variants located in regulatory regions are actually enriched for artifacts (MacArthur et al., 2012) or have low sequence coverage (Wang, Wei, Lam, & Wang, 2011), and, correspondingly, higher coverage (e.g., 60x coverage) and cost are required to accurately infer the genotype. Fourth, the same population ancestry and stratification concerns that apply to GWAS association studies also apply to WGS/WES studies. Fifth, current implementations of next-generation sequencing are limited with respect to their ability to accurately detect structural variants larger than indels (Zhao, Wang, Wang, Peilin, & Zhao, 2013). Finally, unlike the field of GWAS studies that has seen the emergence of study design, genotyping, analysis, replication, and reporting standards in recent years, the field of next-generation sequencing at the moment lacks these community-approved standards (Pulit, Leusink, Menelaou, & de Bakker, 2014), which significantly complicates the interpretation of next-generation sequencing studies that have already produced an extraordinary amount of data.

Next-generation sequencing revolutionized the field of genetics, and this technology offers the field of developmental psychopathology a new tool for identifying the genetic architecture of complex traits in a comprehensive fashion. For example, Sanders and colleagues (2012) performed a WES study of de novo single nucleotide mutations in 238 families from the Simons Simplex Collection, a cohort of pedigrees with at least one child affected with autism spectrum disorder (ASD), two unaffected parents, and (in 200 families) an unaffected sibling. This study estimated that disruptive de novo mutations are found in 14% of probands with ASD and showed that rare non-synonymous disruptive mutations in brain-expressed genes (in particular, *SCN2A, KATNAL2*, and *CHD8*) are associated with ASD with effect sizes similar to those for previously identified large CNVs. WGS/WES studies are rising, slowly replacing (or at least augmenting) GWAS studies of complex traits, and while the challenges outlined in the previous paragraph limit the utility of WGS/WES-generated data, next-generation sequencing is likely to become the new standard in molecular genetic studies of complex traits, signifying the transition to the post-GWAS era or next-generation sequencing era. In this section, we reviewed only two out of several commercially available next-generation sequencing platforms, and the interested reader is welcome to further familiarize

[18]The arrival of Illumina's HiSeq X Ten ultra-high-throughput sequencer in 2014 marked a milestone in DNA sequencing prices, which have been dropping since the advent of next-generation sequencing platforms: i.e., the cost decreased to ~$1,000 per genome (compare with $100,000,000 in 2001 and ~$50,000 in 2010; van Dijk, Auger, Jaszczyszyn, & Thermes, 2014). It is important to note, however, that this estimate is based on projected sequencing of 18,000 genomes per year over a four-year operational period, and only several HiSeq X Ten sequencers have been installed worldwide at the time of the writing of this chapter.

themselves with these platforms by referring to specialized sources (Harismendy et al., 2009; Mardis, 2013).

The next-generation sequencing era will likely be replaced by the next-next (or third-) generation sequencing era grounded in recently developed technologies that do not rely on the amplification of DNA fragments that leads to polymerase errors during library construction, preferential amplification of certain regions over others, and dilution of DNA modifications (e.g., DNA methylation). Single-molecule next-next-generation sequencing approaches such as nanopore sequencing (detection of DNA bases based on their effect on an electrical current or optical signal during the passing of the molecule or the bases through small natural or synthetic nanopores) can potentially overcome some limitations of next-generation sequencing platforms by offering affordable, quicker, and accurate (e.g., due to the absence of the amplification step and longer resulting reads) solutions for DNA sequencing (Schadt, Turner, & Kasarskis, 2010). These methods will likely bring a host of new methodological and analytical challenges with them. Until that time has come, however, current WGS/WES studies rely on next-generation sequencing platforms and approaches described above.

GENE EXPRESSION PROFILING

As we mentioned in the beginning of this chapter, variation in gene expression underlies such key developmental processes as cellular proliferation, differentiation, and plasticity in response to both external and internal factors. Recall that the first stage in protein synthesis, transcription, results in the synthesis of an mRNA molecule that is used as a template at the translation stage. Thus, the concentration of a particular RNA product is indicative of the level of the expression of the corresponding gene in the studied tissue. The full set of gene transcripts (transcribed from genomic DNA) in a cell at a particular stage of development and their quantity is called a transcriptome, and gene expression analysis (also called *transcriptome* profiling) has become one of the most widely applied methods in developmental biology. The main objective of gene expression analyses is to establish patterns of differential gene expression between different samples that might be obtained from the same group of individuals (e.g., different areas of the brain in a within-subject design) or from several groups of individuals (e.g., comparing peripheral blood gene expression levels in individuals who were or were not exposed to toxic stress in a between-subject design). Correspondingly, genes that are found to be differentially expressed between the two samples are likely involved in one or more etiological pathways for the trait.

The majority of gene expression studies rely on the microarray technology that we covered in the SNP genotyping section (in fact, we indirectly mentioned this method when touching upon eQTLs—expression microarray data remain the main source for endophenotypic data on gene expression). Library preparation for such studies requires using RNA to synthesize a complementary DNA (cDNA) molecule that is more stable than the RNA molecule during a process known as reverse transcription. Oligonucleotide probes that are located on the microarray are partially complementary to the most unique regions of each studied gene, and the evaluation of gene expression is based on the analysis of laser-induced fluorescent signals emitted by the fluorophore-labeled amplified cDNA hybridized to the microarray surface. For example, Affymetrix GeneChip Tiling Arrays, one of the most commonly used platforms, uses multiple probes (a probe set containing 11–20 pairs of probes—each pair includes a perfect match probe and a mismatch probe that is created by changing the middle base of the perfect match probe; it is used to measure nonspecific binding and correct for technical artifacts) per gene to arrive at the aggregate signal indicative of transcript abundance in a particular sample. Note that probe intensity confounds the true hybridization signal with other signals (e.g., from cross-hybridization, nonspecific binding, or system noise), and preprocessing methods that adjust for background noise (e.g., by subtracting the mismatch probe intensities from perfect match intensities) and batch effects are necessarily applied to the signal before further analyses.

Gene expression microarray studies rely on the comparison of normalized expression patterns between different samples. For a long time, fold change (the A/B ratio where A and B are intensity levels for a particular gene transcript for two samples) has been used as the main statistic to identify differentially expressed genes with relatively arbitrary fold change value (e.g. >2) cutoffs. However, this approach can produce biased estimates of gene expression and is insensitive to differential expression of genes that have extremely high as well as extremely low expression values (intensities), and inferential statistical methods such as the two-sample t-test (as well as its robust modifications that are less sensitive to outliers) have been proposed to evaluate differences in average expression levels between samples. Like GWAS studies, gene expression studies face the familiar problems of multiple comparisons and low statistical power (e.g., requiring ~32 samples per group to detect a twofold change in the 75% least variable genes

at 90% power and $p = .001$; Wei, Li, & Bumgamer, 2004; note that the current cost for a whole-genome microarray expression profiling is ~$500–750 per sample), and similar approaches have been taken to account (correct) for multiple comparisons or reduce the number of tests by analyzing differential expressions of sets rather than individual genes. For example, the Gene Set Enrichment Analysis (GSEA) focuses on sets of genes that share a common biological function, genomic location, or regulation (Subramanian et al., 2005) instead of identifying individual genes that are differentially expressed in two or more samples. In addition to partially ameliorating the multiple comparisons problem, GSEA has a number of other advantages over single-gene analyses such improved signal-to-noise ratio and its ability to identify and formally evaluate changes in pathways and processes relevant to the studied phenomenon.

In addition to microarray methods, sequence-based approaches have been developed as a method for gene expression profiling. These include early methods that used Sanger sequencing of cDNA and, most recently, RNA sequencing (RNA-Seq). RNA-Seq methods rely on the application of existing high-throughput sequencing technologies (e.g., 454 sequencing reviewed above) to cDNA libraries. RNA-Seq approaches, compared with microarrays, have low background signal given successful mapping of cDNA to the reference transcript sequence and, correspondingly, detect expression levels in the greater dynamic fold range; they are also more accurate at quantifying expression levels, leading to a higher degree of reproducibility (Marioni, Mason, Mane, Stephens, & Gilad, 2008; Wang, Gerstein, & Snyder, 2009). However, sample library preparation and RNA/cDNA fragmentation procedures involved in it can produce specific biases with respect to expression quantification, and special care should be exercised during sample library construction and data analysis to account for these biases.

Transcription levels are typically inferred using the total number of reads mapped onto gene exons normalized by the length of exons that can be uniquely mapped (Morin et al., 2008). Like next-generation DNA sequencing studies, RNA-Seq studies face a number of bioinformatic challenges such as the necessity to perform extensive quality control procedures (e.g., to correct for sequencing platform biases), dependence of statistical power on read depth which is related to both gene expression level and its length (i.e., longer transcripts typically have larger numbers of reads at the same expression level), with appreciable effects on the results of expression profile comparisons (Bullard, Purdom, Hansen, & Dudoit, 2010; Tarazona, García-Alcalde, Dopazo, Ferrer, & Conesa, 2011). Like DNA sequencing studies, RNA-Seq studies in human also greatly depend on the availability of the reference genome builds and the accumulating data regarding the spectrum of transcripts found in human cells. The presence of alternative transcripts (i.e., when the same gene gives rise to multiple transcripts/proteins due to a process known as *alternative splicing*) and problems aligning reads spanning exon junctions significantly complicate the mapping stage of the RNA-Seq studies; correspondingly, instead of the reference genomic DNA sequence, these studies sometimes use de novo assembly of transcripts or specific exon junction-modified sequence libraries to map the raw reads. Read mapping, normalization, expression level summarization and analysis of differential expression represent the main stages of bioinformatic analyses of RNA-Seq data, and multiple alternative computational approaches and tools have been proposed to tackle issues specific to RNA-Seq studies. These tools are comprehensively reviewed elsewhere (Bullard et al., 2010; Oshlack, Robinson, & Young, 2010; Soneson & Delorenzi, 2013).

Gene expression studies investigate expression levels in specific tissues (e.g., whole blood or brain gray matter). This specificity is one of the key features of expression studies, but it calls for extra care during study design, sample preparation, data analysis, and interpretation of results. Human expression studies that focus on complex neuropsychiatric and developmental phenotypes depend on the availability of relevant tissue samples. A natural strategy in this type of study is to examine differential gene expression in tissues relevant for the phenotype—that is, the brain. However, that requires justification of the selection of particular brain regions for the analysis that itself is based on data obtained from post mortem brain samples. In addition to ethical and practical concerns associated with obtaining these samples, such studies face the issue of post mortem RNA stability, and ensuring RNA integrity in these progressively degrading samples is of pivotal importance for precise expression quantification (Birdsill, Walker, Lue, Sue, & Beach, 2011). In the absence of post-mortem samples, it would be tempting to evaluate global differential gene expression patterns between two samples using whole blood samples, as peripheral blood is easier to acquire. However, whole blood gene expression levels are not perfectly correlated with gene expression levels in central nervous system tissues (Sullivan, Fan, & Perou, 2006). Correspondingly, researchers should be extra careful when interpreting results obtained from peripheral

blood samples, especially with respect to genes that are not expressed in either brain or blood, or, in general, show differential expression between blood and brain. Sample type selection represents just one of multiple issues in studying gene expression in developmental populations.

The human transcriptome is dynamic and its temporal dynamics reflect regulatory (re)organization of gene expression throughout the lifespan, which is especially pronounced in the human brain prenatally and neonatally (Colantuoni et al., 2011; Kang et al., 2011). The dynamic nature of the transcriptome, coupled with its tissue specificity (e.g., high variability between different brain regions and even different cortical layers) effectively requires researchers to carefully examine the hypothesis space generated by the combination of these factors and their research question. However, as the field matures, refines its methodology and produces enough publicly available data (e.g., as is realized in the BrainAtlas, http://www.brainspan.org, a public resource for spatiotemporal expression patterns across anatomical brain structures and different developmental stages), it will likely significantly advance our understanding of the biological machinery underlying both typical and atypical development.

FUTURE DIRECTIONS

Within the next few years (or at least for the duration prior to the publication of the next volume of this Handbook), the applications of molecular-genetic findings in the developmental science in general and developmental psychopathology in particular will likely only grow in popularity. Therefore, it is particularly important that the field introduces high standards for the design and methods employed in such studies.

Combining different methodologies in the same study, although challenging and costly, will likely generate a more comprehensive view of the molecular genetic architecture of developmental psychopathology traits. This statement applies to the combination of different phenotyping methods (e.g., by augmenting binary disease phenotypes with quantitative subphenotypes or endophenotypes such as neuroimaging data), as well as molecular genetic methods (e.g., by combining GWAS and WGS/WES methodologies to increase resolution and power).

It is also important, as it is in studies of somatic disorders, to encourage different groups interested in the same phenotype, either typical or atypical, to homogenize the methods used for generating both the phenotypic and molecular data used in the developmental sciences. Finally, the field should exercise high standards for the procedures followed when both original and secondary (partially or completely) analyzed data are available for independent meta- and mega-studies. Homogenization of phenotyping, genotyping, and analyses enables big science projects like the formation of large consortia that are aimed at investigating the genetic etiology of traits based on the pooled data from multiple populations and research groups—a crucial advantage given that small sample sizes remain one of the main obstacles in trait-associated genetic variant discovery.

CONCLUSION

The main goal of this chapter was to provide the readers with a succinct yet comprehensive sampling of the molecular genetics methods used to study human traits, in particular developmental and developmental psychopathology traits. These methods range from the discovery of the regions of the genome shared by individuals affected with a particular disorder to the quantification of the degree to which a particular gene (or genes) is expressed in a particular tissue. This variety of methods can be applied in a targeted (candidate) or a whole-genome fashion, and the choice ultimately depends on researchers' agendas and prior knowledge about the phenotype and its genetic and molecular etiology. We attempted to build our narrative to familiarize developmental researchers with this complex methodological toolbox in a non-technical way. Given the scope of the field, however, interested readers are welcome to consult with a variety of original research and review sources referenced in this chapter. In this section of the chapter, we would like to offer several brief concluding remarks.

Although the title of the chapter (correctly) assumes that all of the reviewed molecular genetics methods can be used to study human development, the extent to which they can be applied to developmental phenotypes in general, and developmental psychopathology in particular, has been limited for multiple reasons. Recruiting developmental populations for interdisciplinary, biologically oriented studies and characterizing them with respect to complex phenotypes is inherently a difficult task, undermined by uncertainties in and costs of phenotyping, issues that deserve a methodological treatment in their own separate chapter. Perhaps even more difficult is the integration of multiple levels of analysis that such studies demand.

As the fields of developmental science and developmental psychopathology are just crystallizing, it is not surprising that comprehensive frameworks for such integration are yet to be developed.

The research methods and studies reviewed in this chapter point at their complexity but also at their heterogeneity with respect to the establishment of gold standards in the field. For example, GWAS studies are probably familiar to most researchers interested in the genetic architecture of complex traits, and although the accumulation of evidence produced by these studies has been rapid, the field has had enough time to reflect upon its methodological but also theoretical limitations and challenges. On the other hand, DNA and RNA sequencing studies that use next-generation sequencing approaches have had a much shorter history, and the authors of this chapter can attest to the significant amount of methodological inconsistencies across these studies. These inconsistencies are in part related to the field's responses to the technological and computational/analytical challenges it is only now becoming familiar with. They are likely to be at least partially resolved in the near future, and public data sharing, although plagued with its own problems (e.g., ethical concerns), will likely play a pivotal role in this process. Crucially, however, most of the progress in complex trait genetics has been tied to studies of somatic disease or adult psychopathology rather than psychological phenotypes and developmental psychopathology. In that respect, the field is open to the new generation of developmental scientists and the interdisciplinary studies that will necessarily capitalize on this progress but that will also face their own challenges.

For better or for worse, molecular genetic methods for the research of complex phenotypes have been embedded into the developmental sciences just as strongly as any method in the neighboring sciences. This, of course, assumes that whatever rigor is characteristic of the utilization of these methods in their native disciplines, such as genetics or genomics, the same should be exercised in the developmental sciences. This, of course, does not assume that there should not be a certain amount of reasonable adaptation of these methods with regard to how and why these methods should be utilized in developmental sciences, but rather that their adaptation should be carried out with caution and with direct and indirect references to the lessons learned from the utilization of these methods in their native disciplines, genetic epidemiology and genetics and genomics.

One of the most important steps in our progress toward understanding the molecular underpinnings of human development via molecular genetics methods is the facilitation of cross-talk between specialists trained in complementary albeit compartmentalized subfields that serve as the foundation for the emergent fields mentioned above. To this end, it is our hope that we have succeeded in providing an overview that can be used as a starting point for the new generation of developmental scientists, but also for seasoned researchers coordinating (or hoping to coordinate) such interdisciplinary research.

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CHAPTER 11

Epigenetic Mechanisms in the Development of Behavior

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INTRODUCTION

Both genes and environmental events have long been recognized for their significant contribution to the development of behavior, and in turn, phenotypic variation among individuals. Recent work with animal models of early-life stress, depression, and addiction along with human studies focused on infant behavior and stress have revealed that genes and the environment are inextricably linked by epigenetic factors, whereby the environment can create biochemical changes that affect gene activity (Branchi, 2009; Champagne, 2010; Dudley, Li, Kobor, Kippin, & Bredy, 2011; Wong, Mill, & Fernandes, 2011). This revelation has afforded a new framework for our understanding of how psychological and social-contextual factors can interact with our biology. These factors have given us too a valuable measure informative of norms and aberrations present at the molecular level. Furthermore, these factors give us a mechanism to understand how risk and protective factors can leave their mark on our genome and a route through which behavior could arise. The birth of epigenetics research thus has major implications for the field of developmental psychopathology and its tenets (Cicchetti, 1993, 2006; Sroufe & Rutter, 1984).

In this chapter, we discuss key studies that have helped define our current understanding of epigenetics in the development of behavior. We draw on work using animal models with relevance to developmental psychopathology and studies in which the translation of these findings has been made to humans. As the development of behavior is a process that extends throughout the life span, a central theme that is also explored in this review is that epigenetic regulation of genes is not a process exclusive to developing organisms, but is an active process that continues throughout life into senescence. Throughout our chapter and within the conclusion, we also raise several questions that need to be addressed in order to advance our understanding of the link between epigenetics and behavioral outcomes.

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[1]Color versions of Figures 11.1, 11.2 and 11.3 are available at http://onlinelibrary.wiley.com/book/10.1002/9781119125556

EPIGENETICS: THE BASICS

Before discussing studies of relevance to the field of developmental psychopathology, it is necessary to understand some basics of epigenetics. In a cell's nucleus, DNA is

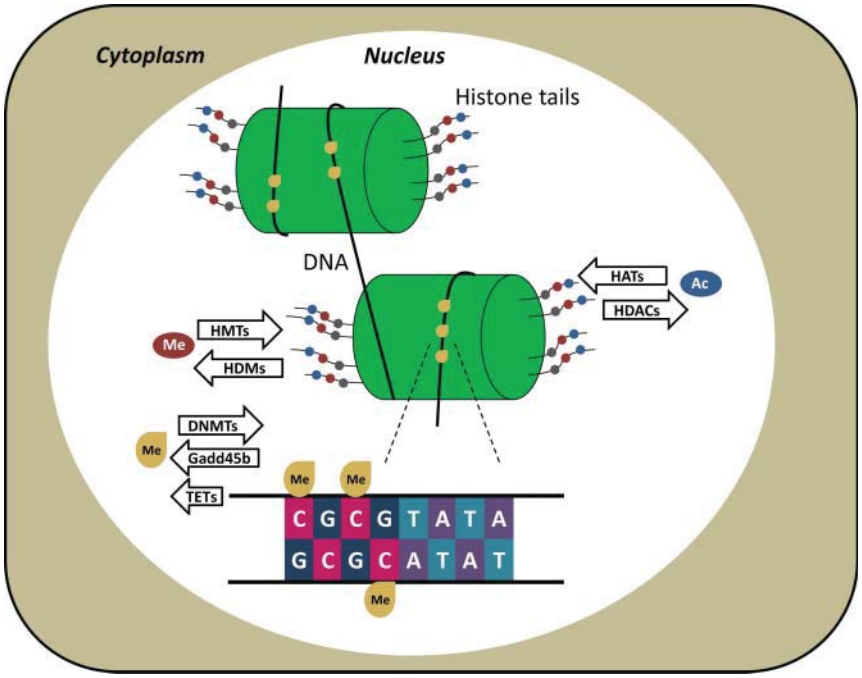


Figure 11.1 In the nucleus, DNA is wrapped around histone proteins, forming a DNA-protein complex called chromatin. DNA-histone interactions occur at the N-terminal tail of histones. On these tails reside many sites for epigenetic marking, including acetylation (Ac-blue), methylation (Me-red), and phosphorylation (P-gray). Acetylation occurs when there is the addition of an acetyl group via an enzyme called histone acetyltransferase (HAT). Deacetylation occurs when the acetyl group is removed by enzymes called histone deacetylases (HDACs). In a similar fashion, methyl groups can be added via histone methyltransferases (HMTs) or removed by histone demethylases (HDMs). Within the bottom portion of the figure is a schematic of DNA methylation, in which methyl groups (Me-tan) can be added to cytosine-guanine dinucleotides by DNA methyltransferase (DNMTs) enzymes. Gadd45b and TETs can facilitate active DNA demethylation. See footnote 1.

wrapped around histone proteins, forming a complex called chromatin (Figure 11.1). An easy way to consider histones is to think of them as spools and of the DNA as the thread that wraps around them. The backbone of DNA is negatively charged so it wraps around the positively charged histones. Without the histones (spools) to wrap around, DNA could not fit inside a cell nucleus.

To help determine whether DNA is accessible for gene transcription, chemical modifications to histones and the DNA strands themselves govern whether chromatin structure is in a state permissive for gene transcription (open and less tightly packaged, a structure referred to as euchromatin) or not (closed and tightly packaged, or heterochromatin). The histone proteins have amino acid tails that protrude beyond the DNA, and these amino acid residues are prone to chemical modifications that include acetylation and methylation (Berger, 2007). Histone acetylation, or the addition of acetyl groups to lysine residues on a histone tail, is a process catalyzed by enzymes called histone acetyltransferases (HATs). CREB binding protein (CBP) is one known HAT regulating chromatin structure. The addition of an acetyl group neutralizes the positive charge on histones, thereby decreasing the interaction with the negatively charged phosphates of DNA. This helps remodel (loosen) chromatin to a state permissive for gene transcription. Histone acetylation is rapid and reversible in an experience-dependent manner, but it too can be long-lived. Histone deacetylases (HDACs) are enzymes that remove the acetyl groups and reverse the effects of HATs. These help drive the state of chromatin back to a more closed form permissive to silencing gene activity. As an aside here, HDACs have much structural diversity and because of this are receiving research attention as possible targets of therapeutic interventions to increase gene activity.

Though far less studied in the behaviors we will review in this chapter, we are learning that histone methylation likewise is a crucial regulator of behavioral change and this modification can either suppress or activate gene transcription depending upon which amino acid residue of the histone is targeted and the degree of methylation that occurs. For example, up to three methyl groups can

be added to lysines, producing mono-, di-, and trimethylation patterns (Akbarian & Huang, 2009). H3K4 di- and trimethylation and H3K9 monomethylation are associated with gene transcription whereas H3K27 di- and trimethylation and H3K9 di- and trimethylation are linked with gene suppression. Histone methylation is catalyzed by enzymes called histone methyltransferases (HMTs), whereas enzymes called histone demethylases (HDMs) catalyze demethylation. Together, histone modifications help regulate gene activity by integrating numerous responses to signal biochemical cascades and repelling/recruiting chromatin remodeling and transcription factors making gene loci either more or less available to transcriptional modulation (Berger, 2007; Kouzarides, 2007).

DNA methylation is another epigenetic process that affects gene activity, and as will become clear in later sections, is an epigenetic factor that has really emerged as a leading candidate biological pathway linking gene–environment interactions to long-term and even multigenerational trajectories in behavioral development. DNA methylation often occurs at cytosine residues of cytosine-guanine (CG) dinucleotides, sequences that are highly underrepresented in the genome but often clustered within so-called CpG islands located within gene regulatory regions. DNA methyltransferases (DNMTs) are enzymes that catalyze the transfer of a methyl group, and de novo DNMTs (DNMT3a and DNMT3b) methylate previously unmethylated CG sites in DNA (Moore, Le, & Fan, 2013). The maintenance DNMT isoform (DNMT1, though it appears to regulate de novo methylation in some cases) perpetuates methylation marks after cell division, regenerating the methyl-cytosine marks on the newly synthesized complementary DNA strand that arises from DNA replication (Moore et al., 2013). The predominant view in the literature is that methylation of DNA is associated with suppression of gene transcription. The precise molecular processes through which this occurs are complex, but in essence methylated cytosines in turn can bind repressor proteins, including the methyl-binding domain protein MeCP2 and HDACs (Moore et al., 2013). DNA methylation (and deacetylation of histones) promotes a higher affinity interaction between DNA and the histone core, ultimately blocking access for transcriptional machinery and thus suppressing gene transcription.

It is important to note that while most evidence indicates that DNA methylation is associated with reduced gene activity, a handful of studies have indicated that DNA methylation can also be associated with transcriptional activation (Chahrour et al., 2008; Uchida et al., 2011). Regardless of suppressing or activating gene activity, DNA methylation is recognized as one of the most stable epigenetic processes affecting gene expression. As for a way to remove the methyl groups, historically in the epigenetics field, demethylation has been viewed largely as a passive process in differentiated cells, whereby multiple rounds of cell division without DNMT-mediated re-methylation is necessary to erase epigenetic marks. The idea of whether there is active DNA demethylation in post-mitotic cells, such as neurons, has been controversial. Our current understanding of active DNA demethylation is via a DNA repair-like mechanism catalyzed by Gadd45b (Ma, Guo, Ming, & Song, 2009) or oxidation by ten-eleven translocation (TET) proteins (Guo, Su, Zhong, Ming, & Song, 2011; Williams, Christensen, & Helin, 2012). A demethylase, MBD2, may also be responsible for active DNA demethylation in some cases (Detich, Theberge, & Szyf, 2002).

Though histone modifications and DNA methylation have been the most-studied epigenetic mechanisms in regards to behavior to date, increasing evidence is showing that genes (and behavior) can also be epigenetically regulated by noncoding RNAs, or RNA transcripts that have no apparent protein product. For example, microRNAs (miRNAs) are small, single-stranded RNAs with around 22 base pairs that can silence gene expression through mRNA degradation, inhibition of translation, and destabilization (Bartel, 2009). While at present we do not have a complete picture of the role of noncoding RNAs in gene regulation and behavior, it is becoming increasingly clearer that dysregulation of noncoding RNA-epigenetic pathways has relevance to understanding behavior and disease etiology (Bredy, Lin, Wei, Baker-Andresen, & Mattick, 2011; Sato, Tsuchiya, Meltzer, & Shimizu, 2011).

EPIGENETIC FACTORS AND OUTCOMES ASSOCIATED WITH PRENATAL ENVIRONMENTAL EVENTS

The intrauterine environment has long been recognized for its major contributory role in optimizing growth and development of an individual, and environmental events within this context are well recognized for their ability to affect behavioral development. For example, exposure of pregnant women to war-related stressors (including dietary restrictions) in the 1940s has been associated with an increase in prevalence of schizophrenia (SZ) and anxiety disorders in their offspring (Susser, Hoek, & Brown, 1998; van Os & Selten, 1998). Maternal emotion and psychological distress during pregnancy have been shown to predict

children's later emotional behavior (O'Connor, Heron, Golding, Beveridge, & Glover, 2002). Though such data (and numerous others) provide compelling evidence that early-life factors can predispose individuals to particular behavioral outcomes over the life course, it has not been until the past decade or so that empirical evidence has yielded a plausible mechanism for this notion.

Beginning in the early to mid-2000s, work using rodents where the prenatal environment could be experimentally altered began to provide direct evidence that one way prenatal events could alter developmental trajectories was indeed through bona fide epigenetic changes to genes. By altering nutritional cues within the prenatal environment while holding all other environmental factors and animals' experiences constant, researchers began to establish causality between prenatal nutritional exposure and phenotypic outcome (Waterland, 2006; Waterland & Jirtle, 2003). In these classic studies, pregnant Agouti mouse dams were provided dietary supplements comprised of methyl donors (e.g., methionine and folate). Offspring born to mothers who had not been fed the special methyl-donor diet had developmental outcomes characterized with yellow coat colors and overeating tendencies. In contrast, offspring born to mothers who had been fed the special diet had brown coat colors and did not overeat. The difference in developmental outcomes between the cohorts of mice was shown to be attributable to DNA methylation differences at genes controlling coat color and feeding behavior.

Since this seminal work, studies focusing on the developmental origin of health and disease have continued to identify links between early nutrition, epigenetic processes, and phenotypic outcomes. Additional work in rodents provides further empirical evidence of epigenetic factors linking maternal over-nutrition to adverse health outcomes in her offspring. For example, consumption of a high-fat diet during pregnancy has been shown to produce offspring that prefer sucrose and fat in adulthood, a phenotype that is accompanied by DNA hypomethylation (mean less methylation) and increased expression of several reward-related genes (including those encoding for the mu-opioid receptor and dopamine reuptake transporter) within the nucleus accumbens or prefrontal cortex, brain epicenters of appetite and reward (Vucetic, Kimmel, Totoki, Hollenbeck, & Reyes, 2010). Individuals who were prenatally exposed to famine during the Dutch hunger winter of 1944–45 have been shown, 6 decades later, to have less methylation of DNA associated with an important imprinted gene regulating body growth (insulin-like growth factor 2 [Igf2]) compared with unexposed, same-sex siblings (Heijmans et al., 2008). A recent study in Gambia has suggested DNA methylation patterns in first generation offspring differ depending on season of conception, in a context where diet varies greatly according to season (Waterland et al., 2010). Finally, mothers who reportedly consumed an unbalanced diet during pregnancy (one that has been linked to elevated blood pressure and cortisol in offspring) have offspring that display altered methylation of genes involved in cortisol regulation and body growth (11β-hydroxysteroid dehydrogenase type 2 [HSD2], glucocorticoid receptor [GR], and Igf2 [Drake et al., 2012]).

A growing body of work has also established epigenetic factors in pathways responsible for the negative impact of environmental toxins on current and subsequent generational offspring. During embryogenesis, exposure to the endocrine disruptor Vinclozolin (achieved by exposing gestating females) causes epigenetic programming of the germ-line that has transgenerational consequences for behavior and disease for future generations. For example, behavioral studies performed on Vinclozolin-exposed F3 generation animals show increased anxiety-like behaviors, hyperactivity, and impulsivity that coincided with alterations in gene expression networks within the amygdala (Skinner, Anway, Savenkova, Gore, & Crews, 2008). In more recent work from this line of research, investigators have shown that a single exposure to Vinclozolin likewise alters male descendants' (three generations removed) response to chronic restraint stress experienced during adolescence (Crews et al., 2012). Specifically, males with only the experience of adolescent stress (no prenatal fungicide exposure) show lower anxiety levels in an open-field test, whereas males with the cumulative experience of Vinclozolin in their lineage (i.e., their ancestors were exposed) and adolescent stress show higher levels of anxiety in the same test. Observations based on their study design are consistent with a two-hit model where exposure to chronic stress during adolescence (second hit) clearly influences subsequent brain development and behavior but they themselves are altered by ancestral exposures and epigenetic programming (first hit).

In 2008, a seminal investigation highlighted the role of epigenetic mechanisms in the maladaptive effects of prenatal stress on adult hypothalamic-pituitary-adrenal (HPA) responsivity and behavior (Mueller & Bale, 2008). Researchers found that adult males born to mothers who had been subjected to gestational stress exhibited marked changes in expression of the corticotropin-releasing factor (Crf) and GR genes, increased HPA-axis responsivity, and a depressive-like phenotype (anhedonia for example). CRF is secreted by the hypothalamus in response to stress, with

consequent secretion of adrenocorticotropin from the anterior pituitary and glucocorticoids from the adrenal gland. Examination of the Crf gene in these adults indicated that the prenatal stress regimen had significantly reduced methylation of specific cytosines with the regulatory region of the Crf gene in both the hypothalamus and amygdala. Reduced methylation parallels their observation of increased Crf gene expression, which together contributed to the depressive-like phenotype present in the offspring.

Additional work in rodent models has been consistent in showing the ability of psychological stress experienced directly by the mother to render epigenetic consequences on offspring. For example, restraint of the mother produces high levels of Dnmt1 and 3a (genes encoding enzymes that are responsible for adding methyl groups to DNA) mRNA in the frontal cortex and hippocampus of her male offspring (Matrisciano et al., 2012). This same study showed that prenatally stressed mice also displayed increased methylation of DNA associated with synaptic plasticity genes (including reelin) and several schizophrenic-like behaviors, including hyperactivity, deficits in social interaction, altered prepulse inhibition, and memory capacity. Restraint stress of pregnant rats has also been associated with changes in methylation of a placental and fetal gene (HSD2) whose product helps protect the fetus against the damaging effects of stress hormones (Jensen Peña, Monk, & Champagne, 2012). Further, variations in the magnitude of the same stressor can produce dramatically different epigenetic consequences. One group has shown that offspring of dams who had been briefly subjected to the stress of being on an elevated platform showed higher levels of global DNA methylation in their frontal cortex and hippocampus (Mychasiuk, Ilnytskyy, Kovalchuk, Kolb, & Gibb, 2011). In contrast, offspring of mothers that had spent much longer time on the platform showed a dramatic reduction in global DNA methylation levels.

As discussed in an earlier section, increasing evidence shows that genes (and in turn behavior) can also be epigenetically regulated by miRNAs. A recent study has provided a link between stress during gestation and long-term alterations in miRNA regulation in offspring (Zucchi et al., 2013). In this study, pregnant rats were exposed to a stressful environment twice daily from gestational day 12 to 18. The two stressors consisted of exposure to restraint for 20 minutes and forced swimming for 5 minutes. Investigators then assessed whether their stress regimen produced any changes in frontal cortex miRNA expression in dams or changes in whole brain miRNA expression of male offspring. They found alterations in miRNA expression in the frontal cortex of dams that correlated with stress-induced behavioral alterations (a decrease in total time spent tail-chasing antepartum compared with nonstressed dams). Specifically, gestational stress caused a downregulation of many miRNAs that are related to stress responses, metabolism, hormonal regulation, and neurological diseases, including miR-329, miR-20a, miR-500, miR-181, and miR-186. Prenatal stress also upregulated several miRNAs, including miR-24–1, which play a role in destabilization and translational inhibition of target mRNA. Significant changes were also observed in the brains (whole) of male offspring. Downregulation occurred in miRNAs that target genes that are related to neurodevelopment, stress responsivity, and brain pathologies. Upregulation also occurred in miRNAs that play a role in cell signaling and stress response, miR-98 (alters neural inflammatory responses), and miR-219 (a putative marker of SZ and bipolar disorder [BD]). While these observations cannot be directly linked to the changes in antepartum behavior observed, they nonetheless demonstrate the capacity of stress experienced by the dam to alter both her and her offspring's miRNA levels.

Fascinating evidence is beginning to emerge demonstrating that simply watching another individual experience stress can also render epigenetic consequences for offspring. Specifically, one report has shown global DNA methylation (frontal cortex and hippocampus), gene expression, and behavioral alterations in offspring of pregnant rats that were housed with another female who was repeatedly subjected to stress outside of the homecage (Mychasiuk et al., 2011). In this study, pregnant Long-Evans rats (during gestational days 12–16) were housed with another female rat that underwent elevated platform and bright light stress (30 minutes twice daily). Female offspring (10–13 days old) prenatally exposed to stress entered significantly less squares in an open field test, indicative of either locomotor deficits or their hesitation to explore novel environments. Investigation of global DNA methylation patterns in bystander-stressed offspring showed an increase in methylation within the frontal cortex and the hippocampus. A total of 558 genes were differentially expressed between the stressed and nonstressed control offspring, including genes involved in biological processes controlling neural development and function. These data effectively illustrate the ability of bystander stress to impact methylation levels within multiple brain regions (with distinct differences between sexes that we did not discuss here).

Our first hint that methylation status of the human genome is equally sensitive to maternal stress and emotion came in 2008. In this study, it was shown that infants

born to mothers that reported high levels of depression and anxiety during their third trimester of pregnancy exhibited increased methylation of the human GR gene (Nr3c1) promoter in cord blood cells (Oberlander et al., 2008). Increased methylation was also associated with increased HPA stress reactivity (change in cortisol levels from baseline) in response to novel visual stimuli at the 3-month visit. These data provided seminal evidence consistent with the notion of fetal programming of the infant's HPA axis by maternal mood. Since that study, this same group has also shown the programming capacity of maternal depressed mood on behavior and development that involves epigenetic changes within the serotonergic system. Specifically, increased maternal depressed mood scores have been associated with decreased maternal (peripheral leukocytes) and infant (umbilical cord) serotonin transporter (SLC6A4) promoter methylation (Devlin, Brain, Austin, & Oberlander, 2010). More recent work has shown an association between extreme psychosocial stress experienced while pregnant and methylation of the GR gene in newborns (Mulligan, D'Errico, Stees, & Hughes, 2012). In this study, war stress (vs. material deprivation or mundane stress) experienced by mothers in the Democratic Republic of Congo had the strongest correlation with birth weight, able to account for 35% of variance in birth weight. Birth weight and stress were also strongly correlated with GR methylation (the higher stress, the greater methylation and lower birth weight).

Together, the studies reviewed in this section indicate that nutritional factors, environmental insults, and life stress during pregnancy are risk factors for a wide range of behavioral outcomes in offspring. More importantly, these studies provide compelling evidence that DNA methylation (or demethylation) is a mechanism whereby prenatal stressors and environmental events could give rise to behavior, including altered stress responsivity and depression. As we discuss in the next section, we have also learned that epigenetic factors are at play during early-life development outside of the womb, and are thus recognized as a mechanism whereby early-life environmental events can create biochemical changes that dictate gene activity and the development of behavior.

EPIGENETIC FACTORS AND OUTCOMES ASSOCIATED WITH EARLY-LIFE POSTNATAL ENVIRONMENTAL EVENTS

The programming capacity of early environmental events outside the womb has become equally clear over decades of research. For example, children and adults with a history of early abuse or neglect show high rates of depression, anxiety, substance abuse and have impaired social functioning and deficits in cognitive performance (Cicchetti & Toth, 2005; De Bellis, 2005; Heim, Shugart, Craighead, & Nemeroff, 2010). One neural impact long presumed responsible for these outcomes is experience-induced changes in the function of the HPA axis. Indeed many clinical studies have demonstrated that early-life stress canalizes HPA axis function, as indicated by hypo- or hypercortisolism and the dysregulation of the circadian rhythm of cortisol production typical of children and adults with a history of maltreatment (Carpenter et al., 2009; Gunnar, Quevedo, & De Kloet, 2007; Rogosch, Dackis, & Cicchetti, 2011). HPA axis dysregulation is also a prominent symptom in adults with a history of child maltreatment and the diagnosis of major depressive disorder or posttraumatic stress disorder (PTSD) (Bauer, Wieck, Lopes, Teixeira, & Grassi-Oliveira, 2010; De Bellis & Thomas, 2003). Nonhuman primate models of early-life adversity likewise demonstrate the negative impact of early-life stress and maltreatment on the HPA axis, showing for example that separation of infants from their attachment figure can provoke increased activity of the HPA axis (Gunnar et al., 2007; Howell & Sanchez, 2011). Variable foraging paradigms that disrupt mother–infant interactions (approximating a neglectful caregiving environment for the infant) yield offspring that are more fearful and have high levels of CRF as well as alterations in noradrenergic and serotonergic function (Gunnar et al., 2007). Together, these observations suggest that epigenetic programming of HPA axis regulation is one way in which early-life environmental events could render an individual with lifelong altered stress responses and increased susceptibility to later-emergent stress- and mood-related psychiatric disorders.

In 2004, investigators brought forth the first direct evidence in support of this notion. At the same time, these data challenged the previously held view that epigenetic mechanisms are static and unresponsive to the environment outside of periods of embryonic development and cellular differentiation. Data they presented indicated that methylation of DNA associated with the GR, a gene underlying stress-responsivity through its regulation of HPA activity, was directly associated with the type of caregiving experienced during the first postnatal week (Weaver et al., 2004). Specifically, they showed that adult male rats that had been reared by nurturing mothers that exhibited high levels of pup licking and grooming (LG) had low levels of methylation of DNA associated with the

GR gene within their hippocampus, while adults who had been raised by less nurturing (low LG) mothers exhibited hypermethylation of GR DNA. These observations were consistent with GR gene expression patterns and anxiety-related behavior of the animals. Animals with low methylation had higher expression of the GR gene and exhibited less stress-responsivity and anxiety-like behavior (less fearful response to stimuli, decreased defensive response, and a more modest HPA response to a stress challenge), while animals with higher methylation had lower gene expression and increased anxiety-like behavior.

It is important to point out here that DNA methylation changes often occur in conjunction with other chromatin changes, including histone acetylation. Histone acetylation at the ninth lysine (K9) residue of histone 3 is a marker of active chromatin, and adult offspring of high-LG mothers when compared with offspring of low-LG mothers had higher acetylated K9 levels. Then through a series of cross-fostering studies, they were able to demonstrate that the levels of GR promoter methylation were a direct product of the mother's behavior during the postnatal period. These data were key in providing an association between the levels of caregiving behavior and DNA methylation of the GR gene promoter. Finally, in an effort to help establish a causal link between the observed epigenetic modifications, gene expression patterns, and adult behavior, they demonstrated that pharmacologically manipulating methylation patterns, via treatment of adult animals with a HDAC inhibitor (trichostatin A), removed group differences in DNA methylation, histone acetylation, and behavior.

Another way to examine the ability of incant-caregiver interactions to program the HPA axis is to separate infant rodents from their mother for a specified period of time. Since rodent pups are dependent on their mother for survival, separation from the mother produces an array of responses, including alterations in HPA activity (Faturi et al., 2010). We have learned that behavioral outcomes in separated infants are also in part due to epigenetic programming of the HPA axis (Murgatroyd et al., 2009). In this study, mice as far as 1 year out from the last infant separation experience were shown to have hypomethylation of arginine vasopressin (AVP) DNA in their paraventricular nucleus (PVN). The product of the AVP gene is a hypothalamic component that induces the synthesis and release of adrenocorticotropin from the pituitary. The lower levels of DNA methylation inversely correlated with AVP expression, as well as reduced binding of MeCP2, a DNA methyl-binding protein typically associated with gene suppression. They found that these molecular effects occurred in parallel with increases in corticosterone secretion (in response to an acute stress challenge and under basal conditions) and memory deficits in an inhibitory avoidance task. AVP antagonism was shown to partially reverse the phenotype. Overall, these results indicate that an early-life stressor activates a key group of stress regulating neurons that are part of the HPA axis, leading to stables changes in MeCP2 function and programing of a key gene involved in the stress regulatory pathway. Since this study, infant separation has been shown to produce less methylation of CG sites associated with the Crf promoter within the PVN, an effect that coincides with heightened plasma corticosterone response to an acute stress challenge (Chen et al., 2012).

Akin to the rodent literature, the human GR gene appears equally responsive to early-life environmental events. For example, increased methylation of GR and ribosomal RNA genes (and a corresponding decrease in transcript levels) have been found in hippocampal samples derived from adult males who committed suicide and had a history of childhood abuse (Labonté, Suderman, et al., 2012; McGowan et al., 2009; McGowan et al., 2008). In another study linking the effects of early-life adversity with epigenetic modification of the human GR gene, parental loss, childhood maltreatment, and disruptions in parental care were found to be associated with increased GR promoter DNA methylation (as determined from leukocyte DNA) and attenuated cortisol responses to a stress challenge (Tyrka, Price, Marsit, Walters, & Carpenter, 2012). Additional work has shown that childhood sexual abuse and its severity show a positive correlation with GR methylation (Perroud et al., 2011). In this study, GR methylation was explored in individuals with Borderline Personality Disorder (BPD), Major Depressive Disorder (MDD) or individuals with a co-morbidity of MDD and PTSD. While the severity of childhood sexual abuse and the number of maltreatment types correlated positively with GR methylation in all of these individuals, those with BPD who experienced repeated sexual abuse with penetration and other abuses showed the highest methylation percentage. This is yet another example linking childhood maltreatment, epigenetic changes, and adult psychiatric disorders.

If we return to rodent models, the broad array of phenotypes affected by maternal care in the rodent model of high vs. low LG, including hippocampal-dependent memory, sexual behavior, fear-like behavior, maternal care, and alterations in drug-seeking behavior (Kaffman & Meaney, 2007) would suggest the ability of early-life events

to epigenetically program a multitude of genes and brain systems. Subsequent research has shown that this is indeed the case. Maternal care has been shown to influence levels of cytosine methylation of the estrogen-receptor alpha (ER-α) gene promoter in the medial preoptic area, an area intimately associated with maternal behavior (Champagne, Weaver, Diorio, Dymov, Szyf, & Meaney, 2006). Activation of ER-α supports maternal behavior expression, and expression of this gene is regulated by a signaling cascade known as the Janus kinase-Stab5b pathway. Lower levels of ER-α gene DNA methylation, increased binding of Stab5b, and increased expression of ER-α were found in adult female offspring of high-LG mothers. These animals showed high levels of licking and grooming towards their own offspring, as well as displaying an arched back nursing position toward their offspring. The opposite was found for adult offspring of low LG mothers. Reminiscent of the outcome regarding fear- and anxiety-like behaviors, variations in maternal care also confer differences in future mothering behavior via epigenetic mechanisms. LG maternal behavior has since been shown to affect γ-aminobutyric acid (GABA) inhibitory circuits, as males that are raised by low-LG mothers have reduced hippocampal levels of the rate-limiting enzyme in GABA synthesis called glutamic acid decarboxylase (GAD1) which is associated with increased methylation of GAD1 promoter DNA (Zhang et al., 2010). Epigenetic changes in this model are known to occur on a much broader genome-wide scale within the hippocampus (McGowan et al., 2011).

Work in other models likewise demonstrates the ability of early-life experiences to epigenetically alter multiple genes and brain regions. For example, infant male rats experiencing repeated separation from their mother and nest environment show altered hippocampal methylation and expression of estrogen receptor (ERβ) DNA (a gene that encodes a receptor responsive to estrogen) (Wang, Meyer, & Korz, 2012) and increased methylation (and therefore reduced expression) of the hippocampal synaptic plasticity gene reelin (Qin et al., 2011). With some of our own work, we have provided a link between caregiver maltreatment, altered DNA methylation patterns of the Brain-derived neurotrophic factor (Bdnf) gene, and aberrant behavioral outcomes (Roth, Lubin, Funk, & Sweatt, 2009).

A known stressor of rat mothers is resource deprivation (nesting material), and we and others have used this to elicit aberrant caregiving behaviors (Ivy, Brunson, Sandman, & Baram, 2008; Raineki, Moriceau, & Sullivan, 2010). In our laboratory, we use this stressor in conjunction with a within litter design to examine the ability of adverse caregiving to alter DNA methylation. We employ three experimental conditions: normal maternal care, cross-foster care, and caregiver maltreatment. The normal maternal care condition consists of leaving infants in their home cage with their biological mother in the room in which they were bred (infants are however briefly handled for marking and weighing purposes). The cross-foster care condition consists of placing infants in a different room and in a different apparatus with a lactating dam. This female is given an hour to habituate to the chamber before receiving infants. She is also given adequate amounts of bedding so that she may nest and nurture infants. The caregiver maltreatment condition consists of placing infants in a different room and apparatus with a lactating dam. This female is not given time to habituate to her new surroundings and is not provided adequate bedding to construct a nest. Infant rats are repeatedly exposed to their designated conditions for 30 minutes daily from postnatal day one through seven. Nurturing caregiving behaviors that we see in the normal care and cross-foster conditions include frequent observations of infant grooming, anogenital licking (to void their bladder), and nursing. Adverse caregiving behaviors displayed in the maltreatment condition include infant dragging, dropping, roughly handling, and active avoidance of the pups (Figure 11.2a). Dams within this condition also spend less time crouching over or nursing the infants and decreased amounts of licking and grooming.

In some of our earliest work with this model (Roth et al., 2009), we first explored the capacity of our maltreatment conditions to alter Bdnf gene expression. We found that this was the case, as adult animals that were exposed to the maltreatment condition during infancy had significantly less Bdnf mRNA in their prefrontal cortex (as a whole) than controls (either normal or cross-foster care). We then explored whether DNA methylation could be involved. We showed that normal adults (i.e., adults with a history of normal infancy) had either no or very little CG dinucleotide methylation within an important regulatory region of the Bdnf gene (DNA associated with exon IV). This was in sharp contrast to the adults who had experienced maltreatment during infancy, where sequencing of that same regulatory region revealed that the same CG dinucleotides were all highly methylated (Figure 11.2b). Next, to establish that the methylation changes were contributing to the gene deficits, we showed that chronic treatment with a DNA methylation inhibitor called Zebularine was able to rescue the adult maltreatment-caused deficits in Bdnf gene expression. Zebularine treatment also lowered methylation levels in maltreated animals.

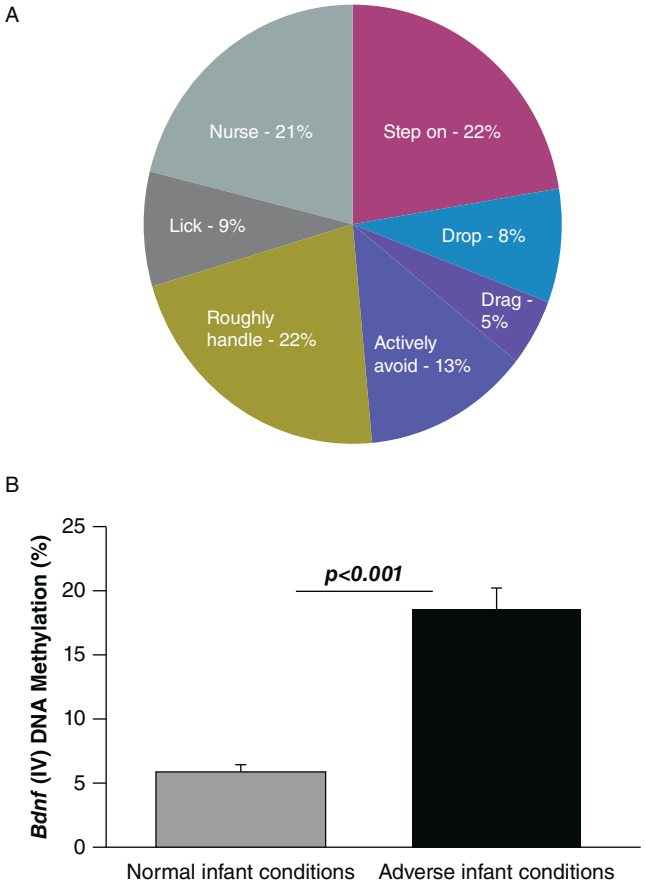


Figure 11.2 Assessment of caregiving behaviors within our maltreatment condition (A) indicates that infants experienced an adverse caregiving environment characterized by maltreatment and low levels of infant licking or nursing. Three months removed from the last experience of maltreatment, (B) adults were found to have significant methylation of Bdnf DNA in their prefrontal cortex. Data recreated from Roth et al., 2009, pp. 761. See footnote 1.

Maternal and social isolation in infant macaques has been linked to hypermethylation of the serotonin transporter gene (Kinnally et al., 2010), and the impact of chronic and unpredictable infant separation on depressive-like behaviors in mice and in their subsequent offspring has been linked to the DNA methylation profile of several stress-related and behaviorally relevant genes (Franklin et al., 2010). In this latter study, litters were exposed to repeated bouts of maternal separation three hours daily during the first two weeks of life. Additionally during separation, mothers were subjected to unpredictable stress. Investigators found that separation (and stress of the mother) led to depressive-like behaviors that were not just present in males that experienced the early-life stress regimen, but in their offspring that were never subjected to any stress and had been raised under normal conditions. For example, when exposed to the forced swim test, offspring spent more time floating indicative of depressive-like behavior. Anhedonia, the inability to experience pleasurable stimuli, is a behavior commonly displayed in depressed individuals. Stressed offspring in their study likewise consumed decreased amounts of sucrose. In parallel, DNA methylation patterns that were present in the germline (sperm) and brains of the male mice that had directly experienced the early-life stress (i.e., the fathers) were present in the brains of the offspring.

Epigenetic regulation of gene loci other than the GR gene has too been linked to childhood experiences. For example, antisocial behavior in females with a history of childhood sexual abuse coincided with both genotype and hypermethylation of DNA associated with the promoter region of the gene encoding the serotonin transporter (Beach, Brody, Todorov, Gunter, & Philibert, 2011; Vijayendran, Beach, Plume, Brody, & Philibert, 2012). Children (male and female) aged 7–10 years and raised in institutional care, in comparison to children of the same age but raised by their biological parents, show greater methylation of DNA associated with a number of genes involved in controlling serotonin and glucocorticoid biosynthesis, immune responses, and cell-signaling pathways involved in memory formation (Naumova et al., 2012). Adolescent and adult DNA methylation levels, including those of genes known to play an important role in cell-signaling pathways within the brain, have been linked to parental stress levels during early childhood years (Borghol et al., 2012; Essex et al., 2013). Further, male individuals with severe abuse during childhood have been shown to exhibit genome-wide changes in hippocampal DNA methylation, including hypermethylation of over 200 gene promoters and hypomethylation of around 100 gene promoters, many of which are involved in neural plasticity (Labonté, Yerko, et al., 2012).

As one final point for this section, a review of the literature suggests that epigenetic changes could underlie why developing males and females have different susceptibility to early-life stress or outcomes associated with stress. Because of existing methylation patterns at certain gene loci during development, stress has the potential to differentially affect males and females. For example, DNA methylation of the ER-α gene is higher in female rodents than males at postnatal day 1 (Schwarz, Nugent, & McCarthy, 2010). Epigenetic regulators are known to differ between sexes early in development, providing another route for stress to differentially affect the sexes. For example, mRNA and protein levels of DNMT3a (Kolodkin & Auger, 2011) and MeCP2 (Kurian, Forbes-Lorman, & Auger, 2007)

within the infant amygdala are higher in females than in males, but by postnatal day 10 these sex differences have disappeared. Dnmt3a is highest in the female and male cortex at postnatal day 10, while Dnmt1 is highest after weaning (PN25) (Westberry, Trout, & Wilson, 2010). Within the MPOA, gene promoters involved in sexual differentiation of the brain show differential epigenetic patterns between males and females at both an embryonic and early postnatal stage (Matsuda et al., 2011). It stands to reason that future epigenetic studies need to incorporate both sexes to fully elucidate the role that DNA methylation plays in sex-specific development of behavior.

EPIGENETIC FACTORS AND OUTCOMES ASSOCIATED WITH EVENTS LATER IN LIFE

In the previous sections we focused on epigenetic alterations that are known to occur in response to environmental factors and events experienced within the intrauterine or caregiving environments. In parallel to developmental studies, research efforts aimed at understanding molecular mechanisms underlying memory processes, drug addiction, and stress outcomes have illustrated that the adult central nervous system (CNS) is likewise sensitive to environmentally driven epigenetic alterations. Evidence suggests that both DNA methylation and histone modifications provide a mechanism for gene-by-environmental interactions throughout the life span.

The process of turning learned information into memories that can be stored and retrieved for the long haul involves gene expression. A diverse series of studies in rodents have demonstrated an important role of epigenetic regulation in learning-induced gene expression. Making the case that histone acetylation is an important process for learning and memory are studies showing that contextual fear memory formation is associated with acetylation of histones within the hippocampus (Levenson et al., 2004), and that mice deficient of the HAT CBP have both deficits in synaptic plasticity and long-term memory capacity (Korzus, Rosenfeld, & Mayford, 2004; Oliveira, Wood, McDonough, & Abel, 2007). The ability to extinguish a conditioned fear memory has been linked to histone acetylation changes within the prefrontal cortex (Bredy et al., 2007), and the beneficial effects of environmental enrichment on restoring learning and memory capacity in cognitively impaired mice have been shown to be mediated by increased hippocampal and cortical histone acetylation (Fischer, Sananbenesi, Wang, Dobbin, & Tsai, 2007). Finally, additional work has shown that in addition to histone acetylation at memory-linked genes there is a complex pattern of histone methylation changes (Gupta et al., 2010).

The capacity of DNA methylation to regulate synaptic plasticity and memory in adult animals has become apparent. In some of the earliest work, investigators reasoned that if DNA methylation remains an active process in the mature brain then it should be able to orchestrate gene–environment interactions relevant to learning and memory. We have learned that this is indeed the case and that both DNA methylation and demethylation are active processes involved in regulating gene expression in long-term memory formation. For example, seminal studies along these lines showed that shortly after fear conditioning (within 1–2 hours), adult rats within their hippocampus had decreased methylation of DNA associated with memory-related genes (Lubin, Roth, & Sweatt, 2008; Miller & Sweatt, 2007), while increased methylation of DNA was associated with memory suppressor genes (Miller & Sweatt, 2007). Demethylation corresponded with active gene transcription, while methylation corresponded with gene suppression. A follow-up study demonstrated longer-lived (30 days) experience-induced changes in cortical DNA methylation (and thus gene expression) following the contextual fear-conditioning paradigm (Miller et al., 2010). Pharmacological agents that alter DNA methylation have been shown to both alter DNA methylation in adult CNS tissue and block hippocampal synaptic plasticity (Levenson et al., 2006) and hippocampus-dependent memory formation (Lubin et al., 2008). Other studies have shown that disruption of other epigenetic regulators including MeCP2 (Adachi, Autry, Covington, & Monteggia, 2009), DNMTs (Feng et al., 2010), and Gadd45b (Sultan, Wang, Tront, Liebermann, & Sweatt, 2012) can also alter plasticity and memory.

Regulation of gene expression is also recognized as a molecular basis of addiction, and epigenetics are increasingly being explored for their contributory role to this process. Acute administration of cocaine has been shown to increase striatal histone acetylation on genes known to play a critical role in cocaine-related behaviors, while chronic cocaine exposure has been found to hyperacetylate these same gene promoters for several weeks (Kumar et al., 2005). Histone methylation has been shown to occur at several gene promoters in the nucleus accumbens after chronic cocaine exposure (Renthal et al., 2009). Further attention in this line of work has turned to characterizing the role of epigenetic regulators, including DNMTs, in the morphological (dendritic spine plasticity in the nucleus

accumbens) and behavioral outcomes (cocaine preference) that may underlie cocaine addiction (LaPlant et al., 2010; Maze et al., 2010).

A growing literature base is providing compelling evidence that epigenetics can help explain how adulthood stressors can leave their marks on genes. In adult rodents it has been demonstrated that either acute or chronic restraint stress (Hunter, McCarthy, Milne, Pfaff, & McEwen, 2009) and chronic social defeat stress (Tsankova et al., 2006) evoke robust changes in hippocampal histone methylation. Social defeat stress is also known to be associated with a lasting decrease in methylation of Crf DNA and a concomitant increase in Crf expression in the hypothalamus of animals that develop social avoidance behavior (Elliott, Ezra-Nevo, Regev, Neufeld-Cohen, & Chen, 2010). Mice in this study that did not develop social avoidance after exposure to defeat stress did not show these epigenetic modifications. Stress-susceptible (inbred BALB/c) and stress-resilient (C57BL/6) male mice are known to show behavioral differences following chronic exposure to mild stressors, and differences in their phenotypes have been attributed to differential patterns of glial cell-derived neurotrophic factor (Gdnf) DNA methylation (Uchida et al., 2011). Specifically, while both strains of mice were shown to display increased methylation of the Gdnf promoter (in the nucleus accumbens) following chronic stress, stress-susceptible mice (BALB) showed additional epigenetic changes that led to repression of Gdnf transcription, including gene promoter interactions with HDACs. Mice that adapted to chronic stress (B6) showed other epigenetic changes permitting Gdnf transcription. These studies provide the first glimpse that there are epigenetic attributes of stress resilience versus stress susceptibility.

In collaboration with David Diamond's group, we have explored the ability of repeated exposure to predatory and social instability stress to alter DNA methylation in adult rodents (Roth, Zoladz, Sweatt, & Diamond, 2011). In this study, rats were randomly assigned to stress or no-stress groups. Rats in the stress group were placed in plastic DecapiCones, which immobilized them. They were then placed in a Plexiglas enclosure and taken to a cat housing room. Within this room, they were placed in a cage with an adult female cat for one hour. The Plexiglas enclosure prevented any direct contact between the rat and the cat, and to promote cat gustatory behavior toward the rat, cat food was smeared on top of the rat's enclosure. Rats in the stress group were exposed to two of these stress sessions separated by a 10-day period. Predictability was controlled by conducting one exposure during the light cycle and one during the dark cycle. Rats in the stress group were also exposed to unstable housing conditions, beginning on the day of the first cat-stress session. Rats in the stress group were housed with a different cage mate daily, and no rat in the stress group had the same cage mate for a period longer than 2 days across the whole 31-day stress period. This psychosocial stress regimen produces rodents that show learning and memory deficits, increased anxiety-like behavior, and glucocorticoid abnormalities weeks to months following the initiation of the stress regimen (Zoladz, Conrad, Fleshner, & Diamond, 2008; Zoladz, Fleshner, & Diamond, 2012).

As depicted in Figure 11.3, we found that these behavioral abnormalities coincided with significant methylation of the Bdnf gene, interestingly the same loci affected by our early-life stress regimen (Roth et al., 2011). Specifically, we found increased methylation of DNA associated with Bdnf exon IV in the dorsal DG and dorsal CA1 of stressed rats, but decreased methylation in ventral CA3. Overall, Bdnf DNA methylation in the dorsal hippocampus was differentially affected by psychosocial stress when compared with the ventral hippocampus. Bdnf mRNA levels were suppressed in CA1, and our data are consistent with the notion that increased methylation is one way that transcriptional repression occurs after psychosocial stress. These data also provide insight into mechanisms likely contributing to increased anxiety-like behaviors and cognitive impairments seen in humans that are maintained for long periods of time after a traumatic experience has occurred.

The ability of acute stressful experiences to evoke epigenetic modifications in humans has been demonstrated in a laboratory setting using the Trier social stress test (TSST). This is a very effective stressful experience for participants, and in this test subjects have to perform a public speech after a period of anticipation as well as perform mathematical problems in front of a panel of interviewers. One group has reported a short-lived increase in methylation of the oxytocin receptor (OXTR) gene in blood samples from male and female TSST participants (Unternaehrer et al., 2012), while another group has reported greater methylation of the NR3C-1 gene after the TSST in females (Edelman et al., 2012).

Together, data from studies reviewed in this section have provided us with a new framework in trying to understand how psychological and social-contextual factors can interact with our biology even outside of sensitive periods of development. These data also tell us that experiences do not have to be confined to early-life developmental periods in order to evoke DNA methylation changes. Whether

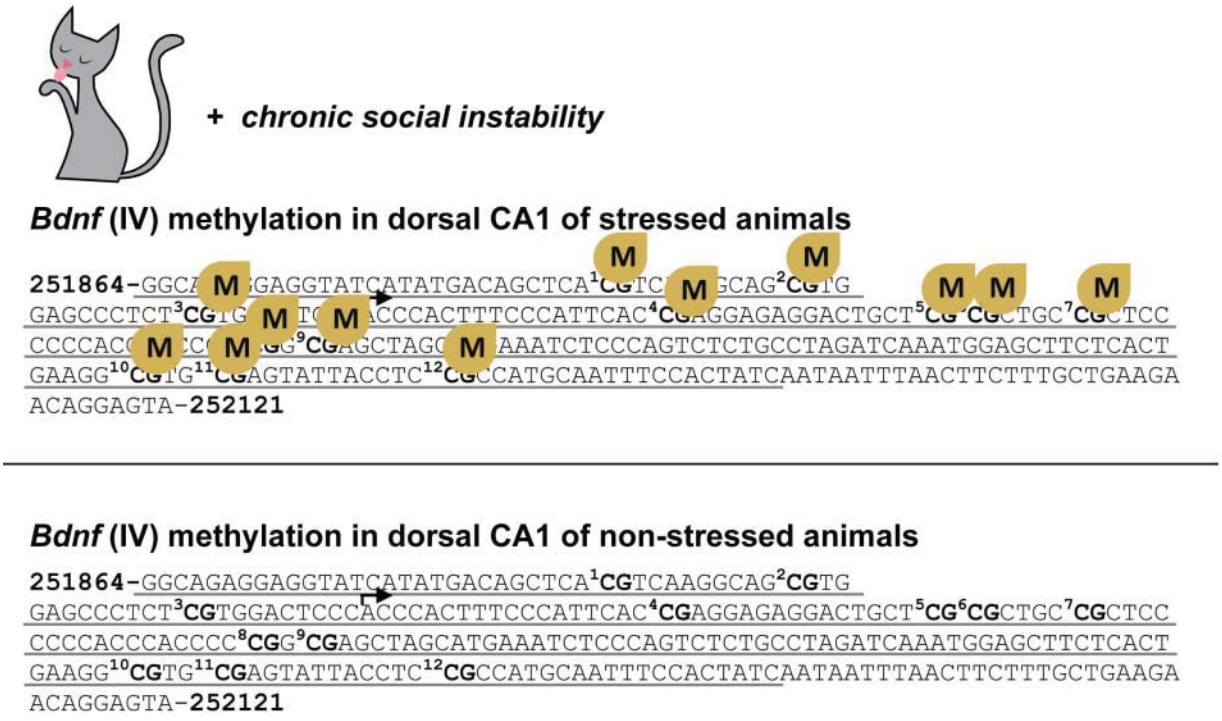


Figure 11.3 Direct bisulfite sequencing analysis in the hippocampus of adult rats that had experienced the psychosocial stress regimen (chronic social instability and repeated exposures to a predator stimulus) revealed significant cytosine methylation (compared with controls) across 12 cytosine-guanine dinucleotide sites within DNA associated with exon IV of the Bdnf gene. See footnote 1. *Source:* Data recreated from T. L. Roth, P. R. Zoladz, J. D. Sweatt, & D. M. Diamond, Epigenetic modification of hippocampal Bdnf DNA in adult rats in an animal model of post-traumatic stress disorder, *Journal of Psychiatric Research, 45*, 922, 2011.

sensitive periods early in life truly represent heightened periods of vulnerability to these types of changes is an issue that has not been systematically addressed. Expression profiles of Dnmt1, 3a, and 3b provide one piece of evidence that this may be the case. Though these genes are detectable in neurons throughout the life span, some of their expression profiles peak (e.g., Dnmt3a) during the early postnatal period (Brooks, Marietta, & Goldman, 1996; Feng, Chang, Li, & Fan, 2005; Goto et al., 1994). Worth considering in the context of this discussion is the possibility that there is a larger gene pool at play during sensitive periods (such as in early postnatal development or adolescence), while instead a much more limited gene pool is responsive to later-life factors. Adding further complexity to this discussion is evidence that experiences do not always translate into immediate changes in DNA methylation, but that changes can emerge after an appreciable delay. For example, we have found some changes in Bdnf methylation that emerge several months after infant maltreatment (Blaze, Scheuing, & Roth, 2013). Further, DNA methylation patterns naturally change with maturation and aging processes (Numata et al., 2012; Siegmund & Connor, 2007). These phenomena then likely have significance in terms of stress incubation and direct versus indirect trajectories leading to later behavior change or the onset of psychiatric disorders.

EPIGENETIC FACTORS ASSOCIATED WITH BEHAVIORAL DISORDERS

Drawing on data from both developmental and adult studies, it is clear that our genome is susceptible to epigenetic modifications, providing a layer of genetic regulation that is sensitive to a lifetime of experiential and environmental factors. The studies we have reviewed up to this point also make the argument that epigenetic changes have functional relevance in terms of behavior. Additional support for this notion came from several known intellectual and psychiatric disorders that have been associated with altered epigenetic marks. At this point the association (i.e., a causal link) between aberrant epigenetic marking of the genome and manifestation of these disorders that we will review here remains speculative for many reasons, several which are listed here. For example, it is difficult to distinguish

preexisting methylation patterns (heritable changes) from those that may have developed in response to a particular life event. Without baseline epigenetic measurements in individuals prior to the development and diagnosis of a disorder, it is also difficult to distinguish epigenetic patterns that led to versus those that developed from having the disorder. Drawing on evidence from the animal work previously reviewed, what we can say is that these types of disorders represent intriguing candidate disorders that might be associated with epigenetic changes triggered during development (or later in life). Another point to keep in mind is the extent to which peripheral measures of DNA methylation (obtained from blood samples or cheek swabs) capture the complexity of methylation alterations present in their brain.

Accumulating observations are consistent with the hypothesis that epigenetic marking of genes could underlie aspects of cognitive dysfunction and psychopathology. This seems especially true in regard to psychiatric disorders that are associated with early-life stress and abnormal brain development and function. In this section, we will discuss three instances of human intellectual disabilities as examples where epigenetic mechanisms have been implicated in developmental delay and cognitive disabilities: Rett syndrome (RS), Fragile X syndrome, and Rubinstein-Taybi syndrome (RTS). We use them to help us illustrate that epigenetically based disruptions are known to lead to particular behavioral outcomes. We will then summarize evidence linking the presence of DNA methylation alterations with SZ, PTSD, mood disorders, and Alzheimer's disease (AD).

Rett Syndrome

RS, estimated to be the second leading cause of intellectual disabilities in women, was first described in 1966 by Austrian pediatrician Andreas Rett (1966) and is an X-linked disease that affects about 1 in 15,000 females by ages 2–18 years of age (Ellaway & Christodoulou, 2001). Development during the first few months of life is normal in RS patients, with symptoms first appearing between 3 months and 3 years of age. The trademark of RS is a display of continuous, stereotypical hand movements, such as wringing, washing, clapping, or patting, which appear after the loss of purposeful hand movement. Other signs of RS include decreased growth (including microcephaly), abnormal respiration, gait ataxia, autism, seizures, and other neurologic dysfunctions. Studies have indicated that in a percentage of patients they have a mutation of MeCP2 (Amir et al., 1999). The role that MeCP2 might play in the symptoms and memory deficits observed in RS is still unclear, but strains of MeCP2-deficient mice have been shown to display several of the characteristics of human RS (Chen, Akbarian, Tudor, & Jaenisch, 2001; Guy, Hendrich, Holmes, Martin, & Bird, 2001; Tate, Skarnes, & Bird, 1996), and overexpression of MeCP2 has been found to actually enhance long-term memory formation and the induction of hippocampal LTP (Collins et al., 2004). These results suggest that levels of MeCP2 are coupled to cognitive performance, and are consistent with the idea that loss of functional MeCP2 protein could play a role in cognitive deficits associated with RS.

Fragile X

Fragile X syndrome is one of the most commonly inherited learning disabilities. It is associated with distinct physical and behavioral features and causes learning disabilities that range from mild to extremely severe, with most patients showing IQs in the range of 50 (Turner, Webb, Wake, & Robinson, 1996). Two genes have been associated with Fragile X: FMR1 and FMR2. The FMR1 mutation is due to an expansion of trinucleotide repeats (CGG), where normal levels of FMR1 are produced if the FMR1 gene contains between 50–200 repeats; however, levels of FMR1 decrease if the number of CGG repeats exceeds 200. (Ashley et al., 1993). Decreased gene expression occurs via mechanisms including aberrant methylation of DNA and formation of restrictive chromatin structure. The FMR2 gene undergoes a similar hypermethylation and transcriptional silencing due to expansion of a CCG repeat (Gecz, Gedeon, Sutherland, & Mulley, 1996; Gu, Shen, Gibbs, & Nelson, 1996).

Rubinstein-Taybi

RTS was first described in 1963 (Rubinstein & Taybi, 1963) and is an inherited, autosomal dominant disease that has been mapped to chromosome 16p13.3, which contains the gene for the transcriptional co-activator CBP (Petrij et al., 1995). Several studies have shown that RTS patients have a variety of mutations in CBP. As discussed in an earlier section, CBP is a HAT that facilitates histone acetylation. Animal models of RTS, with mutant CBP alleles, exhibit deficits in numerous long-term memory tasks and forms of hippocampal synaptic plasticity (Alarcon et al., 2004; Korzus et al., 2004; Oike et al., 1999; Tanaka et al., 1997). The important implication of this work is its suggestion that altered HAT activity is causative of at least part of the cognitive deficits associated with RTS.

Schizophrenia

SZ is a disorder of cognition that is defined by positive symptoms including delusions, hallucinations, and disorganized thoughts and by negative symptoms such as poor motivation, social withdrawal, and apathy. With the onset of SZ occurring typically after adolescence, the environment is thought to play a key role in its etiology. Common observations in the cortex of individuals with SZ include increased Dnmt1 expression and decreased expression of reelin and GAD1 (Guidotti et al., 2007; Ruzicka et al., 2007; Veldic, Guidotti, Maloku, Davis, & Costa, 2005; Veldic et al., 2004, 2007). Deficits in reelin and GAD1 levels have been attributed to altered methylation levels (Abdolmaleky et al., 2005; Connor & Akbarian, 2008; Grayson et al., 2005; Huang & Akbarian, 2007). Daily injections of methyl donors are known to recapitulate hypermethylation of reelin and GAD1 in mice, as well as alter social recognition and prepulse inhibition behaviors (Tremolizzo et al., 2002, 2005). When mice are given subcutaneous injections of valproate, a histone deacetylase inhibitor that can also affect methylation levels, expression of reelin and GAD1 are rescued. Recent genome-wide epigenetic approaches on cortical tissue from SZ patients suggest there are many additional gene loci with altered DNA methylation, including other gene families related to GABAergic and neurotrophic (Bdnf) function (Connor & Akbarian, 2008; Mill et al., 2008). Peripheral measures of DNA methylation implicate epigenetic marking of the monoamine oxidase A (MAOA) gene promoter (Chen, Zhang, Zhang, Shen, & Xu, 2012), DNA associated with several serotonin receptors (Abdolmaleky et al., 2011; Carrard, Salzmann, Malafosse, & Karege, 2011; Ghadirivasfi et al., 2011), and the catechol-o-methyltransferase (COMT) gene (Abdolmaleky et al., 2006; Lott et al., 2012; Melas et al., 2012; Nohesara et al., 2011). Finally, a genome-wide analysis of DNA methylation on peripheral blood DNA samples obtained from monozygotic twin pairs discordant for major psychosis showed numerous loci with DNA methylation differences between twins discordant for SZ and BD (Dempster et al., 2011).

Posttraumatic Stress Disorder

PTSD is a psychiatric disorder that results from exposure to significant trauma**.** Peripheral measures of methylation show strong associations between child abuse, total life stress, methylation of DNA associated with genes related to immune function (such as the cytokine INFγ), inflammation (inflammatory gene IL-6), plasticity (Bdnf), and the diagnosis of PTSD (Smith et al., 2011; Uddin et al., 2010). The Bdnf methylation changes we have shown to take place in the rodent model of PTSD (Roth et al., 2011) are a nice parallel to these reports. In another rodent model of PTSD, there is evidence that methylation of the disks large-associated protein (DIgap2) gene is altered in the hippocampus of PTSD-like rats (Chertkow-Deutsher, Cohen, Klein, & Ben-Shachar, 2010). It is thought that this gene plays an important role in the molecular processes that are involved in the adaptation to traumatic events.

An interaction between methylation status of the SLC6A4 (Koenen et al., 2011) or MAN2C1 (Uddin, Galea, et al., 2011) genes and the number of traumatic events experienced has been reported in PTSD. In humans, Koenen and colleagues found that after controlling for SLC6A4 promoter genotype, people with more traumatic events were at an increased risk for PTSD, but only with decreased SLC6A4 DNA methylation. Individuals exhibiting higher methylation were protected against PTSD. MAN2C1 is a gene that has been implicated in T-cell functioning. When methylation differences were assessed using whole-blood derived gene expression levels in individuals with PTSD and those without PTSD, MAN2C1 showed significant methylation in association with the number of potentially traumatic events experienced (PTEs). Assessment of serum DNA methylation patterns in genomic repetitive elements (LINE-1 and Alu) of US military service members predeployment and postdeployment and with or without PTSD diagnosis suggest DNA methylation operative as a resilience or vulnerability factor (Rusiecki et al., 2012). LINE-1 and Alu are repetitive elements found throughout the human genome that were previously classified as "junk DNA" but now recognized for their role in modification of gene expression.

There is also emerging evidence of a so-called double hit model, in which having a genetic risk allele and promoter DNA methylation may more accurately capture the molecular risk of PTSD. For example, 9-repeat allele carriers of the dopamine transporter (SLC6A3) gene show an increased risk of lifetime PTSD when in conjunction with high methylation present in the SLC6A3 promoter (Chang et al., 2012). Methylation of genes within the pituitary adenylate cyclase-activating polypeptide (PACAP) system, a system responsive to cellular stress and implicated in neurotrophic function, also appears to predict a PTSD diagnosis. Females with high plasma PACAP levels and greater methylation of the PACAP receptor

gene (ADCYAP1R1) also containing a polymorphism show strongest PTSD symptoms and physiological fear responses (Ressler et al., 2011).

Suicide and Mood Disorders

Epigenetic phenomena have similarly been associated with suicide and depression. Postmortem work with brain tissue (including the frontal cortex, amygdala, and PVN) of individuals who committed suicide or had been diagnosed with major depression has shown significant Dnmt mRNA alterations (Poulter et al., 2008), increased Bdnf DNA methylation (Keller et al., 2010), and altered methylation patterns of numerous genes that are known to play a role in neuronal growth, brain development, and cholinergic transmission (Sabunciyan et al., 2012). The findings of altered levels of Dnmt mRNA (Higuchi et al., 2011) and Bdnf DNA methylation (Fuchikami et al., 2011) have likewise been replicated from peripheral measures in patients with major depression. Other findings in depressed patients include increased methylation of genes involved in brain development and metabolic processes (Uddin, Koenen, Aiello, Wildman, de los Santos, & Galea, 2011) and decreased methylation of genes, such as the inflammatory gene IL-6 (Uddin, Koenen, et al., 2011).

Alzheimer's Disease

AD is a neurodegenerative disease that occurs in individuals that are typically 65 and older, and it is a disease that profoundly impacts thinking and memory skills and is characterized by mild to severe dementia (loss of cognitive function). The major neurobiological hallmarks of this disorder are extracellular plaques and intracellular tangles (Mattson, 2004). Aberrant DNA methylation patterns have been reported in both normal and pathological aging, including observations of global hypermethylation and increased methylation of memory targets such as Bdnf in AD patients (Bakulski et al., 2012; Bollati et al., 2011; Keleshian, Modi, Rapoport, & Rao, 2013). In aged rats (not a model of AD, but a model of the natural decline in cognition that occurs with aging), it has been shown that decreased mRNA levels of genes important for synaptic plasticity and memory formation are attributable to hypermethylation (Penner, Roth, Barnes, & Sweatt, 2010; Penner et al., 2011). Altered chromatin plasticity and histone acetylation are too presumed to be involved in cognitive aging and AD, as cognitive impairments in mouse models of AD can be rescued by increasing histone acetylation either via pharmacological manipulation or through exposure to environment enrichment (Fischer et al., 2007).

EVIDENCE OF EPIGENETIC TRANSMISSION OF PHENOTYPES

Another fascinating tenet in behavioral epigenetics research is the idea that the heritable nature of epigenetic changes could allow information acquired during one's lifetime to be passed on to offspring. This is a provocative idea that was initially met with large skepticism, but studies continue to emerge at a rapid pace providing compelling evidence that this actually occurs. Providing some of the strongest evidence of the phenomenon of germ-line epigenetic inheritance, including altered stress responses for 3 to 4 generations removed from the initial environmental insult, are studies exposing pregnant dams to endocrine disruptors (Crews et al., 2012; Skinner et al., 2008) or high fat diets during gestation (Dunn & Bale, 2011), which we have previously discussed.

The observation of nongenetic transmission of caregiving phenotypes has been present in the literature for some time (Francis, Diorio, Liu, & Meaney, 1999; Maestripieri, 2005). For example, Dario Maestripieri used a cross-foster paradigm to explore genetic versus epigenetic determinants of maternal abuse in macaques (Maestripieri, 2005). The offspring that were born to nonabusive mothers were cross-fostered to abusive mothers after birth (control–abuse) and infants that were born to abusive mothers were cross-fostered to nonabusive mothers (abuse–control). These groups were compared with groups of nonabusive and abusive mothers that raised their own offspring. Females exposed to maltreatment exhibited the same abusive behaviors toward their own offspring. In contrast, females exposed to a nurturing caregiving environment did not show any abusive behaviors toward their offspring. Abusive behaviors were significantly different from behaviors seen from nurturing mothers independent of the maternal phenotype. These results suggest that transmission of infant abuse in the macaque is transferred through an epigenetic process rather than a genomic process. Direct epigenetic evidence for a similar phenomenon has come from work in the high- versus low-LG model carried out by Frances Champagne. As pointed out in an earlier section, infant experiences with nurturing mothers (high LG behavior) decreases methylation of DNA associated with ERα gene in the MPOA, producing increased

gene expression and responsivity to hormonally primed maternal behavior (Champagne et al., 2006). As a consequence of these epigenetic modifications, offspring and grand-offspring from high LG mothers become high LG mothers themselves (Champagne, 2008; Champagne & Meaney, 2007).

As experiences in the nest provide a powerful learning environment that serves to program later maternal behavior, we have also explored whether our early-life experience regimen affects maternal behavior of females, and whether the observed epigenetic modifications might be transmittable across a generation (Roth et al., 2009). We found that females with a history of maltreatment (maltreated females) showed the same types of abusive behaviors toward their own offspring that they had experienced themselves as infants, and that the epigenetic modifications acquired in one generation were even transmitted to the next generation of infants. Specifically, 8-day-old offspring (both males and females) derived from the maltreated females had significant methylation of Bdnf DNA in both their prefrontal cortex and hippocampus in comparison to offspring derived from normal-treated females (females who had experienced a normal infancy). The final question we posed in this study was whether the intergenerational inheritance was due to the mother's caregiving behaviors (maltreatment), or was it due to some biological component (i.e., the patterns were not completely erased between generations). A cross-foster design allowed us to address whether DNA methylation alterations were due directly to the mother's caregiving behaviors. Surprisingly, cross-fostering experiments (where offspring born to maltreated females were cross-fostered to normal females and vice versa) suggested that the inheritance was not simply a reflection of the postnatal experience, but likely reflected some unidentified prenatal component.

In an earlier section, the ability of infant separation to produce lasting changes in depressive-like behaviors and methylation of the Crf gene (Franklin et al., 2010) was discussed. From this same study, anxiety and depression-related behaviors, as well as methylation changes, were also found to be present in offspring and grand-offspring derived from males that had experienced the initial separation (Franklin et al, 2010; Weiss et al, 2011). This is an important observation because in rodents once mating is confirmed, males are usually removed from the cage and do not provide care of offspring. Subsequent studies from this line of work have revealed deficits in cognition and social interaction transmitted through the F3 generation (Franklin et al, 2011). Stress-related behaviors induced by social defeat can also be transmitted from the father (Dietz et al., 2011). In a study from Eric Nestler, adult male mice that were exposed to chronic social defeat stress and control mice were bred with normal female mice (females that never experienced any type of stress). Offspring were assessed for anxiety- and depressive-like behaviors using the elevated-plus maze, novel environment response, sucrose preference, and forced swim test. Chronic exposure to social defeat produced social avoidance behavior in fathers. Their offspring too showed greater amounts of social avoidance, even with a submaximal defeat paradigm that normally would not produce a defeated mouse. Furthermore, defeated offspring showed reduced preference for sucrose and decreased latencies in immobility in the forced swim test.

The ability of disruptions in social hierarchy structure during adolescence to have transgenerational implications has been reported by Larry Feig's group (Saavedra-Rodríguez & Feig, 2013). Social instability was achieved by changing cage mate composition twice a week for a 7-week period beginning in early adolescence. Control groups remained housed with the same cagemates throughout the course of the experiment. Mice from stressed and control groups, along with their offspring, were tested on the elevated plus maze, the open field test, and for social interaction. Two months after the end of the stress treatment, females showed increased anxiety-like behaviors in both the elevated plus maze and often field tests. When social behaviors were explored by introducing an unfamiliar same-sex juvenile into a test apparatus, both stressed males and females spent little time interacting. Future generations (from stressed and control parents) were tested on the same behavioral tests. First generation females, like their mothers, spent significantly less time in the open arms of the elevated plus maze and a significant decrease in locomotor adaptation to a new environment (open field test). When social behaviors were explored, female offspring also interacted less with a stimulus animal, just like their stressed mothers. Social interaction behavior in male offspring was not affected. Elevated corticosterone levels were also found in first generation female, but not male, offspring from stressed parents. Finally, cross-fostering experiments indicated that the transmission of the anxiety phenotype was not caused by postnatal caregiving behaviors, and additional experiments demonstrated that fathers could transmit the anxiety and defective social interaction phenotype to F2 and F3 daughters.

TRANSLATIONAL IMPLICATIONS

Throughout the chapter we have discussed the translational relevance of data from animal studies where appropriate. Two additional points we would like to expand upon here are the utility of epigenetic modifications as biomarkers and epigenetic therapy in the treatment of cognitive and mental dysfunction.

As epigenetic alterations are widely known to play an important role in cancer (DNA methylation and histone modifications are found in different human cancerous tumors), they have been long recognized as potential biomarkers for screening, diagnosis, and treatment targets of various cancers (Kristeleit, Stimson, Workman, & Aherne, 2004; Pan, Lu, & Huang, 2007; Seligson et al., 2005). A challenge in translating results from many of the animal studies we have reviewed in this chapter to humans concerns access to relevant tissues since there is accumulating evidence that epigenetic modifications occur with incredible specificity across tissue and cell types (Davies et al., 2012; Iwamoto et al., 2011; Ladd-Acosta et al., 2007). What we do know at this point is that a growing body of work has noticeably demonstrated a link between peripheral-DNA methylation profiles, exposure to adversity, and a risk for and even current diagnosis of psychiatric disorders. For example, analysis of whole blood (Borghol et al., 2012; Naumova et al., 2012) and lymphocyte (Beach et al., 2013; Vijayendran et al., 2012) samples from individuals exposed to various forms of early-life adversity have consistently revealed aberrant methylation patterns that are present on a genome-wide scale. There is evidence of similar stress-induced changes in DNA methylation states detectable in buccal tissue and saliva samples (Essex et al., 2013; Yang et al., 2013). Together, this would suggest system-wide changes, arguing for the utility of peripheral DNA methylation measures as a marker of stress-induced changes that are present on many tissue/systems levels (Gavin & Sharma, 2010).

Further, there is evidence indicating a parallel relationship between blood-DNA methylation profiles. For example, it was shown in one study that methylation patterns of the rodent COMT gene were directly correlated in peripheral blood mononuclear cells (PBMCs) and the PFC (Ursini et al., 2011). Mice chronically exposed to synthetic glucocorticoids show correlations in blood and brain (hippocampus) methylation of DNA associated with the Fkbp5 gene (Ewald et al., 2014). In one of the largest cross-tissue and interindividual comparison of blood and brain methylation patterns in humans, investigators found strong correlations between DNA methylation for blood and brain tissue were present (Davies et al., 2012). Finally, parallel patterns of methylation in T cells (derived from blood) and PFC tissue of rhesus macaques subjected to differential rearing have been reported (Provençal et al., 2012).

A point of optimism that emerges from the literature is that the dynamic nature of DNA methylation (and other epigenetic modifications for that matter) affords an opportunity to perhaps correct aberrant epigenetic marks. This has given birth to what is called epigenetic therapy, where investigators use drugs like zebularine, sodium butyrate, and trichostatin A to relax chromatin structure in order to provide gene transcription accessibility. Indeed the ability of these drugs to correct epigenetic patterns was first recognized in cancer treatment. For example, when a drug combination of 5-aza-2'-deoxycytidine and Zebularine were administered to both murine and human leukemic cells this reactivated a tumor suppressor gene (via demethylation) and decreased tumor growth (Lemaire, Momparler, Bernstein, Marquez, & Momparler, 2005). Further, the drug cocktail increased the life span in mice with leukemia (Lemaire et al., 2005).

The scope of application of epigenetic therapy has continued to be broadened to include possibly enhancing cognition and treating specific symptoms of various psychiatric disorders. HDAC inhibitors have been successfully used to reverse deficits in synaptic plasticity, learning and memory, and stress-related behaviors in rodents (for a review see Abel & Zukin, 2008). We and others have successfully modified patterns of DNA methylation in the adult brain that were associated with early-life experiences (Roth et al., 2009; Weaver et al., 2004). Whether these strategies are capable of altering the epigenome and behavior patterns of humans is not known. Studies, though, are beginning to reveal the incredible sensitivity of human epigenetic states to traditional pharmacological and behavioral therapies proven effective in treating psychiatric disorders.

Consistent with the neurotrophin hypothesis of depression (stress and depression are associated with decreased Bdnf, which can be restored via antidepressant treatment), antidepressant treatment has been shown to restore Bdnf and histone modifications associated with Bdnf IV DNA in depressed patients that showed a positive response to treatment (Lopez et al., 2013). Another study has shown that lithium and valproic acid, two of the most widely used mood-stabilizing compounds for treatment of BD, reduce methylation of DNA associated with the Bdnf gene in

bipolar patients (D'Addario et al., 2012). The final study we will highlight here has demonstrated that a psychotherapeutic approach can be effective at modifying epigenetic states (Perroud et al., 2013). Specifically, BPD patients that underwent a 4-week treatment regimen of intensive dialectical behavior therapy and showed a positive response to the treatment also showed a decrease in Bdnf DNA methylation. Nonresponders, on the other hand, did not show a change in methylation status and instead maintained significantly higher methylation than controls. Further, the changes in methylation states over time were significantly associated with changes in several cognitive measures, including depression scores and impulsivity. Together, the studies reviewed in this section argue for the utility of peripheral measures of DNA methylation as a general biomarker of altered epigenetic states and even as a biological indicator of treatment response.

FUTURE DIRECTIONS

Discoveries to date in rodent and nonhuman primate models make a convincing argument that epigenetic mechanisms underlie cause–effect relations in regard to neurobehavioral development and later stress-driven abnormalities. Results from many animal studies have been translated to humans. As applied to human development and psychopathology, epigenetic studies in humans have likewise provided compelling evidence that DNA methylation alterations are a biological substrate through which a variety of factors can alter the human genome. Though early studies utilized a candidate gene and brain region approach to identify specific sites of DNA methylation changes, more recent studies have begun to utilize a genome- and system-wide approach. Data from these types of studies are telling us that the impact is not limited to a single gene or brain region, but that epigenetic changes are occurring genome-wide and throughout the brain and body. This tells us then that there are epigenetic consequences for gene networks, with functional implications for disruptions at the circuit level.

Despite the fact that our knowledge concerning the ability of experiences to epigenetically modify our genome is progressing, we still have much to learn. Throughout the chapter we have tried to bring up outstanding issues in the field when relevant to particular topics we reviewed. Here we discuss a few others.

Though we can easily say environmental factors have direct effects on gene expression and behavior via alterations in DNA methylation, one of the most important questions for future studies to address is how environmental factors drive these changes. We do know that postmitotic neurons express the enzymatic machinery necessary for modifying chromatin and DNA methylation states (Brown, Weaver, Meaney, & Szyf, 2008; Feng et al., 2005; Ma et al., 2009), providing a susceptible basis for environmentally driven epigenetic modifications. Brain region, and cell-type specificity for that matter, would require qualitative, quantitative, and spatial arrangement of mechanisms capable of orchestrating responses to similar stimuli, which appears also to be in place. In the hippocampus for example, isoforms of Dnmt are known to vary by subregion (Brown et al., 2008) and cell-type (Feng et al., 2005; Siegmund & Connor, 2007). The physical link (i.e., signaling cascades), however, between an environmental stimulus and a change in DNA methylation remains unclear, but hypotheses are developing. In the model of high versus low LG behavior in rats, it is thought that maternal behavior triggers a signaling cascade that involves a serotonergic-mediated increase in cAMP, recruitment of the transcription factor nerve growth factor-induced protein A, and recruitment of CBP and a candidate demethylase (MBD2) to the GR promoter (Hackman, Farah, & Meaney, 2010; Weaver et al., 2007). In the maternal separation model that showed changes in epigenetic programming of AVP (Murgatroyd et al., 2009), separation is thought to depolarize hypothalamic neurons, triggering phosphorylation of MeCP2 (via calmodulin kinase II, which converts it from an inhibitor to an activator of transcription), and demethylation of AVP.

In the last few years there has been the discovery of 5-hydroxymethylcytosine (5hmC), an epigenetic modification that may serve as a intermediary between a methylated and demethylated cytosine, and regardless of its exact role is now commonly considered a sixth base within the genome (Münzel, Globisch, & Carell, 2011; Song & He, 2011). Conventional methods used for mapping DNA methylation, such as bisulfite sequencing, do not differentiate a methylated cytosine from a hydroxymethylated cytosine. The exact role of 5hmC in the brain is not clear, but there is evidence that its role is distinct from that of DNA methylation, and several laboratories have now made the connection between TET proteins and cognition. For example, though able to form a normal associative fear memory, TET1 knockout mice are impaired in their ability to extinguish the memory (Rudenko et al., 2013). Overexpression of TET1 (using a viral-mediated approach) leads to increased 5hmC in hippocampal tissue that impairs hippocampal-dependent fear memory formation (Kaas et al., 2013). Further, we are beginning to see evidence

of changes in 5hmC associated with early-life stress and disease. Maternal deprivation in rhesus macaques has been shown to induce DNA hydroxymethylation changes at numerous gene loci within the prefrontal cortex, including the promoter region of genes that are involved in neurological functions and psychiatric disorders, including REST, MAPK1, and SLC6A4 (Massart et al., 2014). These data tell us that we have an additional epigenetic marker responsive to life events, which may too mediate the impact of such events on brain development and function. Additionally, postmortem data are beginning to strengthen the idea that alterations in brain 5hmC have relevance to brain and psychiatric disorders, including AD (Chouliaras et al., 2013) and SZ (Kato & Iwamoto, 2014). Further research is certainly necessary to fully understand the role of 5hmC in mediating behavioral trajectories.

The final point for further research that we bring up here is that involving telomeres. There is increasing evidence that chromatin modifications are important regulators of telomeres, and as telomere length continues to be implicated in health and disease outcomes it seems critical to understand the link between epigenetics and telomeres. Telomeres are TTAGGG repeats located at the ends of chromosomes. One common analogy that is helpful when picturing telomeres is to compare them to the clear, plastic caps on the end shoelaces. Their main role is to maintain the stability of the chromosome (Blackburn, 1991; Blackburn, 2005). An enzyme called telomerase assists in the maintenance of telomere length, and telomeres shorten every time cells divide. Telomeres are known to shorten with age, and this shortening is influenced by epigenetic regulation and exacerbated by stress (Aubert & Lansdorp, 2008; Blasco, 2007). For example, telomere length is reduced in mothers caring for chronically ill children (Epel et al., 2004). Shorter telomeres have been found in those who had a greater number of childhood adverse events (Tyrka et al., 2010), spent a significant amount of time in institutional care (Drury et al., 2012), or were exposed to violence (Shalev et al., 2012). Asok and colleagues recently showed that high-risk children have greater amounts of telomere attrition when compared with low-risk children, and that longer telomere length was associated with higher parental responsiveness in high-risk children (Asok, Bernard, Roth, Rosen, & Dozier, 2013). All of these studies support the notion that a reduction in telomere length is a biological outcome associated with early-life stress. Given that chromatin structure affects regulation of telomeres, another important piece in the puzzle to solve is how epigenetic changes driven by stress might in turn drive (or be a result of) telomere dysregulation.

CONCLUDING REMARKS

In summary, studies have revolutionized our understanding of the biological changes that occur with environmental adversity, social stress, and traumatic experiences. Work in both animal models and humans have contributed fascinating insight into epigenetic factors that serve as a rich source for interactions between our environment and static genome. Continued elucidation of the regulatory role of epigenetic processes in aspects of normal and abnormal brain development stands to reveal substantial information regarding the molecular processes underlying cognitive and psychiatric disorders, and importantly, routes for more effective treatment strategies.

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CHAPTER 12

Neurogenetics Approaches to Mapping Pathways in Developmental Psychopathology

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INTRODUCTION

Overview of Chapter

The observation of multifinality and equifinality in the development of psychopathology has long been a source of intrigue to psychologists (Cicchetti & Rogosch, 1996). In the case of the former, it has been observed that the same environmental input can have a number of different outcomes depending on the individual. For instance, although it is noted that environmental stress contributes to a range of psychiatric disorders, including major depression and post-traumatic stress disorder, only a subset of individuals exposed to such stress will actually go on to develop disorders. Moreover, when disorder does occur, some individuals appear to react to stress with externalizing behaviors, whereas others develop internalizing problems. Further, some individuals appear to be strongly impacted by environmental stress, whereas others exhibit resilience and achieve positive outcomes in such environments (Masten, 2001). In the case of equifinality, one final end point may be the result of multiple different developmental origins. For example, different types of environments and

Large portions of this chapter are based on Bogdan, Hyde, & Hariri, *Molecular Psychiatry*, 2013; Hyde, Bodgan, & Hariri, *Oxford Handbook in Molecular Psychology,* 2013; Hyde Bogdan, & Hariri, *Trends in Cognitive Science*, 2011; Munoz, Hyde, & Hariri, *Journal of the American Academy of Child and Adolescent Psychiatry*, 2011; Hyde 2015, *Development and Psychopathology*; and Swartz & Monk, 2013, *Handbook of Developmental Psychopathology*. Thus this chapter draws heavily on these sources in combining the ideas and text of these works to provide a more integrated and comprehensive description of the neurogenetics of developmental psychopathology. The work was supported in part by a postdoctoral fellowship provided by the National Institute of Child Health and Human Development (T-32 HD07376) through the Center for Developmental Science, University of North Carolina at Chapel Hill, to JRS. We wish to thank Martha Alves and Hailey Dotterer for their helpful assistance in preparing the chapter.

life events that vary in their nature, timing, and duration (e.g., childhood maltreatment, loss of a loved one, natural disasters) could all have the same outcome: the onset of major depression, demonstrating that there are likely many pathways to the same outcome. The key to understanding these processes is tied to the study of how individual differences interact with, modify, and increase or decrease responsiveness to environmental influences.

A large volume and wide variety of psychological research has documented that individual differences in dimensions of personality, mood, cognition, and environmental experience critically shape complex human behavior and confer differential susceptibility for psychopathology across development (Belsky & Pluess, 2009; Ellis & Boyce, 2011). The integration of neuroscience and psychology has shown that many of these individual differences in personality, mood, cognition, and experience are associated with differences in the brain, including its structure (Kempton, Salvador, Munafò, et al., 2011), connectivity (Thomason & Thompson, 2011; Whitfield-Gabrieli et al., 2009), activity at rest (Jang et al., 2011; Pizzagalli, 2010), and activity during tasks (Hariri, 2009). Moreover, associations between brain structure and function and complex behavior are not "just" correlational: experimental designs, including direct chemical (Bigos et al., 2008) and electrical (De Raedt et al., 2010; Holtzheimer & Mayberg, 2011) manipulation of these neural circuits have been shown to cause behavioral changes. Thus, much current research is aimed at understanding the neural correlates and brain mechanisms involved in the development of psychopathology.

In this chapter we ask where individual differences in brain structure and function arise from and how we can understand the role of genetic background in shaping neural structure and function, particularly as it interacts with experience across development. Specifically, we refer to *neurogenetics* as a discipline that will improve understanding of a complex etiological chain that starts with variability in genes, interacts with variability in experience, with this interaction mediated by the brain at multiple levels of analysis, and is ultimately expressed as behavior or more specifically as cognition, mood, or personality, that may increase risk for maladaptive outcomes, such as psychopathology. Such mechanistic knowledge can facilitate the development of better (and etiologically-based) diagnoses and ultimately lead to novel treatments targeting specific links identified within these complex pathways (Charney et al., 2002; Hasler & Northoff, 2011; Kupfer & Regier, 2011). In other words, by understanding how our genetic background interacts with experience to affect our brain, a deeper, more nuanced, and more complete understanding of psychopathology can emerge, leading to improved treatment and prevention.

An initial step to develop a mechanistic understanding of complex behavior is to identify sources of individual variability in neural signaling pathways (e.g., neurotransmitter systems) and to understand how such variability influences brain function and behavior. Because differences in neurotransmitter availability and function ultimately shape variability in emergent neural pathways, developing links between brain chemistry and circuitry is critical for understanding the biological basis of behavior and psychopathology. Building on nonhuman animal research (Holmes, 2001), positron emission tomography (PET) ligand (Buckholtz et al., 2010), and pharmacologic challenge (Bigos et al., 2008) studies, molecular genetics provides noninvasive and cost effective tools to tap into variability in brain chemistry through the identification of common DNA sequence variation, referred to as polymorphisms. These polymorphisms allow for the modeling of individual differences in brain chemistry and neural signaling pathways, and represent the first step in a cascade that leads from genetic to neural to behavioral differences (Bigos & Weinberger, 2010; Hariri, 2009; Meyer-Lindenberg et al., 2006). Thus, in the first part of this chapter, we provide a detailed overview of neurogenetics, including an outline of the variety of techniques incorporated within a neurogenetics framework and a discussion of how neurogenetics research is contributing to our understanding of these complex molecular signaling cascades.

In the second part of this chapter, we discuss how areas of research and techniques within neurogenetics map onto concepts from *developmental psychopathology*. Guided by a *developmental neurogenetics* framework (Hyde, 2015), we highlight emerging findings from studies that have examined youth internalizing disorders, including anxiety and depression. We discuss interactions between well-established neural underpinnings of internalizing disorders (i.e., corticolimbic circuitry and functioning) with genotype and environmental adversity. More importantly, we outline potential biological mechanisms that can account for interactions between gene, brain, and environment that may ultimately lead to the behavioral outcome of depression or anxiety among some youth. In addition, we discuss potential treatment implications that arise from neurogenetics. Finally, we discuss current challenges in neurogenetics and next steps in research on developmental neurogenetics.

A Brief History of Imaging Genetics and Neurogenetics

The systematic investigation of how common genetic variation maps onto individual differences in behaviorally and clinically relevant brain function was pioneered at the turn of the century by Daniel R. Weinberger and a small group of colleagues at the National Institute of Mental Health. Weinberger and colleagues were specifically interested in advancing our understanding of the molecular genetic architecture of common psychiatric disorders, particularly schizophrenia, which twin studies had demonstrated to exhibit a high degree of heritability. However, rather than attempting to link common genetic variation directly to clinical diagnosis as had been the convention in psychiatry, Weinberger and colleagues focused their association studies on neural phenotypes that were simultaneously more proximal to any molecular effects of polymorphisms and represented intermediate biological processes associated with core disease symptoms and pathophysiology. In other words, Weinberger and colleagues began to systematically map the biological pathways that lay between any given genotype and an emergent behavioral or clinical phenotype (Hariri & Weinberger, 2003).

In the earliest imaging genetics studies, neuroreceptor mapping techniques, such as single-photon emission computerized tomography (SPECT), were employed to map common variation positioned to affect gene expression onto observable in vivo differences in protein availability (e.g., Heinz, Goldman, et al., 2000; Heinz, Jones, et al., 2000). These studies were followed quickly by those using fMRI to map common variants onto variability in brain function associated with core symptoms and pathophysiology (e.g., Bookheimer et al., 2000; Egan et al., 2001; Hariri et al., 2002). Through these earliest studies, imaging genetics emerged as a simple yet powerful approach that not only provided the missing links between genes and disorder but, through illumination of these links, also offered novel targets for treatment. Imaging genetics further introduced a remarkable era of replication in genetic association studies by focusing on relatively homogeneous neural phenotypes rather than heterogeneous behavioral and clinical phenotypes. The almost parallel emergence of gene–by environment (GxE) interaction research in psychiatry (Caspi et al., 2002; Caspi et al., 2003) demonstrated that the ultimate effect of genetically driven variability in brain function on psychopathology likely reflects the moderating role of specific environments through which these pathways can be expressed as relative risk or resilience (Belsky et al., 2009; Grishkevich & Yanai, 2013; Manuck, 2009).

While the value of imaging genetics in advancing the treatment and, possibly, prevention of mental illness was readily and rapidly adopted by the psychiatric community, the approach was initially regarded as little more than a curiosity by neuroscience. However, the application of imaging genetics to illuminate the importance of specific pathways in the emergence of individual differences in a broad range of cognitive and affective brain functions has garnered increasing recognition by even basic scientists (Hariri, 2009). As detailed below, in this broader application of imaging genetics, common polymorphisms of demonstrated importance for specific biological pathways are used to efficiently model emergent variability in brain chemistry and, in turn, test the modulatory effects of this chemistry on cognitive and affective processes supported by discrete neural circuits (Erickson et al., 2013; Forbes et al., 2009; Nikolova, Singhi, Drabant, & Hariri, 2013).

Across disciplines, imaging genetics has now become a widely and commonly employed tool for identifying the biological pathways through which individual differences in behaviorally and clinically relevant brain function emerge and contribute to trajectories of risk and resilience for psychopathology. It is positioned to inform the development of animal models to deepen our understanding of these pathways at the molecular and cellular level (e.g., Chen et al., 2006; Papaleo et al., 2008) and, likewise, translate discoveries from animal models into humans (e.g., Gunduz-Cinar et al., 2013; Joeyen-Waldorf et al., 2012; Wellman et al., 2013). Imaging genetics is further positioned to quickly and efficiently launch detailed investigations of the next generation of candidate genes as they are identified using genome-wide association studies (GWAS) and genomic sequencing (e.g., Bigos et al., 2010). Moreover, MRI-based measures of behaviorally and clinically relevant brain structure, function, and connectivity are increasingly becoming the target phenotypes in GWAS (e.g., Jahanshad et al., 2012; Jahanshad et al., 2013). Thus, imaging genetics is now poised, not to simply map biological pathways for existing genetic associations with behavioral and clinical phenotypes, but rather to drive discovery leading to follow-up association studies with targeted behavioral and clinical phenotypes of biological pathways.

WHAT IS NEUROGENETICS?

Neurogenetics is a discipline that integrates techniques from genetics, neuroscience, and psychology, and attempts to link variability at specific sites on the genome (i.e., polymorphisms) to variability in protein expression and

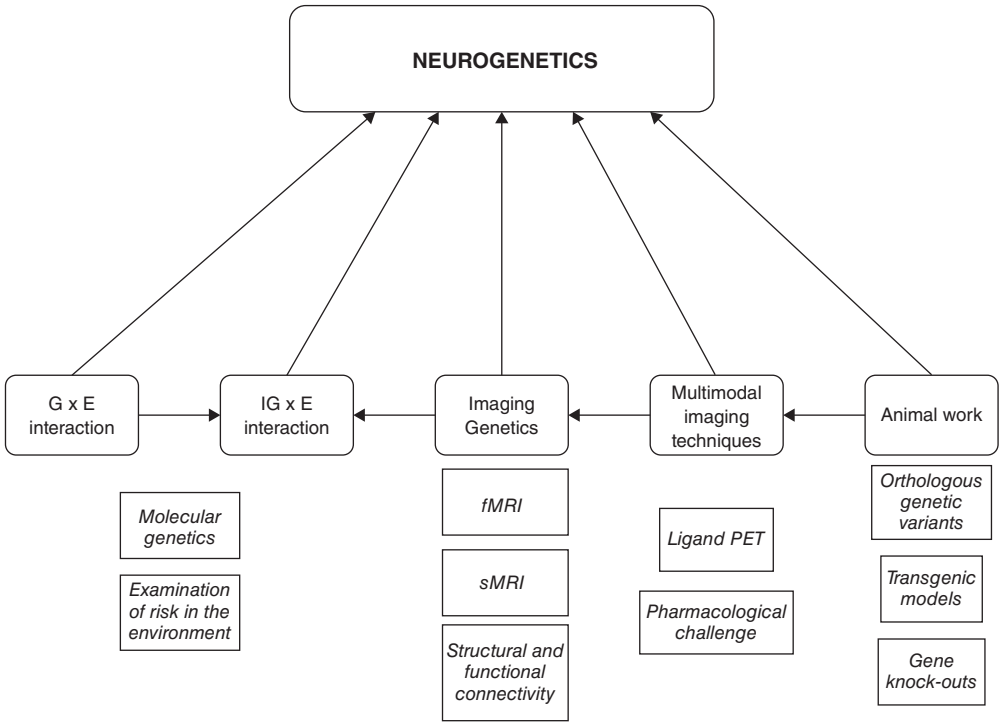


Figure 12.1 Conceptual summary of neurogenetics, a discipline that incorporates several approaches to understand the impact of genes on brain structure and function and subsequent behavior. The core technique within neurogenetics is imaging genetics, which links variability in functional genetic polymorphisms to differences in brain structure and function, particularly using MRI. However, neurogenetics also leverages nonhuman animal models and multimodal and pharmacologic challenge MRI studies to specify complex molecular signaling pathways and, more directly, to experimentally probe neural chemistry. More recently, models within a neurogenetics framework have also incorporated the influence of experience within an imaging gene–environment (IGxE) interaction framework. Through this variety of techniques, neurogenetics is helping to specify the molecular pathways from gene to brain to behavior.

function, brain structure and connectivity, and, ultimately to individual differences in behavior and risk for psychopathology (Bogdan, Hyde, & Hariri, 2012; Hariri, 2009). A significant advantage of neurogenetics is the emphasis it places on integrating evidence from multiple approaches, in particular the combination of (1) *imaging genetics*, (2) other approaches that more precisely examine neurochemistry (e.g., nonhuman animal work, PET studies, pharmacological challenge), and (3) the effect of the environment on behavior (e.g., *GxE interaction studies;* Figure 12.1). In the first half of this chapter, we describe the key elements incorporated within neurogenetics and we examine advantages and ongoing challenges of this approach.

Imaging Genetics

The core of neurogenetics is imaging genetics, a technique that aims to link variability in genes to variability in brain structure and function.

Why Study Genes in the Context of Developmental Psychopathology?

Genes have an unparalleled potential impact on all levels of biology. In the context of disease states, and particularly behaviors as they deviate from normative patterns, genes are fundamental to our understanding of mechanisms. Whereas most human behavior cannot be explained by genes alone, and certainly much of the variance in aspects of brain information processing will not be directly genetically determined, variations in a genetic sequence that impact gene function likely contribute a substantial amount of variance to these more complex phenomena. This conclusion is implicit in results garnered from twin studies that have demonstrated heritabilities of 40–70% for aspects of cognition, temperament, and personality (Plomin, Owen, & McGuffin, 1994). Psychiatric illnesses also cluster within families, suggesting a highly heritable component to disease susceptibility (Moldin & Gottesman, 1997; Weissman, Leckman, Merikangas, Gammon, & Prusoff, 1984; Williamson et al., 1995). Genes, therefore,

have the potential to identify underlying mechanisms of variability in behavior and disease risk, which may be particularly salient in relation to child and adolescent psychopathology that appears at least similar to, and in some cases, *more* heritable than adult psychiatric disorders (Beaudet, 2007; Coolidge, Thede, & Jang, 2001; Lichtenstein & Annas, 2000; Rhee & Waldman, 2002). Within this context, imaging genetics represents the ability to understand the neurobiological mechanisms through which genes can impact variability in emergent behavioral phenomena.

The classic approach used in genetic association analyses involves the use of candidate genes. A candidate gene is a gene whose variation is suspected of being directly associated with an observable behavioral or clinical (i.e., disease-related) property of an individual (called a phenotype). Within a candidate gene approach, the first step is to identify a genetic polymorphism that potentially impacts the function of a behaviorally or clinically relevant biological process. Next, deviations in the frequency of one gene variant (i.e., an allele) in populations expressing the phenotype are determined. Ideally, the genetic variation should have an impact on the molecular or cellular function of the gene or protein (i.e., be a functional variation), and the target phenotype should be stable, robust, and quantifiable. Within an imaging genetics framework, target phenotypes are usually physiological responses of the brain during specific behavioral processes (e.g., amygdala reactivity when viewing threatening facial expressions) or some other measure of brain structure (e.g., gray matter volume or integrity of white matter tracts connecting relevant brain regions) or function (e.g., brain activity at rest or network connectivity during a specific task).

Why Link Genes to Functional Neuroimaging?

Previous investigations of candidate genes have attempted to link functional polymorphisms directly to behavior. Findings from these studies however, have been weak and inconsistent (e.g., variation in the serotonin transporter—the 5-HTTLPR short allele—and negative emotionality; Malhotra & Goldman, 1999). One explanation for these weak and inconsistent findings is the considerable inter-individual differences in dimensions of observed behavior, as well as subjectivity and error in behavioral measures, which necessitate daunting sample sizes to detect even small gene effects (Glatt & Freimer, 2002). In addition, and perhaps more importantly, variability in genes needs to affect a myriad of levels of change to have any measureable influence on behavior. Put another way, gene effects are not expressed directly at the level of behavior, but rather are mediated by effects on molecular and cellular cascades, which may bias information processing in brain circuitries, ultimately mediating behavioral responses to environmental challenge. Thus, for genetic variability to affect behavior, it must also affect brain function at some level. An efficient and effective tool that can be used to explore the impact of these potentially brain-relevant genetic polymorphisms is provided by functional neuroimaging, including fMRI, EEG, and PET. These different imaging techniques enable quantification of activity within specific brain regions during cognitive and emotional tasks performed by a participant. The assumption is that imaging techniques can identify neural pathways through which genetic polymorphisms contribute to the emergence of variability in behavior and thereby risk for psychopathology.

Basic Principles Involved in Imaging Genetics

Three basic principles have been articulated for imaging genetics studies (Hariri, Drabant, & Weinberger, 2006; Hariri & Weinberger, 2003; Munoz, Hyde, & Hariri, 2009): (1) selection of candidate genes; (2) control for nongenotype factors; and (3) selection of appropriate tasks for the subject to perform during functional imaging.

First, there is a need for well-defined functional polymorphisms (i.e., single nucleotide polymorphisms [SNPs] or other structural variants) in coding or promoter regions, which have been previously linked to specific physiological effects at a cellular level with known impact at distinct brain regions. Selecting variants that are *functional* and thus that have known neurobiological consequences (e.g., increases in serotonin signaling or decreases in transcription of a protein affecting neurotransmission) is important because of the emphasis placed by imaging genetics on specifying *mechanisms* through which genes impact brain and related behavior.

Second, there is a need to control for potential confounds. This need arises because potential genetic effects are still relatively small compared to the typically large effects of age, sex, IQ, and environmental influences (e.g., illness, injury, substance abuse). Indeed, because imaging genetics studies focus on a single or relatively few polymorphisms against a background of millions, studies must control for population stratification (Cardon & Palmer, 2003). Population stratification refers to differences in the genetic background of individuals that reflect their unique ancestry, and against which any relationship between specific genotypes and phenotypes can be tested. This point is important in relation to assessing specific diverse

populations who may be at greater risk for developing psychopathology. In particular, among populations marked by heterogeneity in ethnic or racial background, allele frequencies may differ markedly by ancestry, which introduces a major potential confound into studies (for a nuanced discussion of genetic ancestry, see Fujimura & Rajagopalan, 2011).

Third, to successfully identify functional correlates of genetic variation, studies need to choose well-characterized behavioral tasks for participants to perform during functional neuroimaging, which are both sensitive and specific to the brain process under investigation. The ideal tasks for imaging genetics studies are ones that have been established to robustly engage specific brain systems as well as tasks that display adequate variance across individuals. While such criteria increase the likelihood of identifying significant genetic regulation of interindividual variability in brain function and related behaviors, multiple genetic polymorphisms (many of which will be of small effect) acting in concert or opposition in the context of unique environmental challenges will ultimately account for the majority of variance in any given neural or behavioral phenotype (e.g., Buckholtz et al., 2007; Nikolova, Ferrell, Manuck, & Hariri, 2011).

Advantages of Imaging Genetics Studies

Imaging genetics studies have become more common over the last two decades as studies of the brain have become increasingly important in our understanding of the development of psychopathology. An imaging genetics approach offers several strengths in terms of advancing our understanding of the development of variability in brain structure and function as it may relate to complex behavior and psychopathology.

First, by connecting genetic variation to intermediate biological phenotypes (e.g., brain chemistry or circuit function), a plausible, observable, and testable mechanism is provided through which genes could influence behavior (Hasler & Northoff, 2011; Meyer-Lindenberg et al., 2006). For example, several studies have demonstrated a link between variability in the serotonin transporter gene—the short allele of the 5-HTTLPR—and increased amygdala reactivity to threat (Hariri et al., 2006; Hariri et al., 2002) and decreased functional connectivity between the amygdala and prefrontal regions of the brain (Pezawas et al., 2005). Given links between increased amygdala reactivity and anxiety and depression (Fakra et al., 2009; Price & Drevets, 2010), these studies have begun to address how and why variation in the 5-HTTLPR might affect risk for these disorders. In particular, studies examining these associations exemplify much of the promise of neurogenetics by combining different techniques that emphasize the brain as the mechanism that links genetic effects on behavior and genetic variability to differences in brain structure and function.

Second, when the target polymorphism being examined is of known functionality (e.g., altered gene transcription and/or function), it can serve as a proxy for individual differences in brain chemistry. In this way, polymorphisms can inform our understanding of molecular and neurochemical mechanisms through which differences in the brain arise at the genetic and molecular level (Hariri, 2009). For example, in the case of the 5-HTTLPR, the short allele has been linked to decreased transcription of the serotonin transporter gene (Lesch et al., 1996), which in turn affects the amount of serotonin transporter molecules, ultimately affecting the clearance of serotonin from the synapse. Adopting an imaging genetics approach thus emphasizes a multilevel account for biological mechanisms: not only do genetic polymorphisms represent heritable genetic influences, but they also model neurotransmitter differences that affect neuronal firing at synapses via the modulating effect of neurotransmitters.

Third, by focusing on dimensional and relatively objective intermediate phenotypes, imaging genetics research largely escapes the limitations of broad nosological definitions (e.g., *DSM-5* diagnoses), which are typically comprised of heterogeneous symptoms or behaviors and are often subject to methodological biases inherent in self-report (Hasler & Northoff, 2011; Meyer-Lindenberg et al., 2006). Imaging genetics is thus more consistent with the Research Domain Criteria (RDoC) approach now emphasized by the National Institute of Mental Health (Cuthbert & Kozak, 2013; Insel et al., 2010), modeling a multilevel understanding of complex behavior.

Challenges of an Imaging Genetics Approach

Although imaging genetics studies have contributed to our understanding of psychopathology, some major issues are worth noting as we look forward to the next generation of research. First, the majority of imaging genetics studies has established links between genetic polymorphisms and the brain but failed to demonstrate direct and meaningful links to behavioral outcomes (Hariri et al., 2002; Pezawas et al., 2005). As noted above, however, a major advantage of an imaging genetics approach is the modeling of the brain as a mediator linking genetic variability to variability in behavior. Recently, imaging genetics studies have begun to establish such meaningful links by modeling indirect pathways from genes to behavior via the brain

(Fakra et al., 2009; Furmark et al., 2008). Studies that demonstrate indirect pathways between gene and behavior through the brain, when no direct gene–behavior link exists (Fakra et al., 2009), emphasize the importance of using statistical approaches that can model indirect (mediated) pathways (Preacher, Rucker, & Hayes, 2007). Moreover, imaging genetics studies that are able to establish indirect effects highlight that there are important relationships between genes and behavior, even when large direct relationships are not evident. However, to date, very few imaging genetics studies have actually drawn out an indirect pathway from gene to brain to behavior, instead focusing mostly on gene to brain. More research is therefore needed that examines the brain as a mediator of gene–behavior pathways.

A second critical challenge within imaging genetics is to model even greater complexity of genetic effects on the brain. In particular, GxE interaction studies clearly demonstrate the importance of environmental experience in understanding the ultimate effects of genetic variation on behavior and thus the environment should be modeled in future studies (see the following IGxE description). Beyond issues relating to the effect of the environment, the effects of epistasis (i.e., GxG interactions) and the likely small influence of any *single* genetic polymorphism highlight the need for novel analytic approaches. Future studies are needed that investigate epistasis, that is GxG interactions (Buckholtz et al., 2007; Talkowski et al., 2008), cumulative genetic profiles (Nikolova et al., 2011), hypothesis-free imaging using genome-wide association studies (Liu et al., 2010), rare gene or copy number variants (Blakely & Veenstra-Vanderweele, 2011), or novel statistical approaches to integrate multiple genes into models (Gruenewald, Seeman, Ryff, Karlamangla, & Singer, 2006; Hizer, Wright, & Garcia, 2004). Further, beyond interaction effects (GxE, GxG), future studies that incorporate complementary techniques (e.g., neuroreceptor PET, pharmacologic challenge, animal models), or studies that approach the problem of modeling neural reactivity in novel statistical ways (e.g., graph theory: Astolfi et al., 2007; or machine learning: Pereira, Mitchell, & Botvinick, 2009), will better capture molecular mechanisms mediating genetic effects on the brain (Hariri, 2009; Ressler et al., 2011).

Other Relevant Techniques to Examine Neurochemistry Within Neurogenetics

Animal Models

An advantage of leveraging genetic polymorphisms in the context of brain phenotypes is that it allows for more effective synergy with animal models (e.g., transgenic mouse models, optogenetics), which in turn can advance a detailed understanding of the molecular and cellular mechanisms that ultimately link genetic variation to brain to behavior (Blakely & Veenstra-Vanderweele, 2011; Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Holmes, 2008). Animal models allow for many designs that cannot be carried out ethically in human samples. Typically nonhuman animal designs confer greater experimental control and more precise and in-depth measurement of molecular biological pathways. Within psychiatry, nonhuman animal research has traditionally modeled psychopathology and related intermediate behaviors by documenting changes in response to behavioral, environmental, or pharmacologic stimuli and/or changes following genetic manipulation. Because of the ability to manipulate and directly measure brain chemistry and gene function, studies using animal models can therefore target specific molecular mechanisms at specific developmental periods that might otherwise be inaccessible in human studies (e.g., Yu, et al., 2014). In addition, research employing nonhuman animal models offers unique opportunities to control both genetic background and environmental experience, neither of which is practical or ethically feasible in human studies (Holmes, 2008).

Both the presence of orthologous genetic variants and the development of novel manipulations (e.g., transgenic lines, optogenetics) provide researchers using nonhuman animal models with opportunities to identify specific molecular mechanisms for behaviors related to human psychopathology, which also represent potential novel treatment targets (Barr et al., 2003; Fenno, Yizhar, & Deisseroth, 2011; Holmes, 2001). Orthologous genetic variants, which are similar but not identical to human polymorphisms, allow for more direct comparison of nonhuman animals and humans based on shared genetic differences that confer similar effects on gene transcription and/or protein function. For instance, an orthologue of 5-HTTLPR exists in rhesus macaque monkeys (i.e., rh5-HTTLPR) and, like the human variant, the short allele of rh5-HTTLPR is associated with relatively decreased transcription of the gene (Bennett et al., 2002). This functional genetic orthologue has allowed researchers to examine how various factors, such as maternal separation (Barr et al., 2004) and chronic SSRI administration (Bogdan et al., 2011), influence behavior and brain chemistry in experimentally controlled settings (Barr et al., 2003). For instance, it has been shown that following maternal separation, monkeys carrying the rh5-HTTLPR short allele display greater anxiety, agitation, and exaggerated

HPA axis response (Barr et al., 2004; Caspi et al., 2010). Moreover, much like humans, rh5-HTTLPR short allele carriers have greater metabolic activity in the amygdala (Kalin et al., 2008) and demonstrate more risk-averse behaviors (Caspi et al., 2010; Watson, Ghodasra, & Platt, 2009).

Emerging neuroimaging work with rh5-HTTLPR has begun to establish the mechanisms through which these associations with behavioral outcomes might emerge. For example, results from human studies suggest that the behavioral consequences of the short 5-HTTLPR allele may arise via neurodevelopmental influences on brain morphometry (Canli et al., 2005; Pezawas et al., 2005), which has been confirmed in the rhesus model (Jedema et al., 2010). Moreover, the rhesus model also has confirmed human findings indicating that the effects of 5-HTTLPR on adult brain function and behavior appear to be mediated by downstream modulation of other serotonin signaling mechanisms (e.g., 5-HT_{1A} autoreceptor downregulation) (David et al., 2005; Oler et al., 2009). Thus, the availability of orthologous genetic variants allows for testing and validation of observed neurogenetics pathways of individual differences in behavior, genetic disease risk in the context of adverse environments and, perhaps most importantly, the discovery of specific molecular mechanisms mediating neurogenetics effects on behavior and psychopathology.

Similarly, transgenic mouse models have provided invaluable insight into the genetic and molecular components of complex behavior and related psychopathology. For example, serotonin transporter knockout mice (i.e., mice that have been genetically engineered to have an existing gene inactivated) have informed our understanding of how the short allele of 5-HTTLPR in humans may contribute to depression. A series of studies using a knockout mouse model have demonstrated that loss of serotonin transporter function results in a multitude of downstream effects, including regionally specific upregulation and downregulation of both presynaptic and postsynaptic serotonin receptors, which ultimately determine the modulatory effects of serotonin on neuronal signaling (Hariri & Holmes, 2006; Holmes, 2008; Kim et al., 2005). In addition, conditional transgenic models have furthered our knowledge of serotonin function. Unlike the constitutive (i.e., from birth) serotonin transporter knockout model, conditional transgenic models allow experimenters to control the exact *timing* of gene knockout. These transgenic models have demonstrated that similar differences in serotonin signaling (conferred by 5-HTR_{1A} autoreceptor negative feedback and not transporter reuptake) must occur early in development to alter adult brain function and behavior (Gross et al., 2002) and that the long term effects of signaling in these pathways may be specific to sensitive developmental periods (Yu et al., 2014). These results suggest that serotonin transporter function and the resulting effects on brain and behavior vary substantially across development.

Thus both monkey and rodent data suggest that the short allele of 5-HTTLPR appears to exert its influence on behavior and risk for depression through neurodevelopmental mechanisms that affect both downstream 5-HT signaling mechanisms and corticolimbic structure. Further, both of these processes appear to be exacerbated by stressful experiences. Convergent patterns across species help to detail the molecular mechanisms that shape the effects of 5-HTTLPR on brain chemistry, circuitry, behavior, and risk for psychopathology (Caspi et al., 2010), and thus demonstrate the utility of using nonhuman animal model research to inform our interpretation of neurogenetics studies in humans. As noted above, findings from imaging genetics studies are often built on a firm foundation in animal models and can be strengthened via a two-way exchange with this literature (Figure 12.1). Though studies of 5-HTTLPR correlations with amygdala reactivity are often cited in isolation, these studies were built on and informed by nuanced work in nonhuman animal models.

Multimodal Imaging

Because functional genetic polymorphisms appear to be a useful way of representing individual differences in brain chemistry and associated neural signaling pathways, neurogenetics can inform our ultimate goal of identifying the detailed and complex biological mechanisms that give rise to risk for psychopathology. However, to truly gain mechanistic knowledge, neurogenetics is strengthened by incorporating more direct assessment (e.g., ligand PET; Willeit & Praschak-Rieder, 2010) or manipulation (e.g., pharmacological challenge; King & Liberzon, 2009) of brain chemistry in humans and work from nonhuman animal research. The synergy of these different approaches within a neurogenetics framework allows for even more detailed and controlled assessment and manipulation of brain chemistry. The incorporation of a wider range of techniques to assess brain chemistry is a major reason this discipline is now more broadly referred to as *neurogenetics* instead of *imaging genetics*. The term neurogenetics deliberately emphasizes that a range of techniques are critical to this approach and that it is *not solely* focused on using imaging with genetics (Bogdan, Hyde, et al., 2012; Hariri, 2009). Indeed, although imaging genetics has contributed to our understanding of how molecular signaling pathways

affect brain structure and function, genetic variation is a distal and typically static indicator of these pathways.

Therefore, neurogenetics researchers have leveraged two other approaches to better define these pathways at a molecular level. Specifically, neurogenetics also includes the use of multimodal imaging. Multimodal imaging studies use positron emission tomography (PET) in combination with genetic polymorphisms and fMRI to directly probe in vivo neurochemistry (Fisher & Hariri, 2012; Fisher et al., 2009; Willeit & Praschak-Rieder, 2010). For example, work by Fisher, Hariri, and colleagues has used PET, fMRI, and molecular genetics approaches to link genetic variability to brain function, as well as *in vivo* neurochemistry. In particular, these researchers examined the serotonin 1A receptor, a major receptor in the serotonin system for providing homeostatic feedback on serotonin transmission (Hariri & Holmes, 2006). Using PET and fMRI, they demonstrated that the density of serotonin 1A autoreceptors accounts for 30–44% of variability in amygdala reactivity in healthy adults (Fisher, Meltzer, Ziolko, Price, & Hariri, 2006). As previous studies had identified a functional genetic polymorphism in the serotonin 1A receptor gene (the −1019G allele of HTR1A) (Lemonde et al., 2003), this group next examined how this polymorphism affected neural function by using fMRI in an imaging genetics study. They found that the serotonin 1A receptor gene functional polymorphism was related to individual differences in amygdala reactivity and subsequent trait anxiety (Fakra et al., 2009). Taken together, these studies build a molecular mechanism via which variation in the serotonin 1A receptor gene may affect receptor density, which in turn appears to affect amygdala reactivity, resulting in risk for greater trait anxiety. Further, this body of research exemplifies how multimodal neuroimaging, combined with imaging genetics, can begin to build a molecular account for the ways that genetic polymorphisms might affect complex neurotransmitter pathways (e.g., affecting receptors that affect feedback on the 5-HT system) and ultimately influence both neural functioning and subsequent behavior (Fisher & Hariri, 2012; Fisher & Hariri, 2013). Moreover, by leveraging PET with fMRI, neurochemistry can be examined in the same human participants that are undergoing fMRI scans.

Pharmacological fMRI

While multimodal studies involving PET enable direct observation of neurotransmitter binding levels in awake adults, *pharmacological fMRI* designs facilitate direct manipulation of circuits (Honey & Bullmore, 2004; Schwarz, Gozzi, Reese, & Bifone, 2007). More specifically, neural responses are examined after individuals are given drugs that target specific neurotransmitters systems. For example, studies have used acute administration of selective serotonin reuptake inhibitors in combination with fMRI to demonstrate that these commonly prescribed drugs have direct effects on amygdala reactivity (e.g., Bigos et al., 2008). These findings demonstrate that experimental manipulation of specific neural circuits can also cause changes in functioning. In this way, studies are beginning to specify how blocking of serotonin transporters affects amygdala reactivity acutely and chronically. Through PET and pharmacological challenge studies, neurogenetics researchers are thus able to observe more precise molecular mechanisms and experimentally manipulate these pathways. However, while the addition of multimodal neuroimaging and pharmacological fMRI are important components of a neurogenetics approach, these techniques are difficult to carry out ethically among children, and are therefore less helpful when examining younger populations or when asking questions about early development. At the same time, use of synergistic techniques within a neurogenetics framework, even among adults, and incorporation of converging findings from nonhuman animal models, helps lay a foundation for understanding these processes across development (e.g., Yu, et al., 2014).

Imaging Gene–Environment (IGxE) Interactions

As outlined in the previous sections, a neurogenetics approach, informed by nonhuman animal work, uses imaging genetics and other complementary techniques (e.g., multimodal and pharmacological fMRI) to build a more precise and multilevel account of individual differences from gene to neurotransmitter, to brain structure and function, and ultimately to behavior. Until recently, neurogenetics had been solely focused on delineating neurobiological contributions to behavior, and for the most part, had ignored potential environmental influences on these pathways. However, a number of other approaches have led to an expansion of neurogenetics to incorporate conceptualizations of the environment. First, the rise of the field of epigenetics has led to a greater *specification* of the molecular mechanisms through which experience is thought to affect gene transcription and translation (Meaney, 2010). Second, GxE interaction studies at the epidemiological level have continued to gain prominence within research on psychopathology development (Moffitt, Caspi, & Rutter, 2005, 2006). Finally, an increasing number of studies have demonstrated important links between individual variability in experiences and differences in brain

structure and function (Gianaros et al., 2008; Gianaros et al., 2007; Gianaros et al., 2011; Hackman, Farah, & Meaney, 2010; Tottenham et al., 2011; Tottenham et al., 2010). Thus, neurogenetics has evolved further in order to specify how the *environment* could affect and interact with complex biological pathways (Caspi & Moffitt, 2006). We describe this evolution of neurogenetics to incorporate assessments of the environment in detail below.

Considering the Environment: GxE Interactions

Why do some youth exposed to environmental stressors (e.g., abuse) go on to experience psychopathology, while others, exposed to the same stressor, are resilient? Inspired by models of differential susceptibility (Belsky & Pluess, 2009; Ellis & Boyce, 2011), GxE interaction studies have helped to specify why some individuals are more likely than others to succumb to risk. A GxE interaction occurs when the relationship between an environmental experience (e.g., exposure to trauma) and a phenotype (e.g., psychopathology) is contingent on individual differences in genetic makeup (i.e., genetic polymorphisms) (Caspi & Moffitt, 2006; Rutter, Moffitt, & Caspi, 2006). Alternatively, a GxE interaction is observed when the association between genetic makeup and a phenotype is dependent upon environmental experience. As such, GxE interaction research does not presuppose a main effect of either single polymorphisms or environmental experiences but rather emphasizes an interaction between genetic variation and experience.

Theoretical reviews have revealed several key principles for conducting GxE interaction research and evaluating the resulting patterns (Caspi & Moffitt, 2006; Moffitt et al., 2005). First, as in imaging genetics, researchers need to consider the broad heritability of the target behavior and then leverage knowledge generated in physiology and neuroscience to select polymorphisms in candidate genes that are of functional significance in the biological response to the environmental experience. Second, there needs to be evidence of variability in the response to the selected environmental experience, for which accurate measurement and, ideally, quantification should be available. Finally, there should be causal evidence linking the environmental experience with psychopathology if possible.

Because the concept of GxE interactions does not presuppose a large main effect of single genetic variants (or experiences) on behavior but rather emphasizes an interaction with experience, carefully conducted GxE interaction studies can be instrumental in addressing issues of "hidden heritability". Specifically, hidden heritability refers to the general failure of GWAS (and specific candidate genetic variants) to account for much of the variance attributed to heritable factors in quantitative studies (Maher, 2008), the generally weak penetrance of polymorphisms in candidate genes (Maher, 2008), and the lack of consistent replication in genetic association studies of psychopathology (Caspi & Moffitt, 2006; Plomin, 2005). There are therefore a number of advantages for neurogenetics to adopt a GxE interaction approach. First, a GxE interaction approach holds promise to confront the problem of the typically small effects in neurogenetics research, whereby inclusion of environmental factors may inform the effects of polymorphisms on a phenotype (Bogdan, Hyde, et al., 2012). Second, GxE interaction research provides face validity as it represents a more plausible model of development in which individual experiences and genetic background interact to influence relative risk rather than more simplistic models hypothesizing independent effects of particular genes or experiences.

The utility of a GxE interaction approach for the discipline of neurogenetics is exemplified by the influential work of Caspi and colleagues (Caspi et al., 2003), who demonstrated that the depressogenic effects of stress are contingent upon 5-HTTLPR genotype. Specifically, in these studies, a strong and positive relationship between life stress and depression was noted among short allele carriers of a 5-HTTLPR genotype. In contrast, long allele homozygotes of 5-HTTLPR genotype had little or no relationship between stress and depression. These findings have been well replicated (Caspi et al., 2010; Kaufman et al., 2004; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005) and are supported by meta-analysis (Karg, Burmeister, Shedden, & Sen, 2011) and by extensive rodent and nonhuman primate models (Caspi et al., 2010).

For neurogenetics models, the prominence of the 5-HTTLPR genotype is of specific interest as this same allele, as described previously, was linked to amygdala reactivity in some of the first ever imaging genetics studies. This finding has also since been well replicated and further supported by meta-analytic studies (Hariri et al., 2005; Hariri & Holmes, 2006; Hariri et al., 2002; Munafò, Brown, & Hariri, 2008; Pezawas et al., 2005). Moreover, the confluence of these findings suggests that imaging genetics research would benefit from incorporating both the environment and GxE interactions to conceptualize relationships between gene, brain, and behavior. Indeed, GxE interaction research alone cannot reveal the specific biological mechanisms for risk (Blakely & Veenstra-Vanderweele, 2011; Caspi & Moffitt, 2006). Ultimately, for a genetic or environmental variable to affect behavior, it must "get under the skin" (Kendler, 2011; Meyer-Lindenberg,

2011; Rutter & Dodge, 2011): GxE interactions must be instantiated in the brain if they are to affect behavior and the development of risk and resilience. Thus the integration of imaging genetics with GxE interaction studies is critical to our understanding across both literatures, and fits well within a broader neurogenetics framework.

Integrating Imaging Genetics and GxE Interaction Studies

Both GxE interaction studies and imaging genetics studies examine potential relationships between genetic variation and individual differences in behavior or risk for psychopathology. In GxE interactions, the relationship is conditional on experience (i.e., statistical moderation). This conditional effect is necessary to unmask genetic effects (or vice versa). In imaging genetics, a biological mechanism is specified in which variability in brain structure or function enables a link to be drawn between genes and behavior (i.e., statistical mediation/indirect effects). The integration of these two approaches has been termed imaging gene–environment interactions (IGxE) (Hyde, Bogdan, & Hariri, 2011). IGxE informs our understanding of the conditional mechanisms through which genes, environments, and the brain interact to predict behavior and risk for psychopathology. Several recent reviews have demonstrated possible IGxE interactions within a neurogenetics framework, by combining findings from research in animal models, GxE interaction studies, and imaging genetics studies to explain the interactions of genetic variants with environmental variables to predict learning, memory, and psychopathology (Casey et al., 2009; Caspi et al., 2010; Meyer-Lindenberg, 2011). Though these reviews are exciting, empirical studies are only just beginning to test components of IGxE directly. We explore how these conditional mechanisms can be specified conceptually and statistically in single human neuroimaging studies and outline recent studies that have tested components of IGxE interactions.

First, the concept of IGxE can be modeled statistically using a moderated mediation framework (also called conditional indirect effects) (Preacher et al., 2007), in which mediated/indirect effects are moderated by a third variable. Within IGxE, any or all mediated imaging genetics paths (i.e., gene to brain, brain to behavior, and then gene to behavior via brain) may differ depending on the level of a moderator variable (e.g., presence or absence of childhood abuse). As shown in Figure 12.2, there are multiple ways that genetic, neural, environmental, and behavioral variables could interact, and each model yields answers to slightly different questions (see also Preacher et al., 2007). A particularly intuitive IGxE model is a GxE interaction in which the interaction term predicts behavior through its effect on brain function (Figure 12.2, path c). In this case

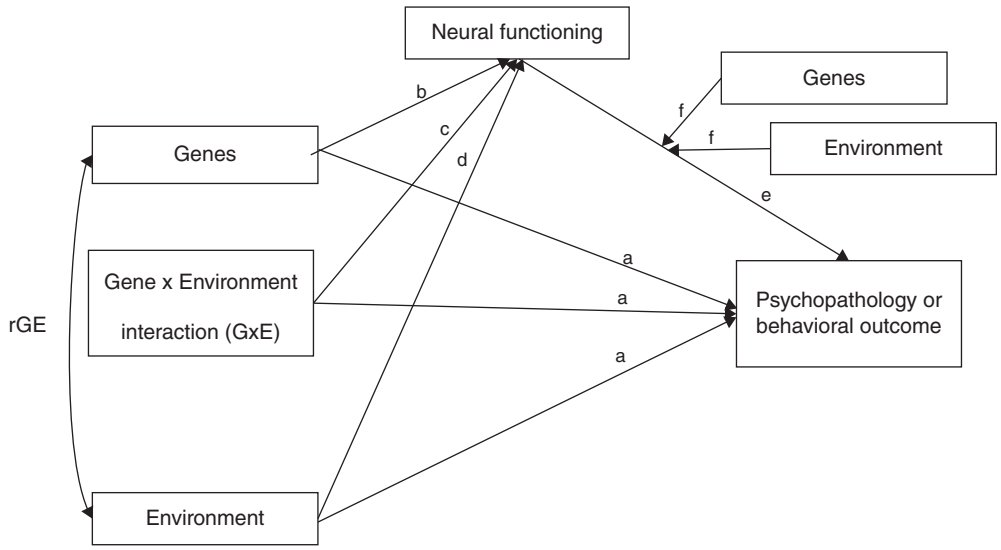


Figure 12.2 Theoretical model of IGxE. A theoretical model of IGxE highlighting how IGxE can be modeled conceptually and statistically. Relationships of the variables are shown for more traditional GxE and imaging genetics paths, as well as new paths possible in IGxE. The a paths model typical GxE relationships; b & e paths model traditional imaging genetics links; d paths show direct effects of the environment on neural functioning; c and e paths model GxE interactions predicting behavior via neural functioning; f paths represent further possible interactions—genetic variation or certain environments moderate associations between neural functioning and behavior. Within SEM models of continuous interactions, the covariance between a genetic variant and an environment is modeled and reflects the correlation (rGE) between specific genetic variants and the environment. *Source:* Adapted from Hyde, Bogdan & Hariri (2011).

there are direct effects of both genetic and environmental variables on brain function, but their interaction predicts nonadditive unique variance, which in turn predicts behavior.

A theoretical example of applying this IGxE interaction model is that increased amygdala reactivity is predicted by both the risk allele of the 5-HTTLPR polymorphism (Hariri et al., 2002), and early experiential risk (e.g., early child maltreatment, McCrory et al., 2013; or socioemotional deprivation, Tottenham et al., 2011). Individuals with the 5-HTTLPR polymorphism and relevant environmental experience could show a *synergistic* increase in amygdala reactivity, which could then further predict increased anxiety symptoms. Alternatively, a positive environment, such as parental warmth, could negate any relationship between genetic variation in serotonin signaling and amygdala reactivity and this lowered amygdala reactivity could then predict average levels of anxiety symptoms.

This example also underlies much of the potential of incorporating IGxE interactions within the discipline of neurogenetics. By combining the power of proximal intermediate phenotypes, evidence from animal models, and potential GxE interactions to clarify relationships, IGxE interaction research is able to provide further insight into the conundrum of hidden heritability. For example, if a genetic variant had no association with a neural or behavioral phenotype in the majority of circumstances, but a robust association in relatively rare environments (e.g., physical abuse), IGxE could potentially detect the association via proximal neural phenotypes. Finally, it is also important to note that within an IGxE model, we specify paths in which genes or experience moderate a brain–behavior link based on studies that support this type of statistical moderation. For example, individuals with a variant in a gene affecting endocannabinoid signaling were found to show greater correlation between reward-related brain reactivity and a measure of impulsivity (Hariri et al., 2009). Additionally, individuals with low social support had a greater relationship between their threat related neural reactivity and trait anxiety (Hyde, Gorka, Manuck, & Hariri, 2011). These studies suggest that the brain–behavior link may not be static across all environments or across different genetic backgrounds.

Within neurogenetics research, approaches that test a "full" IGxE model (i.e., GxE interaction predicts brain function, which in turn predicts behavior via a mediated pathway) are exciting but are only just beginning to emerge (e.g., Glaser et al., 2014). However, several studies have recently been published testing GxE interactions that predict brain function, a critical first step in this emerging field (Cousijn et al., 2010; Drabant et al., 2012; Gerritsen et al., 2011; Ursini et al., 2011). In the first study testing a portion of an IGxE interaction model, Canli and colleagues (2006) reported that the 5-HTTLPR genotype interacted with life stress to predict resting state activity in the amygdala. More specifically, this study found that short allele carriers had elevated amygdala activity at rest, but only among individuals that had experienced more life stress, providing a neural mechanism through which short allele carriers could be more susceptible to the environment at the neural level. In other words, the short allele was only related to amygdala activity at rest for those with greater experience of negative life events, demonstrating an interaction between genotype and environment in predicting brain function.

In a second example of recent research that has tested a portion of an IGxE interaction model, White and colleagues found that emotional neglect was related to threat related amygdala reactivity, but only among individuals with specific alleles of a gene coding for a protein (FKBP5) that affects hypothalamic-pituitary-adrenal (HPA) axis regulation (White et al., 2012). This result is particularly interesting when considered alongside the well-established roles played by both the HPA axis and amygdala functioning in a myriad of psychopathologies. Moreover, the findings of White and colleagues helps to elucidate why some youth with one risk factor (e.g., emotional neglect) may ultimately experience poor outcomes, while others appear relatively resilient. Overall, these and other studies (e.g., Bogdan, Williamson, & Hariri, 2012) are beginning to demonstrate that gene effects on the brain appear to be moderated by experience or vice versa, that experience effects on the brain are moderated by genotype, and that these interactions may affect risk for psychopathology through their effect on brain structure and function (Glaser, et al., 2014).

Challenges to Progress and Advances in the Emerging Field of IGxE

Like that of its parent strategies (i.e., imaging genetics and GxE interaction studies), the promise of an IGxE interaction model is not without ongoing challenges. First, the challenges noted in the imaging genetics section generally apply to IGxE interaction models. Second, incorporating the environment into models introduces additional complexity, including the need to consider carefully any definition of what an environment experience actually consists of (Manuck, 2013; Manuck & McCaffery, 2010). Typically, environment refers to both *experiential* phenomena (e.g., childhood abuse, divorce, or unemployment; Caspi et al., 2003) and *exposure* to

physical forces (e.g., toxins, natural disasters, and acts of violence; Franklin & Mansuy, 2010). However, experiential phenomena and physical forces differ crucially in the degree to which an affected individual contributes to the environmental trigger, little to none with physical forces but possibly a significant amount with experiential factors.

A wealth of research supports the notion that individuals vary in the degree to which they influence their own experiences. By extension, many "experiences" are likely to be correlated with genotype (Burt, 2008; Jaffee, 2011; O'Connor, Deater-Deckard, Fulker, Rutter, & Plomin, 1998). "Experiences" that are influenced by an individual may reflect GxE correlation (rGE): the influence of genetically driven variability in behavior as a precipitator of specific experiential triggers (e.g., heritable difficult temperament resulting in harsh parenting, which in turn are both correlated with later antisocial behavior). Unfortunately, some GxE interaction studies may therefore be biased by rGE in that many of the "experiences" are exposures that could, to some degree, be precipitated by the individual and contingent on their genotype (Jaffee, 2011). Indeed, some GxE interaction studies may actually be finding latent GxG interactions.

Recently, several GxE interaction studies have sought to address the issue of rGE through novel designs such as behavior genetic approaches (Reiss & Leve, 2007). For example, adoption studies are able to separate the extent to which parents and children share genotype (Leve et al., 2010) and twin designs isolate ways that experiences differentially affect individuals with the same genotype (Jaffee et al., 2005). Studies have also addressed rGE by capitalizing on natural disasters (Kilpatrick et al., 2007) or natural experiments (Costello, Compton, Keeler, & Angold, 2003). Within these designs, GxE interaction effects can be explored in a context where individual genotypes are unlikely to be related to the experiential phenomenon (e.g., a hurricane). Studies using experimental manipulation in humans (King & Liberzon, 2009) and nonhuman primates (Bennett et al., 2002), as well as randomized controlled trial treatment designs (Brody, Beach, Philibert, Chen, & Murry, 2009) are also able to exclude rGE through experimental manipulation of experience.

A third challenge facing IGxE interaction models is that they require substantially larger samples than those typically available to have acceptable levels of power. Moderated mediation models require starting sample sizes in the range of 500–1000 subjects to examine the expected small to moderate effects of each variable (Preacher et al., 2007). Moreover, this sample size estimate does not include issues, such as low minor allele frequencies or environmental exposure rates, which could necessitate even larger samples. Though samples of this size might sound untenable, several large scale neuroimaging studies have emerged by expertly piecing together smaller convenience samples (Fennema-Notestine et al., 2007; Yan, Craddock, Zuo, Zang, & Milham, 2013), scanning larger and larger samples of individuals (Butterworth, Cherbuin, Sachdev, & Anstey, 2011; Nikolova et al., 2013; Satterthwaite et al., 2012), using data sharing, open access data (Jack et al., 2008; Marcus et al., 2007; Potkin & Ford, 2009; Yan et al., 2013) and consortium models (Fjell et al., 2012; Paus, 2010; Schumann et al., 2010; Thyreau et al., 2012; Toga, Clark, Thompson, Shattuck, & Van Horn, 2012), and carrying out neuroimaging meta-analyses (Jahanshad et al., 2014), all of which could be leveraged going forward to test IGxE interaction models. However, single studies with standard protocols (or multisite projects with standardized protocols), representative sampling, and coverage of key genes are likely to be the most effective strategies in testing these questions (Falk et al., 2013; Paus, 2010; Schumann et al., 2010).

Fourth, although GxE interaction research alone has increased the depth and complexity of our understanding of factors influencing the etiology of psychopathology, it is certain that even greater complexity exists in the form of GxExE and GxGxE interactions (Kaufman et al., 2004; Rutter & Dodge, 2011; Wenten et al., 2009; Cicchetti, Rogosh, & Oshri, 2011) and that these interactions will have a bearing on the questions that are addressed within IGxE models. For example, in an interesting GxExE study, the 5-HTTLPR genotype– x maltreatment interaction that predicted depressive symptoms in the original study by Caspi and colleagues (2003) was found to be *further* moderated by social support. Specifically, only short homozygotes carries for 5-HTTLPR genotype with both a history of childhood maltreatment *and* low social support showed increased depressive symptoms (Kaufman et al., 2004). This finding emphasizes the complex and multifaceted nature of the relationship between genes, experiences, and behavior, in which some experiences exacerbate risk (maltreatment), while others appear to be protective (high social support). In relation to a broader neurogenetics framework, this finding is also interesting when specifically considered alongside another recent study that found that the well-replicated positive correlation between amygdala reactivity to threat and trait anxiety was moderated by level of social support (Hyde, Gorka, et al., 2011), further emphasizing the complexity inherent in understanding gene–behavior links.

Fifth, it is important to understand that development plays a large role in the unfolding of gene–environment–

brain–behavior relationships. Few GxE interaction studies have examined whether or how findings vary by age or developmental stage (i.e., "Gene x Environment x Development" [GxExD] studies: Hyde, 2015; Vrieze, Iacono, & McGue, 2012). As with GxE studies, it is likely that development has important implications for findings from IGxE models. For example, many studied genetic variants (e.g., MAOA, 5-HTTLPR) appear to have their functional effect in utero or very early in development (Fowler et al., 2007; Jedema et al., 2010; Sibille & Lewis, 2006). In addition, environmental experiences differ in their impact depending on the developmental stage of the individual (e.g., types of stressors might differ for children and adults or there may exist particular sensitive periods for certain risks; Kendler & Myers, 2009; Sroufe & Rutter, 1984). Furthermore, epigenetic studies demonstrate that certain experiences might have a greater biological impact during "sensitive periods" of development (Meaney, 2010).

As emphasized above, IGxE findings may also vary by developmental stage, as experiences (e.g., parenting) will change forms, and their impact on biology and the impact of genotype may be affected by this progression of development (e.g., changes associated with puberty). Moreover, as the brain is changing across development, its relationship to genes and experience is likely to be moderated further (e.g., Yu et al., 2014). Thus, some IGxE findings may be specific to certain developmental periods but, without greater emphasis on development and using IGxE methods in children and adolescents, we are unable to test these hypotheses.

Sixth, as would be applicable to GxE interaction studies and imaging genetics studies, sampling is a major issue, that may be under-appreciated within this field, and especially within neuroscience. Most of the broad neuroimaging literature, which provides a foundation for both imaging genetics and IGxE models, is based on samples of convenience (e.g., college students in subject pools, community volunteers who respond to a flier). These kinds of samples are likely to vary across a number of important dimensions that could affect the consistency and replicablity of findings and distort the relationship between individual differences in brain and behavior (Chiao & Cheon, 2010; Henrich, Heine, & Norenzayan, 2010). Moreover, we know very little about whether or how brain–behavior or gene–brain links are moderated by culture, and even less about how IGxE links may vary based on ancestry (Chiao & Cheon, 2010). Thus, IGxE interaction studies that are thoughtful about sampling and *who* the study will generalize to are mostly likely to lead to "true" findings (for more details on this point see Falk et al., 2013).

Finally, just as GxE and imaging genetics studies have required researchers to bridge several areas and work in multidisciplinary teams, a neurogenetics framework and IGxE studies require even greater knowledge and collaboration. We hope that the conceptual models introduced through IGxE and neurogenetics will garner even greater appreciation for the work of colleagues in disparate fields (e.g., animal neurophysiology, biostatistics, epidemiology, experimental psychology, developmental psychopathology) and help to spur collaborations that will ultimately better specify the development of psychopathology.

Summary of Neurogenetics

In sum, neurogenetics is a discipline that incorporates a variety of approaches and aims to understand the impact of variability in genes on brain structure and function, and subsequent behavior. The core technique within neurogenetics is imaging genetics, which focuses on linking variability in functional genetic polymorphisms to differences in brain structure and function, particularly using MRI. However, neurogenetics also relies on nonhuman animal models to specify complex molecular signaling pathways involved in linking variability in genes to variability in neural signaling and is further complimented by multimodal and pharmacologic MRI studies that can more directly and experimentally probe neural chemistry in awake adults. More recently, models within a neurogenetics framework have also incorporated the influence of *experience* on molecular signaling pathways by using IGxE studies. Through this variety of techniques, neurogenetics is helping to specify the molecular pathways from gene to brain.

However, a major limitation of the field of neurogenetics to date has been its overwhelming focus on studying adult samples and a notable lack of attention being paid to development (though see Viding, Williamson, & Hariri, 2006). That noted, in the second part of this chapter, we turn to an emerging area of research examining youth internalizing disorders using neurogenetics (Swartz & Monk, in press). In particular, we focus on research evidence from studies that have used the different techniques outlined above to examine the development of internalizing disorders, and thus present a model of how neurogenetics can be applied to developmental psychopathology. We focus specifically on internalizing disorders in youth for two reasons. First, much of the foundational neurogenetics research in adults has focused on phenotypes most applicable to internalizing disorders, and thus reviewing similar results in youth can help highlight continuities and discontinuities. Second,

much of the neurogenetics research in youth has been focused on internalizing and thus this outcome provides more fertile ground for review.

DEVELOPMENTAL PSYCHOPATHOLOGY AND NEUROGENETICS

The field of *developmental neurogenetics* is still in its infancy (Hyde, 2015), but in the second part of this chapter, we outline research that highlights a need to more precisely examine the role of development in gene–brain–behavior associations. To begin, we examine how the concepts underpinning both neurogenetics and developmental psychopathology can be integrated within one framework. We outline key points advanced by developmental psychopathology, including its focus on designing ways to conceptualize and measure "disordered" phenotypes, the specification of mechanisms that link risk to outcomes, the importance of conditional relationships, and the concepts of equifinality and multifinality. We then discuss how neurogenetics research can benefit from incorporating these concepts from developmental psychopathology. Having laid out principles of *developmental neurogenetics,* as conceptualized as an integration of neurogenetics and developmental psychopathology (Hyde, 2015), we move into discussing the application of this approach to research that has examined youth internalizing disorders. We focus on brain regions of interest and the application of imaging genetics to internalizing disorders, discuss IGxE interaction studies to date, and outline specific genetic and biological mechanisms that will be the focus of future research.

Developmental Neurogenetics—An Integration of Developmental Psychopathology and Neurogenetics

Incorporating a developmental perspective within neurogenetics opens the field to a range of novel and interdisciplinary questions, the answers to which have great promise for yielding significant advances in our understanding of the development of psychopathology: how do genes interact with the environment to influence neural development? How does neural development and behavior transact with genes and the environment to alter gene expression and elicit environmental supports or risks? How can physiological mechanisms, such as epigenetic regulation, explain the transactional associations between genes, brain, and environment over time? Does the association between genes and neural or behavioral phenotypes change over development? How does neural development influence risk and resilience to the development of psychopathology? Can patterns of neural development predict the onset or course of psychopathology? Can the use of neural development (in contrast to neural activation in adulthood) as a mediator of GxE interaction effects lead to novel insights on the etiology of disorder? How can this knowledge be translated to inform preventive and treatment efforts? In the following sections, we highlight key principles within developmental psychopathology that will guide this research in the future (the points presented here are selected from a more thorough discussion of this topic in Hyde, 2015).

Phenotype—What and Who Are We Studying?

Developmental psychopathology has been at the forefront of designing ways to conceptualize and measure "disordered" phenotypes. Recent evidence suggests that psychopathology, at both a construct and measurement level, can be considered dimensional, rather than categorical, in nature (Krueger & Markon, 2011; Plomin, Haworth, & Davis, 2009). Further, various psychopathologies have high comorbidity and overlap with other psychopathologies (Krueger, 1999; Krueger & Markon, 2006) and diagnostic categories contain great heterogeneity in terms of symptoms, prognosis, and development (Clark, Watson, & Reynolds, 1995; Tsuang, Lyons, & Faraone, 1990).

Early pioneering work in children (Achenbach, 1966), demonstrated that many disorders could be mapped onto broadband meta-factors (i.e., internalizing and externalizing). Research in adults confirms these findings and highlights that much of the "problem of comorbidity" evolves from a meta-structure involving several broad domains (e.g., internalizing) each containing specific "disorders" as subfactors (e.g., anxiety, depression) that share general and specific risks (Krueger & Markon, 2006; Krueger, Markon, Patrick, Benning, & Kramer, 2007). Recent work even suggests that there may be a "p" meta-factor that indicates an overall latent risk for increased distress and greater liability to psychopathology across diagnoses (Caspi et al., 2013; Lahey et al., 2012).

Applying this meta-structure to neurogenetics is particularly important given that many neural and genetic risk factors seem to be rather broad in their effects. For example, in children and adults, amygdala reactivity has been linked to several different disorders, including anxiety (Fakra et al., 2009; Monk et al., 2008) and depression (Price & Drevets, 2010), as well as to externalizing disorders and psychopathy (Blair, 2010; Hyde, Shaw, & Hariri, 2013). Results have been similar for genetic variants, such

as the 5-HTTLPR, which has been associated with these same outcomes, although sometimes in opposite directions (Glenn, 2011; Karg et al., 2011; Sadeh et al., 2010; Sen, Burmeister, & Ghosh, 2004). When considered in the context of research examining the hierarchical nature of psychopathology, neural and genetic studies suggest that variability across many individual genes or brain structures predicts *multiple* disorders due to the shared etiological structure of disorders. Applying models of general (i.e., "p" factor, general internalizing factor) versus specific (i.e., depression, anxiety) factors as an outcome when undertaking neurogenetics studies may help identify which risk factors are general versus specific, or even *how* specific these risk factors are (see Figure 12.3).

More specifically, a general versus specific modeling approach may enable us to conceptualize genetic and neural variation as contributing to dimensions that may be shared or unique to various general psychopathologies, rather than as specific correlates or part of a single "etiology" for one disorder (Buckholtz & Meyer-Lindenberg, 2012). For example, in the case of the short allele of the 5-HTTLPR and high amygdala reactivity, these risk factors instead may contribute to *broad* risk for psychopathology, particularly internalizing liability. It may be that this risk is underpinned by a dimension of neuroticism, emotionality, or emotional dysregulation (Lahey, 2009). For example, having greater amygdala reactivity may make an individual more prone to being emotional, emotionally dysregulated,

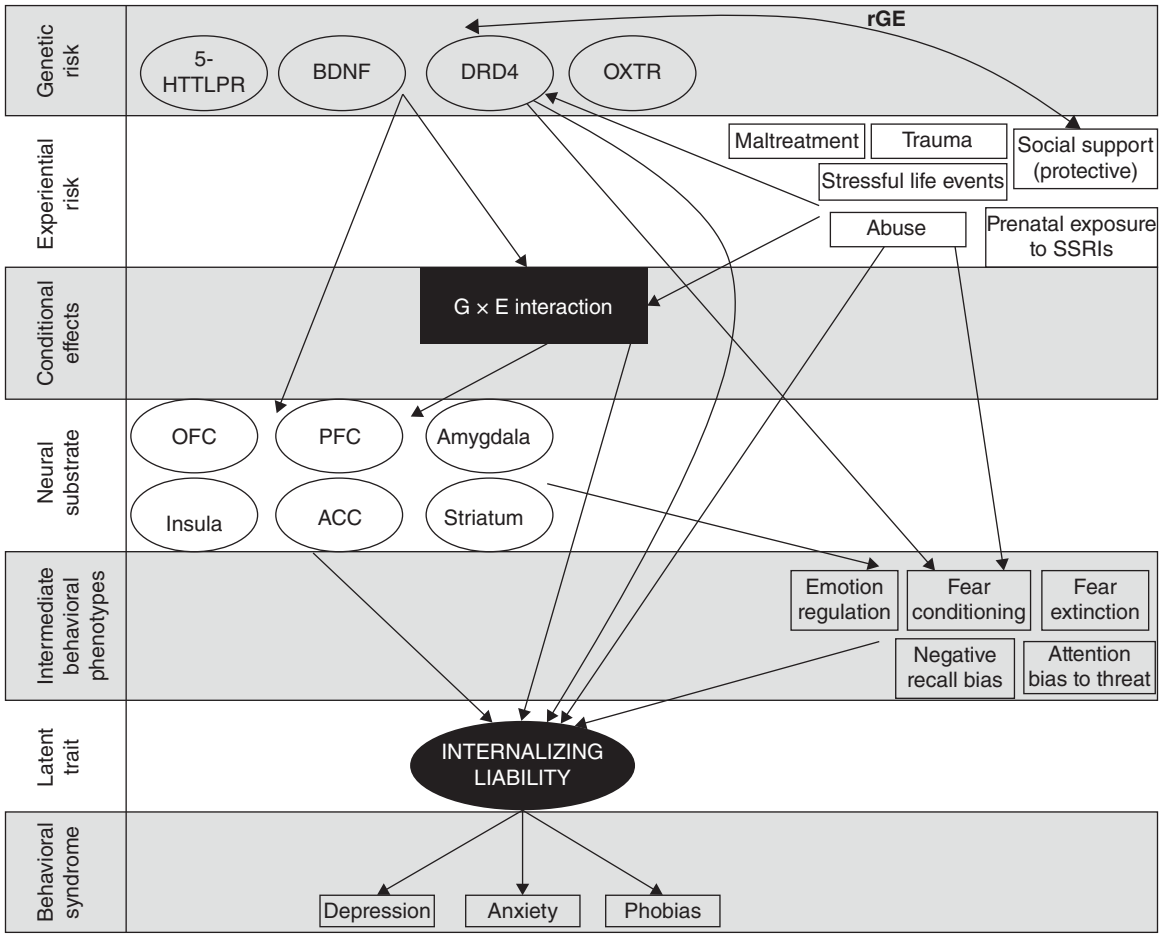


Figure 12.3 A hypothetical neurogenetics model of internalizing disorders in which levels of analysis are plotted on the y axis. Each level of analysis provides examples based on extant literature to date as outlined in this chapter but is not meant to be comprehensive. The arrows show direct and mediated pathways between genes and environment on both neural and behavioral outcomes, and between experiential and genetic risk (i.e., epigenetic effects). GxE interaction effects also have direct and indirect (via brain) effects on development of internalizing psychopathology. Not shown are reciprocal effects that theoretically operate in the opposite direction (e.g., the diagnosis of an internalizing disorder may affect the level of maltreatment or social support an individual receives). *Note:* OFC = orbitofrontal cortex; PFC = prefrontal cortex; ACC = anterior cingulate cortex.

or sensitive to emotional stimuli, which could then increase risk for anxiety and depression. Alternatively, this same risk of having high amygdala reactivity could be linked to some types of externalizing disorders that involve higher levels of emotion dysregulation (Pardini & Frick, 2013). In contrast, having very low amygdala reactivity and being low on emotionality could increase risk for other pathologies, such as psychopathy or callousness (Hyde, Byrd, Hariri, & Manuck, 2014; Hyde et al., 2013). In this case, basic neural functioning, when examined transdiagnostically and within a general-specific model framework, may explain why some disorders overlap and *how* they overlap (e.g., via greater amygdala reactivity and emotional reactivity) (Buckholtz & Meyer-Lindenberg, 2012).

At the same time, while a consideration of dimensional and hierarchical models provides a good fit to data, this approach ignores the usefulness of categories in clinical practice and the marked heterogeneity even within individual diagnoses (i.e., it focuses more on what disorders share at the broad level or which symptoms are important transdiagnostically, rather than addressing the heterogeneity within disorders). As such, while general-specific models can help us to uncover broad and general risk factors for psychopathology, we also need to identify why individuals have different symptom profiles within specific diagnoses. Further, identification of symptom profiles or other attributes of an individual may help to identify subgroups of individuals with a more similar development, course, and etiology of psychopathology, and even individuals that need different or tailored treatments. This idea of parsing down into smaller and more homogenous groups is akin to specifying a third level in the meta-structure of psychopathology.

Developmental psychopathology has long championed this kind of person-centered approach, which moves beyond variable-centered or dimensional analyses. This emphasis has important implications for neurogenetics because finding statistical relationships with a dimensional outcome can result in very different interpretations compared with those findings that arise from results with a small group of individuals who are particularly extreme on certain variables that are associated with etiology, development, or prognosis. Moreover, a person-centered analysis could help to uncover groups of youth that may look similar on one measure (i.e., diagnosis) but may differ in many important ways on other measures (e.g., symptom onset, duration, age of onset). In other words, those with a single diagnosis are not all the same, especially when we consider diagnoses within a developmental context. Neurogenetics research could therefore benefit from examining specific subgroups of more similar individuals together, which may produce more consistent and robust findings than studies that examine broad diagnostic classifications.

Complex Models

As highlighted throughout this chapter, neurogenetics tests a complex array of pathways from genes to proteins to neural circuits to brain function to behavior and each pathway is moderated by context. Developmental psychopathology has much to offer theoretically and empirically to neurogenetics studies in addressing these complex pathways. In particular, the application of multilevel (Cicchetti & Toth, 2009) and complex systems frameworks to understanding complex, reciprocal, and cascading pathways examining multiple levels of analysis has previously been written about extensively (Bronfenbrenner & Ceci, 1994; Sameroff, 1995, 2000, 2010). However, as ecological and complex systems theory is applied to a greater extent within neural and genetic studies, better models can be proposed and tested that contain multiple mechanistic (and interactive) pathways, reaching from molecules to cells to brain structures to traits to symptoms to outcomes, and with well-defined molecular mechanisms specifying both the genetic and environmental precursors to these processes (Beauchaine & McNulty, 2013; Buckholtz & Meyer-Lindenberg, 2008; Meaney, 2010; Roth & Sweatt, 2011).

A second example illustrating how theory and research in developmental psychopathology can help to address complex models is the recent advance in understanding conditional effects. As outlined in the first part of the chapter, an early and dominant model of psychopathology was a diathesis-stress model positing that some individuals had a latent propensity toward a certain psychopathology, which could be unmasked under certain conditions (e.g., high stress). Recent work in the field has brought greater nuance to this idea through the proposal and testing of models of differential susceptibility that posit that some individuals are more susceptible to their environment for better (vantage sensitivity) or worse (vulnerability factors or diathesis stress), or both (differential susceptibility) (Belsky & Pluess, 2009; Ellis & Boyce, 2011). These models focus on genes as markers for individuals who are most vulnerable to negative environments (Belsky & Pluess, 2009), those who may benefit the most from positive experiences (Pluess & Belsky, 2013), and those who are more sensitive to both good and bad environments (Belsky et al., 2009). Although empirical support for differential susceptibility and its range of effects has been limited to date (Cicchetti, Rogosch, & Thibodeau, 2012; Manuck, 2009), this type of modeling approach provides a useful framework for

neurogenetics research to consider interactions between genes, brain, and experience in the prediction of current and future behavior.

Developmental psychopathology also highlights significant complexity that exists in the form of further moderation of GxE interaction effects by genes or environment (Kaufman et al., 2004; Rutter & Dodge, 2011; Wenten et al., 2009; Cicchetti et al., 2011). Researchers have begun to address GxG interactions and the likely cumulative nature of different genetic variants by constructing cumulative genetic profiles (Nikolova et al., 2011; Purcell et al., 2009). This approach mirrors the major impact that cumulative risk models of environmental exposures made within developmental psychopathology (Sameroff, Seifer, Zax, & Barocas, 1987) showing that an accumulation of risk, be it genetic or environmental, is often more important than any single risk factor by itself in predicting poor outcomes (Appleyard, Egeland, Dulmen, & Sroufe, 2005; Sameroff et al., 1987). However, no studies to date have combined cumulative genetics models with cumulative experiential models.

Equifinality and Multifinality

Another important point of emphasis from developmental psychopathology relates to the concepts of equifinality and multifinality. Specifically, these concepts specify that children can arrive at the same point or diagnosis from many different risk factors (equifinality) and children with the same risk factors may end at very different points or diagnoses (multifinality) (Cicchetti & Rogosch, 1996). These concepts help to emphasize that many risk factors are not specific to one outcome, that there are likely multiple pathways and etiologies to any single disorder, and that the effects of risk on outcome are likely probabilistic. In an example of equifinality, multiple different risk factors can influence the development of the same behaviors. For example, a child with experiences of early abusive parenting versus a child with experiences of early warm parenting but later peer bullying, could both exhibit the same symptoms of depression in adolescence. Alternatively, as an example of multifinality, initial risk factors may lead to a wide array of different outcomes. For example, early maltreatment has been linked to both internalizing and externalizing outcomes, and as noted above, several similar neural and genetic profiles have been linked to a wide array of psychopathological outcomes.

Thus, it is important to highlight that the effects of genetic and neural variability are likely to be probabilistic, as highlighted by much of the research described so far. Understanding biological differences between groups high or low on certain psychopathologies only helps us understand *biases* toward certain behaviors. Any single experience, single gene, or functioning in a single brain area is unlikely to be deterministic or to be *the* major factor in the development of complex psychopathology. Rather, each risk, across all possible domains, is likely to bias an individual toward or away from risk via interaction with other factors. For example, studies of the serotonin system and the amygdala have shown that certain genes in the serotonin system (e.g., the short allele of 5-HTTLPR) and increased amygdala activity to threat are linked to anxiety and depression (Fakra et al., 2009; Hariri et al., 2006; Monk et al., 2008; Price & Drevets, 2010). However, many people with both increased amygdala activity to threat and with "risk" alleles in the serotonin system are neither depressed nor anxious (Hyde, Gorka, et al., 2011). Thus, these variables can simply be considered as one small part of a complex probabilistic chain. However, we must also consider that small risk factors or a "push" toward one outcome in a complex system can lead to larger changes (Kauffman, 1996; Sameroff, 1995). In the case of specific neural or genetic profiles, small pushes to a system (e.g., a slightly greater tendency toward or away from anxiety and attention to threat) in one direction may lead to developmental cascades toward or away from risk as the child and the environment begin to shape each other over time (Masten & Cicchetti, 2010). Thus, though the effects of many genetic and neural variables may be small and probabilistic, they may, in some youth and in some contexts, have larger effects due to their role in a developmental cascade over time.

The study of resilience in developmental psychopathology can also inform neurogenetics models (Masten, 2001; Rutter, 2006). Much neurogenetics research has focused on risk and maladaptive outcomes, but these same tools could be leveraged by positive psychology (Seligman & Csikszentmihalyi, 2000). Studies of resilience within a neurogenetics framework could help to identify neural and genetic profiles of individuals who do not go on to develop psychopathology, even under circumstances of great risk (e.g., child maltreatment, high stress) (Feder, Nestler, & Charney, 2009). Alternatively, these studies could help to identify factors that buffer the risk posed by "risky" genes or neural profiles.

Developmental Stage, Age, and the Unfolding of Processes Across Development

A major thrust when developmental psychopathology was first conceptualized was to add a clearer focus on the role of development to psychiatric conceptualizations of disorder.

Though neurogenetics is certainly poised to answer questions about development, much of the neurogenetics literature has focused on adults, with little work carried out among younger populations and very few studies testing the moderating role of development. However, there has been increased recognition across imaging and genetics research of the need for a developmental focus in neurogenetics (Viding et al., 2006). In particular, observations from a range of disciplines suggest that characterizing GxE interaction effects on neural and behavioral phenotypes requires the incorporation of a developmental perspective.

For example, Lenroot and Giedd (2011) have argued for the need to examine the interaction of age with GxE interaction effects, noting that twin studies in the area of quantitative genetics demonstrate that heritability estimates for brain development and psychopathology vary across different stages of development (see also Vrieze et al., 2012). Thus, the relationship between genes and phenotypes may *change* as a function of development due to factors, such as puberty, that trigger or change gene expression. Further, in the field of social genomics, Cole and colleagues (2011) provided a potential demonstration of *antagonist pleiotropy,* or the notion that the risk or protection afforded by a gene may be reversed by contextual factors such as developmental stage. Specifically, they demonstrated that a functional polymorphism in the promoter for the *IL6* gene associated with increased inflammation in older adults actually plays a protective role in adolescents, leading to decreased levels of inflammation in adolescents exposed to social stress. This study suggests that the effects of genes—and whether they can be considered "risky" or "protective"—depends on the developmental stage under investigation.

Also complicating the developmental picture is evidence suggesting that early influences can have latent effects that do not emerge until later stages of development, with several studies illustrating various considerations that researchers must make when considering development. For example, Ansorge and colleagues (2008) found that administering selective serotonin reuptake inhibitors (SSRIs) to mice during early postnatal development led to increased anxiety-related behavior that only manifested after the developmental period corresponding to puberty in mice. Moreover, this effect appeared to be limited to early developmental exposure to SSRIs, as administering SSRIs at a later stage of development had no significant impact on anxiety-related behavior. Thus this study emphasizes that some *exposures* will only affect these pathways when the exposure occurs during a sensitive period and that certain *outcomes* may only be observable after a particular developmental stage (e.g., Yu et al., 2014). In another example of developmentally sensitive effects, Petersen and colleagues (2012) found that the interaction between 5-HTTLPR genotype and stressful life events had the most robust effect on the development of anxiety/depressive symptoms measured in later adolescence at 16–17 years versus early adolescence. Thus, in this study the GxE interaction appears specific to a certain developmental stage for the *outcome*.

Finally, in a study that hypothesized specific biological mechanisms that could underlie these types of developmental stage-dependent effects, Casey and colleagues (2009) examined the effect of a valine-to-methionine substitution at codon 66 (Val66Met) in the brain derived neurotrophic factor (*BDNF*) gene. The Met allele of the Val66Met *BDNF* polymorphism is associated with decreased secretion of BDNF, a neurotrophic factor hypothesized to affect plasticity and changes in brain regions associated with learning, including both the hippocampus and amygdala. Given its association with learning and plasticity, the *BDNF* polymorphism may be linked to internalizing problems such as anxiety disorders, which are characterized by abnormal fear learning (e.g., overgeneralization of fear conditioning and reduced extinction of fear learning). In a demonstration of an age-dependent association between genotype and behavioral phenotype, Casey and colleagues observed that children with a Met allele of the Val66Met *BDNF* polymorphism exhibited differences in response latencies in a fear conditioning task relative to Val homozygotes, suggesting greater acquisition of fear learning in the Met group. In contrast, these effects appeared to be reduced in adolescents in the sample. The influence of the *BDNF* polymorphism on neural and behavioral phenotypes has been hypothesized to differ by developmental stage because expressed BDNF levels in the brain change over development, showing increases from childhood and peaking in young adulthood (Casey et al., 2009). Because expressed BDNF levels increase during adolescence, the association between the Val66Met *BDNF* polymorphism and fear-related learning may be altered during this developmental stage relative to childhood.

Taken together, the evidence from across these studies suggests that the association between GxE influences and neural function depends on both the developmental period in which an individual is exposed to a developmental influence (biological or environmental) and the stage of development in which the outcome is tested. Indeed, the influence of certain genes on neural function may be due to the emergent effects of these genes on brain development occurring specifically during the adolescent period. Given the potential latent effects of early developmental influences

on psychological outcomes, as well as the possibility that certain genetic polymorphisms may act differentially as risk or protective factors at different stages of development, it is critical as we move forward to consider the developmental stage of participants in neurogenetics studies both in terms of when *experiences* are measured (and when they occurred) and when *outcomes* are measured.

Summary

In sum, there appears to be promise in the integration of neurogenetics and developmental psychopathology (Hyde, 2015). First, the integration of these approaches points to a need to consider psychopathology, at the measurement and construct level, as both dimensional and overlapping in nature. Examining specific versus general correlates of genetic and neural variability may help to identify how these variables fit together and how they contribute to the development of psychopathology. Moreover, while evidence supports a dimensional and hierarchical approach, research is also needed that specifies these risk processes at a person-level by identifying groups of individuals that are more homogenous in development, symptoms, outcomes, or treatment response. Neural and genetic studies have already helped to support the notion that within some psychopathologies, there exist subgroups with unique or different correlates. However, neither broad nor person-centered approaches have yet to be applied to neurogenetics studies. Thus, further integration of these concepts into neurogenetics is needed to help uncover how neural and genetic processes might operate to predict broad and general outcomes, as well as specific subgroups of youth, within existing diagnoses. Moreover, by providing more accurate and broad or specific outcomes (with less error), we may help to increase the precision within neurogenetics studies.

Second, the emphasis in developmental psychopathology on adopting an interdisciplinary approach, particularly in its adaptation of ecological and complex systems models and its appreciation of complex interactions, can help inform changing views of the structure of psychopathology and maladaptive behaviors.

Third, studies of equifinality, multifinality, and resilience have provided important future directions for neurogenetics. In particular, now that studies have begun to establish more robust relationships between genetic and neural variables and psychopathology, a next major step will be to help define why these risks predict poor outcomes for only some people. In other words, what pathways contribute to "normal" functioning for many individuals with "risky" genetic or neural profiles? Why do some individuals that carry the 5-HTTLPR not have "elevated" amygdala reactivity? Why does elevated amygdala activity only predict heightened anxiety in the absence of social support? These questions have major treatment and prevention implications in identifying who is protected from the negative effects of risk and how they are protected. For example, if protective effects can be found in neural or environmental domains, then these variables can be targeted in interventions.

Fourth, as emphasized above, findings within neurogenetics research are likely to vary with developmental stage, as experiences will change forms and their impact on biology and the impact of genotype may be affected by the progression of development. Moreover, as the brain is changing across development, its relationship to gene and experience is likely to be moderated further. Thus, some findings may be specific to certain developmental periods. However, without greater emphasis on development and employing neurogenetics research in children and adolescents, we are unable to test these hypotheses (see next section on application of neurogenetics to the study of youth internalizing disorders).

NEUROGENETICS AND YOUTH INTERNALIZING DISORDERS

As outlined in the first part of this chapter, neurogenetics offers great potential for understanding the development of psychopathology by linking candidate genes to functioning of the neural circuitry associated with disorders, and specific environmental conditions under which such associations are likely to arise. Further, an integration of neurogenetics and developmental psychopathology provides a useful framework that guides a more nuanced understanding of the complex unfolding of interactions between gene, brain, environment, and behavior across the life course. An emerging body of literature has applied a neurogenetics framework to understanding the development of internalizing disorders in youth. We outline findings from studies that have investigated internalizing disorders among samples of both adults and youth, with research into adult internalizing disorders typically preceding or guiding studies of younger populations. We have chosen to focus our examples for how neurogenetics research can be applied to internalizing disorders, as the vast majority of research to date has been carried out in this area. In a final section we examine the next steps for research in this field and exciting new possibilities that could be borne out through developmental neurogenetics.

Brain Regions of Interest

Among adult samples, many studies have examined structure, functioning, and connectivity of corticolimbic circuitry. This circuitry includes cortical regions, such as the prefrontal cortex, and subcortical limbic regions, such as the amygdala. A reliable finding is that both major depressive disorder and anxiety disorders (e.g., social phobia and generalized anxiety disorder) are associated with altered functioning of corticolimbic circuitry (Price & Drevets, 2010). For example, one of the most consistent findings in the clinical neuroscience of internalizing disorders is heightened amygdala reactivity to threatening or negative stimuli in patients with anxiety or depressive disorders (Etkin & Wager, 2007; Groenewold, Opmeer, de Jonge, Aleman, & Costafreda, 2013; Hattingh et al., 2012). Greater amygdala activation to threatening stimuli is also associated with increased severity of anxiety symptoms (Phan, Fitzgerald, Nathan, & Tancer, 2006). The heightened amygdala reactivity seen in adults with these disorders is thought to arise from decreased regulation by prefrontal cortical regions, including the ventral and dorsal prefrontal cortex and the rostral anterior cingulate cortex. This notion is supported by evidence for decreased functional connectivity between the amygdala and prefrontal cortex in individuals with internalizing disorders (Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010; Hahn et al., 2011; Lu et al., 2012; Prater, Hosanagar, Klumpp, Angstadt, & Phan, 2013).

Studies using diffusion tensor imaging, which assesses the microstructural properties of white matter tracts, also suggest reduced fractional anisotropy (FA) in white matter tracts connecting the prefrontal cortex and amygdala, including the uncinate fasciculus (Phan et al., 2009; Tromp et al., 2012). This reduced FA may indicate reduced myelination of this white matter tract in adult patients. Indeed, decreased white matter connectivity predicts reduced prefrontal cortex-amygdala functional connectivity in adult patients with generalized anxiety disorder, suggesting that this may contribute to reduced prefrontal cortex regulation of amygdala activity (Tromp et al., 2012). In sum, internalizing disorders in adults have been associated with increased amygdala reactivity as well as disruptions in structural and functional connectivity between the amygdala and prefrontal regulatory regions.

The amygdala and prefrontal cortex have been associated with a number of intermediate behavioral phenotypes linked to internalizing disorders. For example, both animal models and human neuroimaging studies suggest a consistent role for the amygdala in fear acquisition and conditioning, whereas the ventromedial prefrontal cortex is associated with extinction of fear learning via inhibition of the amygdala (Milad & Quirk, 2012). Thus, heightened amygdala activation and decreased connectivity between the ventromedial prefrontal cortex and amygdala could lead to increased fear conditioning and difficulty with extinguishing acquired fears. These intermediate behavioral phenotypes have been linked to a number of anxiety disorders (Lissek et al., 2013; Lissek et al., 2005). Likewise, given its role in detecting emotionally relevant stimuli in the environment, the amygdala has been linked to processes such as biasing attention toward threat (Pessoa & Ungerleider, 2004), and thus may play a role in the well-replicated finding of attention bias to threat in anxiety disorders (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van, 2007). Moreover, given the role of cortical regions in cognitive control and emotion regulation (Ochsner & Gross, 2005), reduced functional connectivity between the prefrontal cortex and amygdala may be associated with the emotion regulation abnormalities characteristic of internalizing disorders (Foland-Ross & Gotlib, 2012). Thus, the neural abnormalities identified in adult internalizing disorder patients are consistent with the intermediate behavioral phenotypes thought to contribute to the development and maintenance of these disorders.

Neuroimaging research with children and adolescents with internalizing disorders has broadly mirrored the work carried out among adults, and also provides evidence of corticolimbic dysfunction, although studies with samples of children and adolescents are still relatively uncommon. For example, paralleling findings for anxiety in adults, heightened amygdala activation has been observed in both children and adolescents with anxiety disorders (e.g., Monk et al., 2008). Interestingly, this finding appears to be highly dependent on the timing and context of the threatening stimuli. Specifically, brief presentation of threatening faces, tasks that require participants to rate their own subjective fear, or evaluation of threatening stimuli elicit heightened amygdala activation in youth with anxiety disorders relative to controls (Beesdo et al., 2009; Guyer et al., 2008; McClure et al., 2007; Monk et al., 2008; Swartz, Phan, Angstadt, Fitzgerald, & Monk, 2014). In contrast, presentation of threatening faces for relatively longer periods of time or rating of nonemotional aspects of faces (e.g., nose length) do not appear to elicit heightened amygdala reactivity in anxious groups (Beesdo et al., 2009; McClure et al., 2007; Monk et al., 2006; Swartz, Phan, et al., 2014).

In addition to explicit processing of threatening stimuli, implicit emotion processing tasks, including rating the gender of emotional faces, are also associated with

amygdala hyperactivity among children and adolescents with anxiety disorders (Blair et al., 2011; Thomas et al., 2001). As with adults, there is evidence of altered functional connectivity between the prefrontal cortex and amygdala among anxious youth, including decreased ventrolateral prefrontal cortex-amygdala connectivity when threatening faces are briefly presented (Monk et al., 2008) and increased ventrolateral prefrontal cortex-amygdala connectivity when rating the desirability of disliked and potentially threatening peers (Guyer et al., 2008).

Among adolescents with major depression, heightened amygdala activation has also been observed (Beesdo et al., 2009; Yang et al., 2010). In addition, depression among youth is associated with altered functional connectivity, including decreased medial prefrontal cortex-amygdala connectivity (Perlman et al., 2012) and increased subgenual anterior cingulate cortex-amygdala connectivity (Connolly et al., 2013; Perlman et al., 2012). Finally, decreased FA in the uncinate fasciculus has been observed in adolescents with major depression (Cullen et al., 2010), suggesting that, similar to adults, heightened amygdala reactivity may be associated with reduced regulation by the prefrontal cortex. Due to the central role that corticolimbic circuitry appears to play in the development of internalizing disorders, the majority of neurogenetics research in this area has thus aimed to characterize genetic influences on the structure and function of these brain regions.

Imaging Genetics and Internalizing Disorders

The genes involved in regulating serotonin signaling have been a focus of many imaging genetics studies of internalizing disorders in adults due to serotonin's role in modulating corticolimbic function and the therapeutic effects of pharmacological interventions, including selective serotonin reuptake inhibitors for treating anxiety or depressive disorders (Fisher & Hariri, 2013). In particular, the 5-HTTLPR has received a great deal of research attention. In earlier studies, genetic variation in the 5-HTTLPR was classified dichotomously as either the short (S) allele (decreasing expression of the serotonin transporter) or the long (L) allele. Subsequently, researchers identified an A to G SNP in the L allele, with the L_G genotype acting similarly to the S genotype in conferring reduced transcription of the serotonin transporter; whereas the L_A genotype is associated with increased expression (Hu et al., 2006). Thus, because some of the studies described include the S, L_G, and L_A allele classification, we use the terms low-expressing allele to refer to the S or L_G alleles, and high-expressing allele to refer to the L_A allele, rather than the traditional short vs. long dichotomy in describing this area in more detail.

As noted previously, the first imaging genetics studies examining the 5-HTTLPR were performed in adults and demonstrated that the low-expressing allele is associated with increased amygdala activation during the processing of threatening stimuli (Hariri et al., 2002), an effect confirmed through meta-analysis (Munafo, Brown, & Hariri, 2008). Additional research demonstrated that the low-expressing allele predicts altered connectivity between prefrontal regulatory regions and the amygdala (Pezawas et al., 2005) suggesting that the low-expressing allele may lead to decreased prefrontal regulation, which in turn results in heightened amygdala response. Using diffusion tensor imaging (DTI), the low-expressing allele of the 5-HTTLPR has also been associated with decreased FA in the uncinate fasciculus (Pacheco et al., 2009), suggesting that structural connectivity between the amygdala and prefrontal cortex may play a role in the effects of the low-expressing 5-HTTLPR allele. Thus imaging genetics findings in adults indicate that the low-expressing allele of the 5-HTTLPR predicts the same alterations in corticolimbic structure and function as seen in adult patients with anxiety or depressive disorders (though as noted previously this mediated pathway has not been directly tested).

In typically developing children and adolescents, the low-expressing allele of the 5-HTTLPR is also associated with increased amygdala activation to threatening or negative stimuli (Battaglia et al., 2012; Furman, Hamilton, Joormann, & Gotlib, 2011; Lau et al., 2009). For example, Battaglia and colleagues (2012) found that in adolescents, the low-expressing allele of the 5-HTTLPR was associated with increased amygdala activation to angry faces, which was associated with a greater number of social anxiety symptoms. In another example, Furman et al. (2011) found that among typically developing adolescent girls aged 10–15 years old, those with the low-expressing allele of the 5-HTTLPR displayed a faster time to peak in amygdala BOLD signal when focusing on a sad mood state relative to carriers of the high-expressing allele.

In addition to the amygdala, regions associated with other aspects of emotion processing have been linked to 5-HTTLPR genotype in samples of youth. For example, adolescents with the low-expressing allele of 5-HTTLPR demonstrated greater attention bias to subliminally presented fearful faces during a probe detection task, as well as increased activation in parietal regions associated with attention allocation (Thomason et al., 2010). In a separate study of 8-year-old children, the low-expressing allele of the 5-HTTLPR was related to increased activation in

the dorsal striatum and anterior cingulate cortex when viewing sad movie excerpts relative to carriers of the high-expressing allele (Fortier et al., 2010).

Taken together, studies conducted among typically developing children and adolescents indicate similar gene–brain relationships to those seen in adults. Specifically, the low-expressing allele of the 5-HTTLPR appears to be associated with heightened reactivity to threatening or emotional stimuli. In many of these studies (e.g., Battaglia et al., 2012; Thomason et al., 2010), heightened neural reactivity is associated with increased anxiety symptoms or behavioral phenotypes, such as attention bias to threat, that are reliably associated with clinical anxiety (Bar-Haim et al., 2007). In sum, findings from imaging genetics studies to date have described a pathway through which a common genetic variant is associated with patterns of neural functioning that are in turn associated with anxiety-related symptoms or behaviors. In this case, findings in youth have paralleled findings in adults, indicating that these pathways may develop early in life.

However, although findings appear to replicate across different ages, studies have typically paid little attention to development and its potential moderating effect on the magnitude of effects. This point is particularly interesting when considering that the brain areas implicated in imaging genetics studies (i.e., cotricolimbic circuitry) show protracted structural development into adulthood (Toga, Thompson, & Sowell, 2006). Indeed, several studies have now demonstrated that activation of these brain areas and their structural and functional connectivity varies across development (Casey, Tottenham, Liston, & Durston, 2005; Gee et al., 2013; Swartz, Carrasco, Wiggins, Thomason, & Monk, 2014). For example, a recent study demonstrated that, in response to emotional faces, amygdala-medial prefrontal cortex connectivity switched from positive to negative during the transition from childhood to adolescence and that this change in connectivity was paralleled by a linear decline in overall amygdala reactivity (Gee et al., 2013). Interestingly, Gee and colleagues hypothesized and found some support for the notion that this developmental change in connectivity could underlie normative decreases in anxiety from early childhood to early adolescence. Taken together, the findings from recent studies highlight the importance of considering development when replicating neurogenetics findings among youth and emphasize that there are really two separate, though related, questions to ask when adopting a neurogenetics framework, (1) do findings in adults show a similar pattern in children or adolescents, and (2) does age or developmental stage moderate findings?

Though much of the literature has focused on the first question, the second question may actually yield more useful findings in attempting to understand the development of internalizing disorders, and fits well within a neurogenetics approach to understanding psychopathology. For example, a recent study by Wiggins and colleagues (2012) demonstrated that carriers of the low-expressing allele of the 5-HTTLPR evidenced a cross sectional increase in amygdala activation with age from 9–19 years old whereas this developmental increase was not seen in high-expressing allele carriers. Moreover, in low-expressing allele carriers only, there was a negative association between functional amygdala-ventral medial prefrontal cortex connectivity and age. The findings from this study suggest that age may moderate the links between genotype and brain function, with the adult-like pattern of increased amygdala activation and decreased prefrontal-cortex amygdala connectivity in low-expressing allele carriers only being evident in older adolescents.

In another important example of developmental moderation of gene–brain–behavior relationships, Lau et al. (2009) compared the link between 5-HTTLPR genotype and amygdala function in children and adolescents with anxiety disorders relative to typically developing youth. In typically developing youth, Lau and colleagues found an expected association between the low-expressing allele of 5-HTTLPR and heightened amygdala activation to threatening faces relative to high-expressing allele carriers. However, contrary to the adult literature, children and adolescents with anxiety disorders with the *high-expressing* allele of 5-HTTLPR also had *heightened* amygdala activation compared with anxiety disorder patients with the *low-expressing* allele. Given the small sample size and the small number of participants in the high-expressing allele group, these results need replication in a larger sample. However, if replicated, the findings could indicate that genes have different associations with brain function in individuals who develop clinical disorders at a relatively young age compared with healthy peers or compared with normative samples of adults.

IGxE Interaction Studies in Youth

As described in the first part of this chapter, GxE interaction studies indicate that the influence of genes on psychological functioning depends on environmental context. Several recent studies have tested components of an IGxE interaction model and demonstrate that GxE interactions have implications for brain functioning. For example, research in adults has demonstrated that life stress

interacts with the low-expressing allele of 5-HTTLPR to predict increased amygdala activation to subliminally presented fearful faces (Williams et al., 2009), as well as baseline amygdala activation (Canli et al., 2006). In contrast, in a sample of 18-year-olds, Walsh and colleagues (2012) found that the low-expressing allele of 5-HTTLPR predicted increased amygdala activation to emotional faces but did not find support for an IGxE model, as childhood adversity did not interact with genotype or directly predict amygdala activity. At the same time, Walsh and colleagues did find that recent negative life events at age 17 had an additive effect in predicting heightened amygdala activation, indicating that both genetic variability and variability in experience influenced amygdala reactivity, though these effects did not appear to result in nonadditive interactions. The lack of observed effects of childhood adversity on amygdala function could be in part related to a broad definition of adversity in this study (e.g., childhood abuse, family dysfunction, occasional violence, lack of warmth, or lack of communication between family members), highlighting the need for close attention to be paid to both the operationalization and measurement of environmental stress.

Aside from difficulties relating to assessment of the environment, however, these preliminary three studies exemplify the utility of examining IGxE interactions within a neurogenetics framework, particularly in demonstrating how an IGxE framework might translate across developmental stages. Given the importance of identifying protective factors for youth psychopathology development, future research is needed to examine whether positive environmental influences also interact with genotype to influence amygdala activation in children and adolescents. For example, as described previously, Kaufman et al. (2004) found that social support moderated the relation between 5-HTTLPR genotype and child maltreatment. In contrast to maltreated children with the low-expressing allele of 5-HTTLPR who experienced positive social support, those who lacked positive social support showed high levels of depressive symptoms. Thus, future studies could test whether social support moderates the association between 5-HTTLPR genotype and amygdala reactivity, or the association between amygdala reactivity and report of depressive symptoms. In applying neurogenetics within an IGxE model in this way, future studies could more precisely examine potentially protective factors that buffer negative GxE interaction effects on the developing brain.

Beyond the Walsh et al. (2012) study that examined 18-year-olds, two other papers from the Teen Alcohol Outcomes Study (TAOS), a study of teens at genetic risk for psychopathology, have examined IGxE components in youth. Bogdan and colleagues built on an earlier study, previously described in this chapter, which examined a gene affecting HPA axis function (*FKBP5*) that moderated the link between emotional neglect and threat-related amygdala reactivity in this sample of teens (White et al., 2012). In the subsequent study, Bogdan et al. (Bogdan, Williamson, et al., 2012) examined a different gene related to another component of HPA axis function (the mineralocorticoid receptor) in this relatively large sample of children and adolescents aged 11–15 years old ($N = 279$). Results suggested that genetic variation in the mineralocorticoid receptor influenced threat-related amygdala reactivity. However, similar to the findings of White and colleagues (2012), prior childhood emotional neglect was also related to amygdala reactivity and also moderated the effect of this HPA-axis related genotype on neural reactivity (Bogdan, Williamson, et al., 2012). This study is thus a useful example of a how parts of an IGxE model could be tested among youth (see also Glaser et al., 2014). Moreover, these two studies demonstrate the thoughtful application of IGxE: the authors examined genes related to an important system (the HPA axis) associated with an experiential variable (early maltreatment) and brain region (threat-related amygdala reactivity), which has been implicated in many outcomes associated with early maltreatment and HPA axis dysregulation (e.g., depression, PTSD, anxiety disorders).

Overall the preliminary results from studies testing components of an IGxE model provide potential mechanisms that may help us identify the developmental pathways through which gene–environment interactions affect brain function. Hopefully in the future these interactions can, in turn, be linked to behavior and risk for psychopathology (i.e., Glaser et al., 2014). Specific findings relating to additive or interactive effects of stressful life events and maltreatment with genotype on amygdala activation suggest that increased amygdala reactivity to negative stimuli may mediate GxE interaction effects on the development of internalizing disorders.

Beyond 5-HTTLPR: Other Imaging Genetics Findings in Youth Applicable to Internalizing Disorders

The functional polymorphism in 5-HTTLPR has been one of the most extensively investigated candidate genes in imaging genetics studies. However, recent imaging studies in children and adolescents have also begun to examine associations between a number of other candidate genes

and corticolimbic functioning relevant to internalizing outcomes. For example, Lau et al. (2010) examined the Val66Met polymorphism of the *BDNF* gene in relation to amygdala response in adolescents with an anxiety or depressive disorder relative to typically developing controls. They found that the Met allele, which is associated with decreased neurotrophic function, predicted increased amygdala activation while rating subjective fear among adolescents with an anxiety or depressive disorder but not in controls.

Outside of genes affecting amygdala reactivity, another candidate gene that has been examined in relation to internalizing problems is a polymorphism of the dopamine receptor D4 subtype (*DRD4*) and its functional variant (7R+), which is associated with decreased dopamine signaling. Perez-Edgar and colleagues (2014) found that *DRD4* genotype and caudate activation moderated the link between early behavioral inhibition and adolescent anxiety. In this study behaviorally inhibited participants with the 7R+ genotype and stronger caudate activation to reward showed increased levels of anxiety in adolescence. Thus, genes and associated neural function may moderate associations between early childhood temperament and adolescent internalizing outcomes. These findings help us further identify a subset of individuals most at risk for internalizing problems via their early risk temperament and genetic or neural risk profile. Importantly, this study also identifies neural and genetic factors that may help to elucidate why not all children with "risky" early temperaments (i.e., behavioral inhibition) go on to demonstrate clinically significant levels of an internalizing disorder.

A third relevant candidate gene is a single nucleotide polymorphism in the oxytocin receptor gene (*OXTR*, rs2254298; G>A). Among adolescent girls, Furman, Chen, and Gotlib (2011) found that homozygosity for the G allele was associated with decreased amygdala volume. Furman et al. posited that this relationship may be due to decreased regulation of corticosteroids by oxytocin, which may then be associated with atrophy of the amygdala. Given that the G allele is found in higher frequencies in patients with depression, this study provides another example of a link between a gene and a neural structure (the amygdala) frequently implicated in depression, helping to delineate the developmental pathways through which risk genes may have their effects.

Although each of these candidate genes outlined above may explain a relatively small amount of variance in brain structure and function, cumulatively and in interaction with environmental stressors, they are likely to have greater predictive power in helping to determine which individuals are at risk for disrupted development of corticolimbic circuitry. For example, individuals with multiple genotypes associated with altered amygdala structure and function (the low-expressing allele of 5-HTTLPR, the Met allele of the Val66Met *BDNF* polymorphism, and homozygous G alleles in the rs2254298 polymorphism of the oxytocin receptor gene) may be at particularly high risk for the development of anxiety or depressive disorders, whereas individuals with only one of these risk alleles may be relatively buffered from this effect. Future research examining multiple genes and their associations with multiple regions (prefrontal cortex, amygdala, striatum) will be necessary to examine potential additive and interactive effects (e.g., Nikolova et al., 2011).

Finally, whereas studies described in this chapter have almost exclusively relied on a candidate gene approach to select functional polymorphisms with known effects on a neurotransmitter system or protein of interest, an alternative approach uses GWAS to search for genes that are associated with the functioning of a candidate neural region. Using this approach, a novel candidate polymorphism in the *DOK5* gene, which is associated with neuronal development, was found to be associated with amygdala activation in adolescents with bipolar disorder and among typically developing controls (Liu et al., 2010). Studies using GWAS and other related exploratory techniques could be used to identify other potential candidate genes that may be linked to corticolimbic function and the development of internalizing disorders. The downside to GWAS studies is that they require very large sample sizes, which are difficult and costly to collect when examining neuroimaging phenotypes.

Biological Mechanisms Underlying Neurogenetics and GxE Interaction Findings

As this chapter has highlighted, there is now evidence that the low-expressing allele of 5-HTTLPR interacts with childhood maltreatment or stressful life events to predict the development of depression in adolescents and adults (Caspi et al., 2003; Kumsta et al., 2010; Petersen et al., 2012; although see Laucht et al. (2009) for evidence of the high-expressing allele predicting greater internalizing problems in adolescents). As we have noted in previous descriptions of neurogenetics and IGxE, emerging research suggests that a major molecular pathway through which GxE interactions affect behavior is via brain chemistry (Hyde, Bogdan, et al., 2011). In particular, emerging research in epigenetics suggests a potential pathway through which environmental stress

interacts with 5-HTTLPR genotype to influence the development of internalizing disorders. For example, preliminary evidence suggests that DNA methylation of cytosine-phosphate-guanosine (CpG) sites in the promoter region of the 5-HTT gene may play a role in the previously observed GxE interactions in internalizing disorders (Beach, Brody, Gunter, et al., 2010; Kinnally et al., 2010; Kinnally et al., 2011; Philibert et al., 2007; Philibert et al., 2008). In particular, methylation of CpG islands in the promoter region of genes is thought to make the promoter region less accessible to transcription factors, decreasing the expression of the gene (for more extended reviews on this topic see Bagot & Meaney, 2010; Meaney, 2010; van IJzendoorn, Bakermans-Kranenburg, & Ebstein, 2011).

DNA methylation of the 5-HTT promoter region is one potential mechanism through which GxE interaction effects may occur. Research from the Iowa Adoption Studies has suggested that methylation of this region may be sensitive to environmental stressors, providing evidence that a history of child abuse is associated with increased methylation in the promoter region of the 5-HTT gene (Beach, Brody, Todorov, Gunter, & Philibert, 2010). Greater methylation at certain CpG sites in the serotonin transporter gene region has also been shown to be associated with decreased mRNA transcription, and a lifetime history of major depression (Philibert et al., 2008). Maltreatment thus appears to be associated with a molecular mechanism that decreases the transcription of the serotonin transporter, and there is a trend for this mechanism to be associated with a greater risk for having a lifetime history of depression.

Taken together, these studies provide preliminary evidence that early environmental stressors, such as child abuse, alter methylation levels of CpG sites in the serotonin transporter gene region. This altered methylation appears to result in decreased expression of the serotonin transporter, which could potentially affect corticolimbic development and function. Importantly from a neurogenetics perspective, these mechanisms may differ further by genotype. For example, in nonhuman primate work, Kinnally and colleagues (2010) found that the low-expressing allele of the rh5-HTTLPR was associated with increased methylation of CpG sites on the 5-HTT gene in macaques, which in turn was associated with decreased levels of serotonin transporter mRNA. This pattern of associations suggests that, similar to findings in humans, higher methylation leads to reduced serotonin transporter expression in nonhuman primates. Additionally, increased methylation was found to interact with early life stress (separation from mother or unpredictable food availability) to predict higher scores on a behavioral measure of stress reactivity (Kinnally et al., 2010; Kinnally et al., 2011).

This emerging body of research, when considered alongside pioneering research on rodents by Meaney and colleagues (e.g., McGowan et al., 2009; Meaney, 2010; Weaver et al., 2004), demonstrates potential neurogenetics mechanisms by which well-replicated GxE interactions appear to affect brain neurochemistry and function, and subsequent risk for psychopathology. Taken together, research from humans, nonhuman primates, and rodents suggests a potential pathway for epigenetic influences on the development of psychopathology. In particular, increased methylation of the 5-HTT gene leads to reduced transcription of the serotonin transporter (Philibert et al., 2008) and heightened stress reactivity in nonhuman primates (Kinnally et al., 2011). Importantly from a neurogenetics perspective, early environmental stress (e.g., child abuse) leads to increased methylation of the serotonin transporter promoter region, and methylation levels may be moderated by 5-HTTLPR genotype (Beach, Brody, Todorov, et al., 2010; Kinnally et al., 2010), thus providing a mechanism for a GxE interaction in which individuals with the low-expressing allele who are exposed to stressful life events are at increased risk for developing psychopathology.

These preliminary findings signal an exciting potential direction for future research. However, incorporating epigenetics into IGxE designs will require careful consideration of a number of theoretical and methodological concerns. First, although we can assume that DNA sequences assessed in adulthood have not changed from early development, the same may not necessarily be true for epigenetic modifications, given that they are subject to environmental influence (Houston et al., 2013). Thus, as noted throughout, although much of the research to date has examined experiences that occur in childhood (e.g., maltreatment), studies carried out in humans have typically not examined outcomes in youth, nor focused on childhood trajectories of these behaviors. Thus longitudinal work, especially with a developmental psychopathology focus on mechanisms and trajectories of behaviors, is needed to chart these complex molecular pathways across development and complex trajectories of behavior in youth.

Second, a major limitation of research to date is that methylation levels have been assessed peripherally in blood cells, which may not match methylation levels in the brain, especially given that methylation levels vary by cell type (Houston et al., 2013). As yet, it appears there is no straightforward association between peripherally measured methylation levels and methylation in the brain.

In particular, it is possible that the association between peripheral and central nervous system methylation levels could vary depending on the gene of interest, or the brain structure in which methylation levels are examined (Ursini et al., 2011).

Third, the mechanisms linking increased methylation of the 5-HTT gene to increased risk for psychopathology need to be further delineated. Although studies have shown that methylation of the 5-HTT gene alters mRNA transcription of the serotonin transporter gene, the developmental consequences of methylation for brain structure and function remain to be examined. Given the aforementioned limitations, progress in this area will require research that spans methodologies to triangulate a developmental pathway, while accounting for the strengths and limitations of each method. Animal research will clearly be important in this regard because it is possible to assess methylation levels in brain regions of interest, and test whether these match methylation levels assessed peripherally. Animal models, such as those used by Kinally and colleagues, also allow for experimental manipulation of environmental stress and rearing conditions (Kinnally et al., 2010; Kinnally et al., 2011). However, animal models necessarily limit the conclusions that can be drawn regarding complex human phenomena, such as social anxiety or depression. Postmortem studies in humans have also examined methylation levels directly in brain regions of interest and linked these to potential environmental stressors (e.g., McGowan et al., 2009). There are, however, a number of limitations to these studies, including the inability to assess the consequences of observed methylation levels for brain function.

An example of a research design incorporating a number of these proposed research directions examined a common functional variant in the gene regulating Catechol-O-methyltransferase (COMT), an enzyme that breaks down dopamine in the prefrontal cortex (Ursini et al., 2011). The *COMT* gene has a common functional polymorphism: Val158Met. The Val allele is associated with greater *COMT* activity, lower levels of prefrontal dopamine, and reduced prefrontal efficiency. In contrast, the Met allele is associated with less *COMT* activity via decreased thermostability, greater prefrontal dopamine, and, subsequently, increased prefrontal efficiency. This polymorphism may be an important candidate for GxE interactions because methylation at the region investigated in this study is possible on the Val allele, where there is a CpG site, but not on the Met allele (Wiers, 2012). Because *COMT* breaks down dopamine in the prefrontal cortex, greater methylation of the Val allele leads to reduced expression of *COMT*, leading to greater availability of dopamine in the prefrontal cortex and greater prefrontal cortex efficiency.

Incorporating research from animal models into their study, Ursini and colleagues demonstrated that *COMT* methylation levels measured peripherally in blood cells were significantly associated with *COMT* methylation levels in the prefrontal cortex in rats, suggesting that peripherally measured methylation levels correspond to those in the brain region of interest. Then, incorporating a human IGxE design, Ursini and colleagues examined the association between peripherally-measured *COMT* methylation levels, environmental stress, and prefrontal cortex function during a working memory task performed during fMRI scanning. In this portion of the study, they found that environmental stress predicted reduced methylation in Val/Val participants. Moreover, reduced methylation was associated with reduced working memory performance. The imaging component provided evidence that greater life stress and reduced *COMT* methylation were associated with decreased prefrontal cortex efficiency during the working memory task. When applying these findings to what we know about the genetic and molecular pathways affected by *COMT* variation, this study could be interpreted to show that methylation actually biased individuals toward the sequence-based variation conferring greater flexibility and adaptability via increased phasic dopamine signaling; stress-induced changes in methylation may then alter this bias and confer risk for psychopathology.

This study demonstrates how research can be integrated across a number of domains to better elucidate the processes through which genes and the environment interact to influence neural function, thus exemplifying much of the promise of neurogenetics. Using an animal model, Ursini and colleagues provided preliminary evidence that peripherally measured *COMT* methylation levels matched those in the region of interest (the prefrontal cortex). In humans, they demonstrated that environmental stress reduces *COMT* methylation (measured peripherally) and that reduced methylation coupled with greater stress is associated with prefrontal cortex function. Because methylation can only occur on the Val allele, this research has begun to indicate a potential pathway through which a GxE interaction may occur where the presence or absence of environmental stress has a stronger influence on Val allele carriers. Overall, these types of studies signal an important need for greater cross-talk and collaboration across a range of disciplines, as it is clear that no one method alone will be sufficient for identifying the mechanisms through

which GxE interactions influence risk and resilience in the development of psychopathology.

Summary of Research Examining the Neurogenetics of Internalizing Disorders

To summarize, neurogenetics studies have begun to elucidate a number of developmental pathways through which GxE interaction effects may contribute to the development of internalizing disorders (Figure 12.3). Studies have highlighted a number of genetic polymorphisms that affect neural development and neurotransmission, including polymorphisms in genes that influence the reception or secretion of serotonin, BDNF, dopamine, and oxytocin. These candidate genes can in turn be linked to the development and function of neural regions that are affected by the proteins these genes code for. For instance, the 5-HTTLPR genotype, which modulates serotonin reception, can be plausibly linked to altered function of corticolimbic circuitry, including reduced functional connectivity between the prefrontal cortex and amygdala. Administration of oxytocin has been shown to dampen amygdala activity (Kirsch et al., 2005), creating a potential link between *OXTR* genotype and amygdala function. BDNF is expressed in the amygdala, and thus *BDNF* Val66Met genotype may contribute to individual differences in plasticity and fear learning in the amygdala (Casey et al., 2009). Amygdala function, in turn, is linked to processes, such as fear conditioning and attention bias to threat, whereas prefrontal cortex-amygdala connectivity is associated with fear extinction and emotion regulation, all intermediate behavioral phenotypes associated with internalizing disorders. These neural phenotypes serve as key bridges between genetic variation and behavioral and psychological outcomes.

Additionally, environmental stress has been shown to interact with genotype to predict amygdala function (Canli et al., 2006), and environmental support has been shown to moderate the association between amygdala function and anxiety (Hyde, Gorka, et al., 2011). Thus, the environment interacts with genotype and neural function at multiple levels in this model, further elucidating the developmental pathways through which genes and environment interact to influence the development of psychopathology. However, despite the progress made to date, a developmental perspective has still been largely lacking from such explorations. As discussed above and illustrated by the relatively small number of studies described examining neurogenetics of internalizing in youth, the majority of imaging genetics research has been conducted in adults, which may be problematic for informing our theories of the development of psychopathology. When studies are conducted in adults, they are either performed in healthy controls (who may be relatively resilient to the development of psychopathology) or in adult patients (whose neural function may reflect the consequence of disorder rather than the cause). When studies have been conducted in children or adolescents, they often include a wide cross-section of ages and have generally not considered moderation of GxE interaction effects by development or developmental pathways. Thus, an important direction for future research will be to incorporate a developmental perspective into neurogenetics designs, particularly as outlined above considering points from developmental psychopathology.

FUTURE DIRECTIONS

Ongoing Challenges and Future Directions for Neurogenetics Research of Internalizing Disorders

To return to the questions posed at the beginning of this section, research in the nascent field of developmental neurogenetics as applied to internalizing disorders has demonstrated the importance of incorporating a developmental perspective into research. Initial studies, including those of Wiggins et al. (2012) and Casey et al. (2009), provide preliminary evidence for "age–genotype" interaction effects on behavioral and neural phenotypes, indicating that the association between a gene and a phenotype of interest will vary depending on *when* the association is measured. There are several reasons that we could see such developmental effects, each of which has important implications for future directions in this field. Many brain structures, including the prefrontal cortex and amygdala, undergo protracted development throughout adolescence and thus the association between genes and brain function may depend on age. For instance, several recent studies have shown that there are cross sectional linear *declines* with age in amygdala reactivity to emotional faces (Gee et al., 2013; Swartz, Carrasco et al., 2014). Thus, if amygdala reactivity is normatively higher in children, the association between genotype and phenotype may differ in children relative to other earlier or later developmental stages. If brain functioning can be measured and examined as a trajectory over time, we may be able to examine how individuals differ from the decreasing trajectory that occurs during adolescence or if variations from this trajectory predict maladaptive outcomes. Moreover, some

effects may be latent, or may be only activated after certain developmental stages, such as when puberty triggers changes in gene expression.

Casey and colleagues (2009) have proposed another mechanism through which "age × –genotype" interactions may occur: because expressed levels of proteins can vary over development, the effect of a genetic variation that decreases or increases expression of that protein may vary by developmental stage because the absolute levels of protein available vary by age. Thus, a genotype that codes for an "ideal" amount of protein expression in one environment at one developmental stage may not be ideal at another developmental stage. Thus, although relatively few IGxE studies that include an additional assessment of moderation by age have been conducted to date, initial theoretical and empirical considerations suggest that there is great promise in taking a developmental perspective to neurogenetics approaches.

A related question has been to pinpoint the biological mechanisms through which genes and the environment interact to influence development. Again, we have barely scratched the surface when it comes to addressing this question, but preliminary studies incorporating epigenetics have suggested a plausible pathway through which environmental stress can "get under the skin" and influence the development and functioning of the brain. This area of research is subject to some novel methodological difficulties given the lack of straightforward associations between peripherally measured methylation levels and methylation levels in brain regions of interest. However, these limitations also highlight the promise of a neurogenetics approach. In particular, studies of epigenetics will benefit greatly from the incorporation of animal models, imaging genetics, GxE approaches, and PET and multimodal imaging approaches to better link experience to the complex molecular pathways leading from gene to brain to behavior.

Other questions to date remain largely unanswered. In particular, we know very little about whether patterns of neural development in childhood or adolescence could be used to predict onset of disorder. Moreover, we are yet to examine whether knowing about neural development patterns, could better identify genetic risk markers that could be used to relatively inexpensively and noninvasively assess an individual's risk for the development of psychopathology. Given the current gaps in the literature, we outline several directions for future research that could lead to significant progress in this area: First, the reliance on cross-sectional research to date indicates a need for the mapping of neural development using longitudinal approaches. There are several large-scale longitudinal studies that have done such mapping in structural brain development (e.g., Gogtay et al., 2004; Shaw et al., 2008), but to date, only a handful of longitudinal studies have examined changes in brain function (e.g., Koolschijn, Schel, de Rooij, Rombouts, & Crone, 2011; Ordaz, Foran, Velanova, & Luna, 2013; Pfeifer et al., 2013). Mapping the longitudinal development of brain function, including amygdala reactivity and prefrontal cortex-amygdala connectivity, is an important first step in forming hypotheses about how development might moderate GxE interaction effects on neural function, or how trajectories of neural development could mediate GxE interaction effects on disorder onset. Additionally, studies that compare trajectories of typical brain development to trajectories of brain development in individuals at risk for disorder (e.g., individuals with a high number of risk alleles of candidate genes or heightened familial risk due to a family history of disorder) can help to highlight early markers of the boundary between adaptive and maladaptive brain development. This step will be important in determining whether altered patterns of brain development could be used as early indicators of risk for disorder. These future directions point to a need both for large-scale, longitudinal functional neuroimaging studies and the training of neuroscientists in statistical approaches for the analysis of large data sets and longitudinal measures of behavior and brain functioning (e.g., Nagin & Tremblay, 2001).

Second, a notable limitation of many imaging genetics studies conducted to date is that sample sizes have been too small to investigate moderation of effects by age, sex, or race/ethnicity. In general, these studies have analyzed all participants together, and when race/ethnicity is considered, the approach is usually to select for White/Caucasian participants or reanalyze results to ensure they hold in the subsample of participants that are White/Caucasian. Lacking the power to test for moderation effects of gender is problematic given the noted gender differences in internalizing disorders (and differential effects of pubertal hormones on brain development), with females tending to have higher rates of depression and anxiety from adolescence onward. Moreover, lack of power to test for differences across race/ethnicity categories is also problematic, given that allelic frequencies vary by race/ethnicity and may even have different or opposite effects in different groups. For instance, there is some evidence to suggest that the association between the 5-HTTLPR and brain function in Asian populations is opposite to that found in Caucasian populations, with the high-expressing allele predicting greater anxiety and reduced prefrontal

cortex-amygdala connectivity (Long et al., 2013). Thus, failure to take into account potential differences could mask significant effects or lead to conclusions that are not accurate for all racial/ethnic groups.

Treatment Implications

There is significant promise in using neurogenetics and developmental psychopathology to inform translational efforts (Bogdan, Hyde, et al., 2012; Hyde, 2014). For example, the promise of examining subgrouping and person-centered approaches to studies of psychopathology, particularly those examining neural and genetic correlates, is that if these studies identify a group of youth or adults with a distinct etiology (e.g., those with early-onset depression), then we may be better able to tailor interventions to these individuals (e.g., Hyde, Waller, & Burt, 2014). Moreover, if empirical studies identify factors (i.e., early anxiety symptoms, certain genetic polymorphisms) that predict a different course of a disorder, then these factors may be important in identifying those at highest risk early for preventative interventions (e.g., Dishion et al., 2008; Hankin, 2012). Genetic variation and brain function may also help to identify treatment response and thus be considered before interventions are even started (Bryant et al., 2008; Ising et al., 2007; Uhr et al., 2008). Thus, as medicine moves toward both a more tailored and personalized model of care at the individual level, and a more preventative model of care at the population level, identifying factors that delineate subgroups of individuals that need different treatments or that can be targeted earlier with preventative interventions will be increasingly important and may help to increase the effectiveness of both prevention and intervention models (Simon & Perlis, 2010; Willard & Ginsburg, 2009).

More specifically, by deconstructing the molecular mechanisms underlying gene–brain–behavior pathways, especially in collaboration with animal models and in vitro research, neurogenetics has the potential to inform novel therapeutic targets. For example, combining evidence from studies linking *HTR1A* rs6295 with anxiety through amygdala reactivity with prior work demonstrating effects of the polymorphism on the capacity for negative feedback inhibition, suggests that targeting 5-HT_{1A} autoreceptors, perhaps as an adjuvant to SSRI treatment, may produce greater clinical effect. In fact, a recent study in a transgenic mouse model of 5-HT_{1A} autoreceptor function demonstrated that reducing autoreceptor levels prior to SSRI administration converted nonresponders into responders (Richardson-Jones et al., 2010). Thus, neurogenetics research with *HTR1A* rs6295 has identified a novel therapeutic target (i.e., antagonism of 5-HT_{1A} autoreceptors) and a marker that could be used to individually tailor treatment (i.e., for C allele homozygotes).

Another example of how neurogenetics can inform treatment and prevention comes from research on TREK1, a background potassium channel. Inspired by a *TREK1* knockout mouse study showing that deletion of *TREK1* results in a depression resistant phenotype (Heurteaux et al., 2006), human studies have linked variation in the human *TREK1* gene (*KCNK2*) to depression (Liou et al., 2009), blunted striatal response to reward (a neural profile associated with depression; Dillon et al., 2010), as well as antidepressant treatment response (Perlis et al., 2008). More recently these findings have led researchers to develop antidepressant medications that antagonize TREK1. One such compound designed to inhibit TREK1 has been associated with a positive antidepressant response, hippocampal neurogenesis, and increased serotonergic signaling in rodents (Mazella et al., 2010). Though the potential of this novel treatment mechanism has yet to be tested in humans, it does further document how neurogenetics research can spur therapeutic advancements by identifying novel targets. These examples highlight the great potential of neurogenetics to inform targets for novel interventions and ways to better personalize psychiatric treatment. However, they also underline the importance of additional research in this area that is translational in nature.

Next Steps in Research

Drawing across this chapter, there are a number of important future steps arising for the next generation of research. In particular, there are several key methodological steps and developments needed in the tools we use to examine gene–brain–behavior links. Further, there are theoretical advancements needed in the way that we model complex and conditional relationships, including the effects of development, further moderation of GxE interaction by additional genes or environments, and the importance of incorporating epigenetic mechanisms into models.

First, there is need for imaging genetics studies to draw out indirect pathways from gene to brain to behavior, instead of focusing solely on gene to brain associations. In particular, we need research that examines the brain as a mediator of gene–behavior pathways longitudinally. As outlined, within a neurogenetics framework, this research will benefit from leveraging what we know from complementary biological techniques that probe the chemistry of the brain, including pharmacologic challenge studies and

animal models. We also need ways to increase sample sizes within imaging genetics research, which will support the testing of increasingly complex pathways, particularly if this can be done with repeated neuroimaging data collection across development. Looking ahead, neurogenetics will benefit from scanning larger and larger samples of individuals at a population level, using data sharing, consortium models, and neuroimaging meta-analyses. The use of larger sample sizes will also enable closer examination of the potential moderation of GxE interaction effects by sex or race/ethnicity, which are too often overlooked in studies that focus on homogenous subgroups, such as White/Caucasian participants. Failure to take into account potential differences according to gender or race/ethnicity may mask significant effects or lead to conclusions that are not accurate for all subgroups. As a field, we also need to be open for further collaboration with colleagues who are developing novel statistical modeling methods, including advanced computational and statistical techniques, as well as data mining approaches such as machine learning and graph theory. Finally, as we develop increasingly complex models that incorporate the influence of the environment in IGxE interaction studies, we need to be more precise in our operationalization of the environment. In particular, by incorporating an emphasis highlighted in developmental psychopathology on adopting an interdisciplinary approach, neurogenetics will benefit from the use of ecological and complex systems models that will help to inform changing views of the structure of psychopathology and maladaptive behaviors. Finally, by adopting more genetically informed designs we can begin to highlight which environmental effects are independent of genotype.

Second, from both methodological and theoretical perspectives, we need to be better at modeling increasingly complex conditional relationships, including GxGxE and GxExE. In considering the potential for further moderation of GxE interaction effects by genes, we will be able to build on a significant body of literature examining cumulative genetic profiles (Nikolova et al., 2011; Purcell et al., 2009). Likewise, modeling the role of the environment is usefully informed by cumulative risk models of environmental exposures within developmental psychopathology, highlighting the fact that an accumulation of "risk" is often more important than any one 'single' risk factor. Combining cumulative genetics models with cumulative experiential models is a key next step in neurogenetics research.

Third, a further source of complexity is the role of developmental stage (D) in influencing GxE and IGxE interaction effects (i.e., GxExD). As outlined, we believe that neurogenetics has much to gain from incorporating key tenets of developmental psychopathology to create an integrated developmental neurogenetics framework (see Hyde, 2015). Through the integration of these approaches, future next steps in neurogenetics research will involve an examination of broader liability for psychopathology (i.e., within a general-specific modeling framework), deconstruction of diagnostic classifications within a person-centered framework to identify even greater homogeneity with subgroups of individuals, incorporation of the concepts of equifinality and multifinality within models, and a focus on the temperamental, personality, or endophenotypic building blocks of psychopathology that serve as more objective outcomes with which to assess gene–brain–behavior links. Importantly, models from developmental psychopathology can inform modeling of these complex, multilevel questions and will help to guide efforts to examine the role of development in these processes.

In particular, future neurogenetics research needs to be more sensitive to potential developmental effects. First, studies are needed that include an examination of the effects of "age x gene" interactions within imaging genetics studies to determine whether the influence of genes on brain function varies at different ages or developmental stages. A second and related aim is for studies to examine how genes affect trajectories of brain development using prospective longitudinal designs. Longitudinal research on cortical thickness and IQ suggests that the trajectory of brain development can be more predictive of outcomes than the end points of development (Shaw et al., 2006). Thus, the association between genes and trajectories of brain development during childhood and adolescence may provide greater predictive power than that afforded by examining genes and brain function solely in adulthood (see also Casey et al., 2009). Indeed, although there is preliminary evidence from behavioral and health research of age x gene effects, we have barely scratched the surface on how these manifest as differences in the development of brain structure and function.

Third, in relation to neurogenetics research examining the development of youth internalizing disorders more specifically, there are some overlapping directions for future research that could lead to significant progress in this area. Importantly, there is a need for prospective longitudinal functional neuroimaging studies that can prospectively examine changes in brain function and whether trajectories of neural development mediate GxE interaction effects on anxiety or depression. In relation to a developmental

psychopathology framework, studies that examine individuals with high cumulative experiential or genetic risk are also needed. In addition, we are only just beginning to understand the full extent of the implications associated with epigenetic mechanisms and in particular, how environments interact with genotype to affect an outcome. However, the transmission of epigenetic markers from parent to offspring is a further source of risk for individuals, and one that precipitates examining environments, not just in the lives of individuals, but also that of their parents.

Related to this point is the need for research to move beyond a single candidate gene approach. As mentioned above, candidate genes only account for a small percentage of variation in neural phenotypes of interest. One approach, as we have suggested, is to incorporate cumulative genetic profiles (Nikolova et al., 2011) or to use statistical methodology to identify how individual genes fit with a neural or behavioral phenotype (e.g., Gruenewald et al., 2006). Likewise, using GWAS approaches with neural phenotypes (or developmental trajectories of neural phenotypes) as outcomes of interest has the potential to identify novel genetic polymorphisms that may provide additional predictive power. Ultimately, a more nuanced approach to characterizing genetic risk, environmental risk, GxE statistical effects, and neural development will hopefully lead to more precise characterization of the developmental processes through which genes and environment interact to influence risk or resilience for psychopathology, which will have important translational implications for the early detection of risk for disorder and early intervention and prevention efforts. Though these types of developmental neurogenetics models are relatively novel, they hold great promise and are an exciting new approach to understanding the development of psychopathology.

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CHAPTER 13

Self-Regulation and Developmental Psychopathology: Experiential Canalization of Brain and Behavior

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A central problem in development concerns origins; understanding how the multiple sources of information that direct the development of the organism originate and interrelate over time (Oyama, 2000). From its initial definition as "the study of the origins and course of individual patterns of behavioral maladaptation . . . however complex the developmental pattern may be" (Sroufe & Rutter, 1984, p. 18) the discipline of developmental psychopathology has directly addressed the need to understand the origins of mature forms of behavior in terms of developmental processes. Developmental psychopathology has served as a driving theoretical force in shaping the vast array of scientific disciplines that are directly concerned with development, with "the dynamic interplay of processes across time frames, levels of analysis, and contexts" (Carolina Consortium on Human Development, 1996). Recognition of the common focus on development across disciplines has given rise to what is known as developmental science and to a set of principles by which developmental science is defined. As stated by Magnusson and Cairns (1996) these principles include (1) an understanding of development as holistic and requiring an examination of reciprocity among systems across levels; (2) the contextually bound nature of development; (3) the role of novelty in development; (4) the centrality of time and timing in development, on multiple scales and metrics; (5) the problem of reductionism and the tendency to study one aspect of development in isolation; and (6) recognition of what is known as correlated constraint, or the organized and conservative nature of development. In combination, these principles describe an understanding of the person situated within time frames, levels of analysis, and contexts and offer insight into a developmental understanding of psychopathology.

EXPERIENTIAL CANALIZATION

In the application of general principles of developmental science to the study of developmental psychopathology, we focus on the holistic and contextually bound nature of development and the principle of correlated constraint. We are particularly interested in these principles as they relate to the psychobiological process referred to as experiential canalization (Gottlieb, 1991). The concept of canalization represents an attempt to formally describe the phenomenon of differentiation in development; the emergence of specific and well-ordered forms and behaviors from initially undifferentiated prior states. Canalization, as a descriptive term, contains no prior assumptions about the sources of information that direct the canalizing or shaping process in development. What is implied in the term, however, is the idea of a progressive narrowing of possibilities—of paths taken and foreclosed. As such, it is an apt term for describing the principle of correlated constraint, the constraining of development by the process of development itself. In research on psychological development, this constraining of possibilities is a central feature of cognitive and perceptual development. A canonical example is found in research on language development in infancy. With repeated exposure to a given language in infancy, the child gains experience discriminating phonetic contrasts common to that language while losing the ability to discriminate phonetic contrasts not encountered in that language (Kuhl et al., 1992; Werker & Tees, 1986). Simultaneously with such gain through loss in language development, however, infants acquire an increased ability to integrate sensory experience from multiple sources—visual, auditory, and affective—leading to the further tuning and elaboration of perceptual networks in response to experience (Pons et al., 2009).

As it is generally and historically understood, the concept of canalization describes inevitability or determinism in development; the assumption that information is present in the organism or in the environment that directs development to specific endpoints. As reviewed by Gottlieb (1991), canalization was first invoked by Holt (1931) to describe motor development from the prenatal to the early postnatal period. This initial use of the term was framed within learning theory and the shaping of behavior by conditioned responses. In keeping with the general tenor of psychological research in the first half of the twentieth century, this early use of the term was framed within the assumption that experience is responsible for the shaping of behavior, and that the process of development is shaped by general but ubiquitous experiences acting on initially diffuse and undifferentiated patterns of motor activity.

In contrast to the initial use of canalization from the perspective of learning theory and implied assumptions about the experiential source of the information in directing the development of the organism, a very different and more commonly understood view of the concept was subsequently proposed by Conrad Waddington. Waddington's conceptual model proposes genes as the primary source of information shaping the development of the organism. In contrast to a conception of development as a progressive narrowing or shaping of abilities by experience, the use of the term as associated with Waddington describes a developmental process that is resistant to the influence of experience and that is characterized by a self-righting tendency in response to variation in experience.

Distinct from both the learning theory and genetic interpretations of canalization, the meaning of canalization from the perspective of developmental psychobiology differs from the views proposed by Holt and Waddington (Gottlieb, 1991). It recognizes both biological and experiential influences across multiple levels of analysis and situates them within the individual's developmental history. The framing of canalization proposed by Gottlieb and Kuo (1965) integrates biological and experiential information to address the question of *how* development occurs. As such, it is concerned not so much with the ultimate origin or the endpoint of development as it is with the pathway, with the developmental trajectory and consequences for later development conditioned on earlier occurring developmental processes. Without positing a primacy to any particular source of information, biological or experiential, it proposes an understanding of psychological development as essentially probabilistic as opposed to predetermined, but one that can appear to be highly stable and resistant to change. Identifying the ways the different constituent components of development combine to create stability in physical and psychological development is the objective of the experiential canalization approach; this then allows for the identification of potential points of malleability and specific time points and variables that can be manipulated to bring about change in the developing system. In this way, the concept addresses the paradoxical nature of development as a process of change that is characterized by stability and resistance to change.

Perhaps the most direct illustration of the experiential canalization approach as the combined action of biological and experiential influences on development is seen in Gottlieb's research on the recognition of the maternal call in wood and mallard duck hatchlings. Gottlieb's embryological experiments indicated that the seemingly innate and instinctual tendency of hatchlings to identify and maintain proximity to conspecifics (duck mothers) is

dependent on prenatal experience. Specifically, in order to exhibit the prototypical imprinting behavior exhibited by hatchlings, it is necessary that the embryo experience its own hypersonic vocalizations. In the absence of this experience, imprinting can occur to a variety of species (Gottlieb, 1997). That is, the developmental system—including genetic, physiological, and environmental input, pre-, peri-, and postnatally—is plastic and open to canalization. Here, behavior can be considered a leading edge of development (Cairns, 1991), as the embryonic ducklings vocalization is the primary mechanism of development. That is, behavior organizes the components of the developmental system into a new and stable configuration and acts to maintain that configuration.

A related example in humans, referred to already, is the development of intersensory perception and perceptual narrowing in infancy. The integration of multimodal information occurring very early in development—prenatally and postnatally—provides the basis for the development of increasingly precise perceptual abilities, reducing the amount of information that must be processed in order to bring about a particular behavioral response to stimulation (Lewkowicz, 2000). Perceptual integration can provide for the facilitation or inhibition of sensory processing in one modality by another, for example enhanced auditory perception by the visual modality. From an experiential canalization perspective, the timing and type of modality specific stimulation is central to the process of perceptual development. Experience, primarily through temporal rate and frequency, drives a process whereby the organism acquires increasingly integrated and differentiated information about the world. The act of perceiving integrated information provides the basis for further and more differentiated integration of perceptual processes. Similar processes are also described in dynamic systems theory approaches to motor development, and the idea that as perception shapes action, so action shapes perception (Thelen, 1995).

A MODEL OF SELF-REGULATION DEVELOPMENT

To apply the experiential canalization model to self-regulation development, we look to prior thinking on self-regulation (Luu & Tucker, 2004; Posner & Rothbart, 2000) and define it as the volitional and non-volitional (conscious and non-conscious) management of emotional, attentional, and physiological responses to stimulation, both internally and externally generated, for the purposes of enacting intentional goal-directed, motivated behavior. In this broad definition, self-regulation includes influences at multiple levels of analysis ranging from the genetic to the neural and physiological to the behavioral and social-cultural. Here, self-regulation can be understood to be composed of a set of interacting processes with well-defined biological substrates that are hierarchically organized and integrated by development into particular forms and behaviors. A model of these components and their hierarchical organization is presented in Figure 13.1. This figure presents an architecture or architectonics of self-regulation that is open to the canalizing process of experience at each level. In this, it can be understood both as a model of influences on behavior at a given point in time as well as developmentally over time, as processes at one level influences the development of processes at multiple other levels, as in the general developmental psychobiological model in Figure 13.2.

At the top of the model in Figure 13.1, the fifth level, are the executive functions, defined as cognitive abilities associated with holding information in mind in working memory, the inhibition of highly automatic or prepotent responses to stimulation, and the volitional shifting of

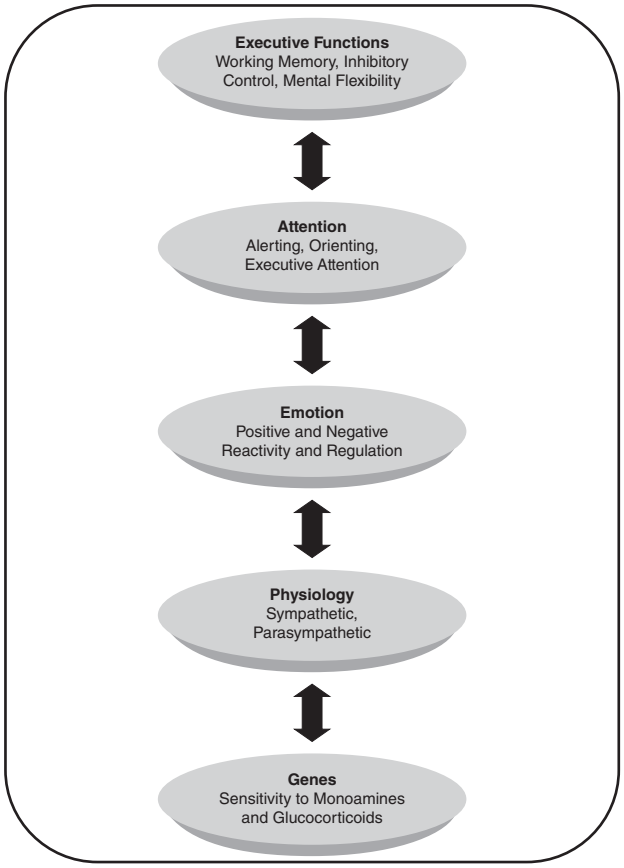


Figure 13.1 The architecture of self-regulation.

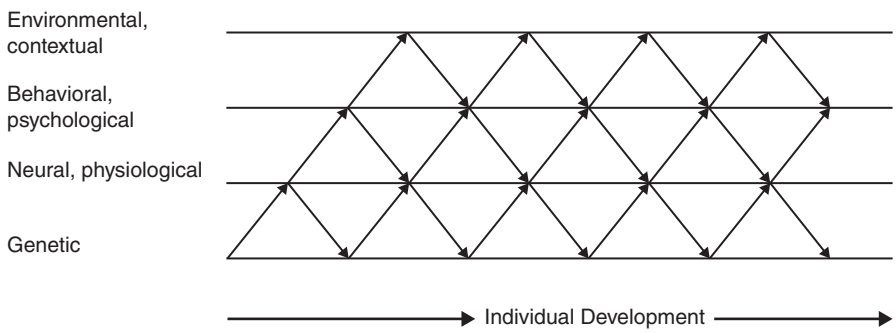


Figure 13.2 The developmental psychobiological model.

attention among distinct but related dimensions of a given stimulus. Executive functions are widely studied in typical and atypical development (Diamond, 2013). The construct originated in neuropsychological research to describe an array of cognitive and behavioral deficits in individuals associated with planning and decision making, primarily in the instance of damage to specific brain areas in prefrontal cortex (PFC; Fuster, 2008; Luria, 1973). Deficits in this set of cognitive skills in various psychopathologies have led to increased interest in executive functions and to their typical and atypical development.

Executive functions are one aspect of the volitional control of arousal and in some ways are synonymous with the motivated and intentional control of behavior. Importantly, for the model in Figure 13.1 and for a developmental model of psychopathology, however, executive functions are only one, and perhaps the least stable or most vulnerable aspect of the self-regulation system. Executive functions are, relatively speaking, chronometrically slow, volitionally effortful, and resource intensive aspects of cognition. Neurobiologically, executive functions are dependent on the integrity of prefrontal cortex (PFC) and the neural circuitry linking PFC with multiple brain regions, including limbic, temporal, and parietal areas. These brain areas that are interconnected with PFC and that both influence and are influenced by PFC, are those represented by the third and fourth levels in the model in Figure 13.1, namely emotional and attentional reactivity and regulation. The brain areas associated with attention include three networks that underlie three functionally, anatomically, and neurochemically distinct aspects of attention, namely altering, orienting, and executive attention, or the volitional control of the focus of attention. The alerting system is activated by norepinephrine originating in midbrain and involves specific areas of frontal and parietal cortex. The orienting system includes the temporal parietal junction, superior parietal cortex, and frontal eye fields and is activated by the cholinergic system. The executive system includes anterior cingulate cortex, insula, and basal ganglia and its primary neurotransmitter is dopamine (Petersen & Posner, 2012; Posner & Rothbart, 2007; Posner, Rothbart, Sheese, & Voelker, 2012). The brain areas associated with emotional reactivity and regulation include structures of the limbic system, notably the amygdala, anterior cingulate, and ventral, lateral, and medial areas of PFC (Davidson, 2000; Dolan, 2002; Ochsner, et al., 2004). All of these brain areas are activated by the above neurotransmitters as well as serotonin.

Activity in the circuitry that underlies reactivity in attention and emotion systems is chronometrically fast relative to executive functioning, and consequently stimulation can drive emotional and attentional responses in ways that shape brain development and support or undercut executive function abilities. The neural basis for this relation occurs in part through the activity of the neurotransmitters described above. The action of these neuromodulators is represented in the second level of the model in Figure 13.1 as the stress response. The stress response system includes the distinct but interrelated sympathetic-adrenal system and resulting levels of catecholamines, primarily dopamine and norepinephrine, and the hypothalamic-pituitary-adrenal (HPA) axis and its end product, the glucocorticoid hormone cortisol. Cortisol results from a cascade of activity in the hypothalamic-pituitary-adrenal (HPA) axis in which stimulation initiates the release of corticotropin releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus leading to the secretion of adrenocorticotropic hormone from the pituitary and resulting release of cortisol from the adrenals. Circulating cortisol then feeds back on the HPA system to inhibit CRH and the resulting production of cortisol (Gunnar & Quevedo, 2007).

CRH also potentiates the sympathetic-adrenal system leading to complex interactions between the HPA axis and

the autonomic nervous system (ANS). Although, the time course of cortisol is slow, taking minutes to reach peak levels, cortisol has more rapid effects at the cell membrane occurring in a time frame of seconds rather than minutes. Studies focusing on physiologically faster actions of glucocorticoids have indicated ways the HPA axis interacts with the ANS (Groeneweg, Karst, de Kleot, & Joels, 2011). CRH facilitates catecholamine release, leading to what is termed a permissive effect of glucocorticoids on indicators of ANS activity such as heart rate (Sapolsky, Romero, & Munck, 2000). Here, interactions among the components of stress physiology are intricate and more research is needed on how they are related developmentally. One investigation of the combined effects of glucocorticoids and catecholamines on behavior in an adult rat model indicated that stress-induced elevations in dopamine are blocked by a glucocorticoid receptor antagonist and that this manipulation was associated with higher levels of working memory performance on a complex maze learning task following stress induction (Butts, Weinberg, Young, & Phillips, 2011). Also in a rat model, high levels of glucocorticoids acting at receptors in PFC both impair working memory and enhance memory consolidation for emotionally arousing events. Importantly, these effects are mediated by a membrane bound steroid receptor, not by activity within the cell nucleus, and dependent on levels of norepinephrine (Barsegyan, MacKenzie, Kurose, McGaugh, & Roozendaal, 2010).

More generally, the feed forward-feedback nature of the stress response system is central to higher and lower aspects of the self-regulation model. As levels of NE, DA, and cortisol rise, they potentiate activity in the emotional and attentional networks that influence executive function abilities. This activation is understood as signaling from limbic and brainstem structures to PFC that levels of stimulation are occurring that require effortful attention and control. That is, as neurotransmitters rise to moderate levels, they increase neural activity in PFC. At very high levels, however, hormone increase is associated with decreased activity in PFC and increased activity in subcortical brain areas associated with reactive responses to stimulation, the capture of attention, and also with robust formation of declarative memories of highly emotional events, the so-called flashbulb memory phenomenon (Diamond, Campbell, Park, Halonen, & Zoladz, 2007). As demonstrated primarily by the research of Goldman-Rakic (1995) and Arnsten (2009), the functional form of the relation of hormone levels to executive function abilities such as working memory is the classic inverted U-shaped curve first identified by Yerkes and Dodson (1908). The inverted U-shaped curve describes the well-known colloquial relation between performance and anxiety in which moderate levels of stress are understood to facilitate performance. Notably, however, in this model and in the original paper by Yerkes and Dodson describing it, moderate levels of stimulation in rats, operationalized as mild electrical shock, was associated with increased performance only on complex learning tasks. In contrast, performance on simple reactivity tasks, such as fear conditioning, was linearly and positively associated with stimulation; with simple tasks, the higher the increase in stress hormones, the better the learning, as in the emotional memory phenomenon.

The mechanism linking moderate stress with complex learning has to do with the fact that neural activity in PFC is sensitive to levels of catecholamines. At moderate levels of catecholamine increase, synaptic activity in PFC is increased and synaptic long-term potentiation, the process through which neurons communicate and form networks, takes place. At very high levels of catecholamine increase, however, the opposite occurs. Instead of increasing synaptic activity and LTP, synaptic activity in PFC is decreased, as neurons in this brain area work less well when exposed to high levels of catecholamines. (The loose analogy that is sometimes used is that of an internal combustion engine, in which an optimal mixture of fuel and oxygen are needed in order for combustion to take place. When the amount of fuel or oxygen is too great or too small, the mixture is difficult to ignite and combustion does not occur.) In other brain areas, however, notably those associated with emotional, attentional, and motoric reactivity to stimulation, such as a vigilant and hyper attentive state, the relation between catecholamine levels and synaptic activity is linear. That is, as catecholamines reach levels that lead to decreased activity in PFC, shutting down brain areas associated with complex cognition and reflective thinking, they are turning on brain areas associated with reactive and less reflective responses, namely the amygdala, a key structure in orchestrating automatic and nonconscious responses to stimulation associated with fear, anxiety, and vigilance to threat.

The Inverted U

The model of self-regulation presented here suggests that the concept of the inverted U can be applied to self-regulation generally. From a bottom-up perspective, as levels of emotion and attentional reactivity and associated neuromodulators rise they support effortful self-regulation through executive functions that are important for

performance and learning on complex tasks. And vice versa, from a top-down perspective, executive functions allow the organism to reflect on information and to direct attention and emotional arousal with cascading consequences through the levels of the model in Figure 13.1. In the model, when stimulation becomes overwhelming or underwhelming, or when top-down control is compromised in some way, bottom-up processes take over and lead to reactive behavior. That is, behavior is more directly under the control of highly learned responses and outside stimulation and less under the control of internally generated information and control—in a word, less reflective.

High levels of stimulation leading to a sustained stress response and rising catecholamine and glucocorticoid levels flip the brain from a top-down mode of control associated with PFC and reflective thinking to a bottom-up mode of control associated with the amygdala and reactive responses to stimulation (Arnsten, 2009). Such an aspect of brain function has clear benefits to survival and evolutionarily speaking is highly conserved across species. In times of threat, it is important for bottom-up processes to take control of attention, emotion, and motor responses to stimulation. The bottom-up form of control assists in the process of survival because it is faster from the perspective of neuronal activity than top-down control (see LeDoux, 1996, 2012). The mechanism by which neural activity is flipped from a top-down to a bottom-up mode of control is related to the types of neural receptors for catecholamines and glucocortioids that predominate in different brain areas and variation in their sensitivity to levels of these hormones. For example, a receptor for norepinephrine (NE), the alpha2 receptor, proliferates in PFC and has a high affinity for NE, meaning that it is active at low to moderate levels of NE and potentiates synaptic activity. Similarly, the dopamine D1 receptor is also present in PFC and sensitive to moderate increases in dopamine. The NE alpha2 and dopamine D1 receptors have complimentary roles in supporting working memory and are both sensitive to increase in NE and DA, respectively. At increases beyond a moderate level, however, they become inactive (Arnsten, 2009). In contrast, different types of receptors for NE are present in the region of the amygdala and hippocampus, the alpha1 and beta receptors, and they are less sensitive to increases in NE and become increasingly active as levels rise. Similar relations are observed for types of glucocorticoid receptors, and along with receptors for catecholamines, provide the neurobiological basis for the inverted U-shaped curve between stress and performance outlined previously.

Genetic Variation

Notably for understanding the hierarchical relation among levels of analysis in the model of self-regulation in Figure 13.1 at the base of the model are variants in genes, both single nucleotide polymorphisms and variable number tandem repeats that are associated with sensitivity to and variation in levels of the relevant hormones that act as neuromodulators in the neural circuitry that underlies self-regulation. For example, a variant of a single nucleotide polymorphism (SNP), the catechol-o-methyltransferase gene (COMT) has been widely studied, particularly as a potential contributing cause of schizophrenia. This gene is associated with the break down or catabolism of catecholamines, dopamine and norepinephrine, in PFC. Individuals who have a G to A substitution, resulting in a valine to methionine substitution at position 158, catabolize dopamine less efficiently than do individuals with the valine version of the gene. Individuals who are heterozygous for the gene display intermediate levels of dopamine catabolism relative to those who are homozygous for the valine or methionine version of the gene. The functional activity of the gene in relation to behavior is seen in the role it plays in regulating catecholamines, particularly dopamine in PFC. Given the relatively low density of synaptic dopamine transporters in PFC, dopamine removal from the synapse results more from the activity of enzymes that break down dopamine and norepinephrine into inert components than from the removal of dopamine from the synapse through cellular transporter mechanisms. Given the inverted U shape relation of catecholamines to synaptic activity in PFC, a number of studies have shown relations of COMT val158met genotype to executive functions.

Generally speaking, the form of this relation has been one in which individuals homozygous for the met version of the gene, meaning that they break down catecholamines less quickly, exhibit higher levels of working memory and executive cognitive task performance due to the increased presence of catecholamines in PFC. That is, consistent with the inverted U-shape relation between stress and performance described previously, moderately higher levels of catecholamines, in this case due to the benefit of a genetically conferred characteristic, should be associated with a higher level of executive function ability. Studies of the COMT gene and similar genes associated with catecholamine activity for the most part, however, have been carried out in laboratory contexts and have not taken into account where on the inverted U shape curve an individual may be situated, experientially speaking. Several studies,

however, note that expectations concerning the relation of the COMT gene to behavior must take into account the context and temperament of the individual, or what might be considered the initial starting point or background state of the brain prior to completing an executive cognitive task (see Tunbridge et al., 2007, for review). For example, pharmacological manipulation of catecholamine levels through amphetamine administration results in a higher level of performance among val carriers relative to met carriers (Mattay et al., 2003), an effect opposite from what would be expected under typically occurring conditions.

EXPERIENTIAL CANALIZATION OF SELF-REGULATION DEVELOPMENT

The experiential canalization model of self-regulation is one in which the developmental shaping of the self-regulation system over time is open to the combined influences of individual biology and experience at all levels, from the genetic to the social and cultural. In the model, it is therefore essential to take into account the history of the organism when examining one aspect of the individual, such as COMT genotype, in relation to any other. Clear examples of this point are seen in demonstrations of the relation of genetic background and early experience to risk for psychopathology in widely cited analyses from a longitudinal sample, a birth cohort, in Dunedin NZ (Caspi et al., 2002, 2003). Here, the relation of genes that regulate monoamine (MAOA) and serotonin (5-HTT) metabolism to later psychopathology were dependent upon the quality of early experience. Specifically, in the Dunedin sample, individuals carrying the version of the MAOA gene that confers less efficient metabolism of monoamines were increasingly likely to exhibit antisocial behavior as adults if they had experienced maltreatment in childhood (Caspi et al., 2002). Similarly, for individuals carrying the version of the serotonin transporter gene that confers less efficient metabolism of serotonin (lower serotonin transporter availability), the effect of stressful life events on depression was increased (Caspi et al., 2003). To be clear, in both of these studies, adverse early experience was a risk factor for later psychopathology for all individuals in the study. The risk associated with that experience, however, was even greater for individuals carrying the gene associated with less efficient metabolism of the relevant neurotransmitters (dopamine, norepinephrine, serotonin).

Although impressive in many ways, what is most notable about these findings is the idea that what is beneficial under advantageous circumstances is detrimental in adverse circumstances. That is, while the maintenance of catecholamines in the brain confers benefits to self-regulation and reflective thinking under low stress conditions, it is disadvantageous under high stress conditions. The neurobiological basis for the way in which acute stress affects psychological function and behavior by increasing catecholamines and flipping the brain from a more reflective to more reactive mode of control in the short run is well established. What is less clear, however, is the extent to which this neurobiology has long-term implications for psychological development and risk for the development of psychopathology, such as that in the examples above. Given the role of experience in brain development (Greenough, Black, & Wallace, 1987) and the formation of neural networks by processes of LTP occurring in response to experience (Hebb, 1949), it is conceivable that tendencies toward more reactive or more reflective modes of self-regulation could become increasing well established, potentially early in development that would be maintained behaviorally in a way that would have long term implications for psychological outcomes and risk for psychopathology.

Much more longitudinal research is needed to address this central point in the development of self-regulation, for which an experiential canalization approach focusing on stress and stress hormones can be helpful. The basis for such an approach is rooted in concepts of allostasis and cybernetics (Pribram, 1960). Decades of research on stress physiology have demonstrated that stress physiology adaptively adjusts as a cybernetic system to current and expected challenges. Unlike homeostatic systems that must maintain functioning within a relatively narrow band around a given set point to support the optimal functioning of the organism (e.g., body temperature around 98.6° Fahrenheit), stress response systems are allostatic, able to adaptively adjust set points and ranges in response to experience as needed. In this process of allostatic adjustment, the brain plays the key mediating role as it is shaped by experience to adjust physiologic systems to meet an expected future (McEwen & Gianaros, 2011). From the joint perspectives of allostasis and cybernetics, the self-regulation of behavior is a manifestation of physiological set points and accompanying cognitive representations of these set points (Luu & Tucker, 2004). Experience in concert with biological systems acts to establish increasing stability in patterns of behavior through its influence on stability in neural networks (Derryberry & Rothbart, 1997; Posner & Rothbart, 2007).

Numerous studies have confirmed that PFC is central to the regulation of stress response physiology and that levels

of catecholamines and glucocorticoids in part shape the development of this area of the brain (Holmes & Wellman, 2009). Consistent with the experiential canalization model of self-regulation, stress early in life is understood to shape the strength of connections between prefrontal and limbic structures that underlie self-regulation (Cerqueira et al., 2007). For example, a series of studies has shown that induced stress in adult rats leads to changes in the structure of neurons in PFC with consequent effects on attention and set-shifting executive cognitive types of abilities (Liston et al, 2006; Radley et al., 2006). These studies indicate that early stress can lead to the types of functional deficits that are observed in various forms of psychopathology and strongly indicate early stress as one potential contributor to the pathogenesis of psychiatric disorders through its influence on the development of self-regulation.

Available human data are consistent with the findings of stress manipulation studies in animal models and indicate the effect of stress hormones on PFC and executive functions. Pharmacological manipulations affecting glucocorticoids as well as catecholamine levels have demonstrated the role of these neurochemicals in executive function abilities (Alexander et al., 2007; Lupien et al., 2001). Of pressing interest are the various pathways through which naturally occurring chronic stress in individuals' lives may lead to self-regulation difficulties and to increased risk for psychopathology. Early life stress, primarily operationalized in terms of the adverse events usually associated with the experience of growing up in poverty, has been shown to lead to alterations in resting levels of stress hormones such as cortisol in children (Blair et al., 2011; Evans, 2003; Lupien et al., 2005). As well, early poverty has been associated at the molecular level with differential expression of genes associated with adrenergic and glucocorticoid function. In one study, genome wide transcriptional profiling found that low SES in childhood was associated with up regulation of genes associated with adrenergic neural receptor function and down regulation of genes associated with glucocorticoid receptor function in adulthood; a pattern consistent with an expected higher level of reactivity and less prototypically effective regulation of physiological reactivity in individuals experiencing poverty in early childhood (Miller et al., 2009).

Experiential Canalization as Life-Course Strategy

Implicit in the idea of the allostatic shaping of stress response systems is the notion of a tradeoff between short-term benefit and long-term disadvantage. Central to the experiential canalization model and also the related adaptive calibration model of stress response physiology (Del Giudice, Ellis, & Shirtcliff, 2012) is the idea that alterations to physiology occurring in response to stress are an adaptive and probabilistically normative response to conditions of disadvantage. Alterations to stress physiology and to the neurobiological self-regulation system in response to an expected environment, particularly early in development, are central to a developmental and evolutionary understanding of psychological and physical functioning. Evolutionary biological models across a variety of species indicate that, in conditions of high disadvantage and in which resources and support are low, effective strategies for garnering resources and for surviving to maturity and engaging in opportunities for procreation are optimized through the tuning of stress physiology to potentiate high reactivity and low reflective behavior. Although such reactivity may have some long term cost, the potential for surviving to realize this longer term cost is reduced in conditions of disadvantage. In contrast, in highly resourced and supportive environments, alteration of stress physiology in ways that support more reflective behavior with positive consequences for longer term benefit is advantageous. A well-resourced future is one that can best be utilized and optimized through planning and reflection on multiple possibilities.

The idea that development is shaped by environmental context in ways that are designed to maximize fitness within that context is observed across a variety of species from plants, to fish, to mammals. A notable example of the shaping of such a defensive response in development, persisting across generations, is seen in the modest example of the radish. High levels of damage by herbivores induce phenotypic changes in radish leaf production and in seed production in ways that make the leaves less appealing as a food source and as a result promote fitness in environments in which herbivory is high (Agrawal, 1999). A similarly modest example, in this instance in an insect, the water flea, exposure of the mother to the chemical signal of a predator induces morphological changes in offspring that render them less vulnerable to that predator over subsequent generations, even in the absence of any exposure during development of the offspring to that signal. In these examples, environmental programming of individual development is mediated through the mother, through what is referred to as the maternal provision. In a review of the literature on environmental programming, Cameron et al. (2005) provided several examples across a variety of species from plants to insects to mammals in which the experience of the parent induces a phenotypic change in the offspring, often for successive generations.

Sensitivity to Context

A key point implicit in the foregoing is the realization that the relation between one level of influence in the self-regulation model, such as genetic background associated with catecholamine metabolism, and experience extends beyond merely increasing risk for later psychopathology. The gene variant or stress response that confers risk in adverse circumstances may be the one that confers benefit in more advantageous circumstances. The recognition of such increased susceptibility to experience (Belsky & Pluess, 2009) or biological sensitivity to context (Boyce & Ellis, 2005), as this phenomenon is referred to is perhaps central to understanding how individuals who look very similar in certain respects may end up with very different outcomes. Such multifinality in development, the emergence of divergent developmental pathways and endpoints from similar starting points, is expected and may hold some promise for understanding processes of risk and resilience in developmental psychopathology. Fulfilling this promise will involve some understanding of the short and long term implications of the inverted U-shape relation between stress and self-regulation for psychological and behavioral development (Blair, 2010). It may be that any longer term effects on brain development and synaptic functioning are malleable and may offer clues as to how effects of early experience can be overcome by later experience. As well, it may be for some, that later experiences can exert disadvantageous effects despite early advantage.

An important point here concerns the fact that in samples demonstrating an association between a specific gene variant, be it MAOA or any other gene, and disadvantageous experience, the number of individuals with the relevant version of the gene and high adverse life experience are usually a small percentage of the total population (e.g., Caspi et al., 2002; Kim-Cohen et al., 2007). This indicates that the association between the specific gene variant and the adversity being examined can account for only a portion of the pathologic outcome being examined. That is, complementary to multifinality, there is also equifinality, or multiple ways individuals come to the same developmental outcome. Here, reported interactions between gene variants and environments in the prediction of outcomes are perhaps best seen as exemplary of the relation between biology and experience in the study of developmental psychopathology. Multiple genes are related to the activity of catecholamines and glucocorticoids and multiple types of experience can combine with those genes to lead to psychopathology or to resilience despite risk. Discerning common pathways among these heterogeneous influences is a complex undertaking but one in which psychobiological theory and understanding of self-regulation as a recursive feed forward and feedback driven system can provide a useful organizing framework.

Gene Expression

An overarching point essential to issues of multifinality and equifinality in development is that the recursive nature of the model in Figure 13.1 extends to the genetic level. That is, just as executive function processes can both control and be controlled by levels of arousal in emotion and attention systems, so do stress physiology and genes interact through processes of gene expression that shape and are in turn shaped by levels of stress hormones. The HPA axis cascade and action of glucocorticoids on relevant neural targets is generally physiologically somewhat slow, occurring over minutes or hours. Here, glucocorticoid effects on neural activity and structure are largely gene mediated, meaning that they affect processes in the cell nucleus and influence DNA transcription (de Kloet, Karst, & Joels, 2008; Joels & Baram, 2009). As such, the self-regulation model posits that experience shapes development in two directions: As experience acts on stress physiology to influence levels of circulating hormones, it is working "upstream" to affect emotion, attention, and executive function skills that work to regulate stress physiology. It is also working downstream, through cortisol to affect gene expression in ways that also affect levels of stress hormones and, consequently, reactivity and regulation of emotion and attention and executive functions. In theory, the feedforward–feedback loop of self-regulation is understood to be developing over time in response to experience, perhaps rapidly early in the life course, to establish set points or sensitivity for reactive as opposed to regulated responses to stimulation (Luu & Tucker, 2004). Experience and biology are understood to combine to determine the sensitivity of the self-regulation system.

The defining psychobiological model of a canalizing process in self-regulation development, although not necessarily referred to as such, is found in research on the effect of maternal behavior on development in a rat model. As shown in the rat, expression of a gene associated with glucocorticoid receptor density in the hippocampus is determined by specific types of maternal behaviors occurring within the first 8 postnatal days. Expression of this gene is associated with the ability to regulate hypothalamic-pituitary-adrenal (HPA) axis responses to

stress and, in turn, with self-regulation behaviors influenced by stress hormone activity. Specifically, offspring of rat mothers that lick and groom their pups frequently and nurse in an arched-back manner (LG-ABN) manifest reduced reactivity and enhanced regulation not only of glucocorticoid levels but also greater learning and memory and reduced avoidance in the face of novel and/or threatening stimuli (Liu et al., 1997; Liu et al., 2000). Notably from the perspective of experiential canalization and adaptive phenotypic plasticity, the high licking and grooming maternal behavior associated with glucocorticoid receptor gene expression in the hippocampus and increased cognitive and behavioral regulation in offspring is facilitated in resource rich environments but reduced in resource poor environments (Meaney, 2001). That is, to some extent the maternal behavior that offspring receive is influenced by the characteristics of the environment in which the mother is situated when conceiving and rearing her offspring. The idea here is that in high-resource environments, the mother rat would be foraging away from the nest for relatively short periods of time and therefore engaging in more of the LG-ABN behavior while in low resource environments the opposite would be true. Such an environmentally driven change in maternal behavior leading to changes in stress physiology and hence behavioral development of offspring is a canonical example of a canalizing process in development.

EXPERIENTIAL CANALIZATION OF SELF-REGULATION DEVELOPMENT AND RISK FOR PSYCHOPATHOLOGY

Understanding the distribution of genes and processes of gene expression in populations and the ways genetic background and gene expression are related to one another developmentally is a key scientific goal for research in developmental psychopathology and human development generally; one for which the experiential canalization approach can provide a useful theoretical framework. Important in this goal is an understanding of the relation of biology and experience to developmental outcomes within the model of self-regulation. Here, the model of self-regulation development describes what can be considered an endophenotype, or intermediate phenotype (Gottesman & Gould, 2003). The endophenotype describes combinations of physiological, anatomical, cognitive, and neural processes that are implicated in but by no means unique to psychopathology. The endophenotype is understood to encompass a well-defined and coherent set of processes and behaviors that in part characterize a given disorder. As such, it is well aligned with new directions in the identification and classification of mental disorders on the basis of genetics and brain structure and function as well as behavior referred to as Research Diagnostic Criteria (RDoC; Insel et al., 2010).

The self-regulation system provides an elaborated model of the intermediate phenotype that provides insight into interaction among processes at multiple levels of analysis and various pathways to the occurrence of a given disorder and means to treat it. In the clinical and developmental literature on psychopathology broadly, self-regulation is widely studied in the form of the regulation of emotion and attention and also executive functions. Many aspects of the components to the self-regulation model outlined above are the topic of extensive research in schizophrenia, attention-deficit/hyperactivity disorder, anxiety disorders, and depression. In keeping with the general idea that the study of typical and atypical development are mutually informative, the processes of the typical development of executive function, attention, and emotion from the experiential canalization approach, particularly in the context of high risk, whether from poverty, prior family history or both, can inform understanding of self-regulation in research in developmental psychopathology. To this end, we review research on the typical development of self-regulation, focusing on our own and others work with the aim of outlining ways developmental processes may increase risk for psychopathology or alternatively promote resilience in the context of risk.

Typical Development of Executive Functions

Definitions of executive functions have ranged somewhat widely within a circumscribed set of abilities from the more to less inclusive. Given the role executive skills in planning and problem solving and effortfully regulating aspects of cognition and motivation, some have argued for relatively inclusive definitions of executive functions that involve general planning and problem solving skills (Welch, Pennington, & Grossier, 1991). Others, in contrast, have focused more narrowly (Aron, 2008). Increasingly, however, the field has settled on the domain general cognitive skills of working memory, inhibitory control, and attention shifting as the operational and conceptual definition of executive control (Diamond, 2013). That is, cognitive control generally involves the integration of these skills in task performance. This is seen in widely used measures

of executive function (Davidson, Amso, Anderson, & Diamond, 2006; Zelazo, 2006) and has tended to be validated in studies examining the relation of executive function components to performance on comprehensive executive function tasks (Miyake et al., 2000).

A complete review of research on executive functions is not appropriate here; however, from the perspective of the experiential canalization model of self-regulation development and its application to developmental psychopathology, the protracted developmental course of executive function abilities and their association with prefrontal cortex, a slow maturing brain region (Gogtay, Giedd, et al., 2004), recommends these cognitive skills as potentially valuable indicators of experiential influences on development and on risk for and prevention of psychopathology. The genesis of the executive functions construct in the neuropsychological literature (Luria, 1963) and intense interest in executive functions in the instance of brain damage or dysfunction (Duncan, Burgess, & Emslie, 1995; Waltz et al., 1999) further illustrates the applicability of these cognitive abilities to a developmental understanding of psychopathology. In typically and atypically developing samples, studies of executive function have of necessity employed a variety of measures, primarily due to the restricted age range in which various measures can be used. This makes cross-study and cross-age comparisons difficult. As well, research on the development of executive functions has tended to be cross sectional and has focused on age-related change as well as issues relating to measurement and to construct definition and validity, including the differentiation of executive functions from other aspects of cognitive ability, particularly general intelligence (Blair, 2006). Longitudinal research on the development of executive functions in childhood or throughout the lifespan is relatively rare. Nonetheless, useful information about executive function development can be gleaned from several analyses (e.g., Anderson, 2002; Welsh, Pennington, & Grossier, 1991). Studies with older children and adults have examined typical tasks from the neuropsychological literature and found that performance on these batteries follows a trajectory in which ability increases steadily throughout adolescence into young adulthood. For example, Luciana and colleagues found in a cross sectional sample of 9–20-year-olds that recall-guided action of single units of spatial information develops until 11 to 12 years while the maintenance and manipulation of multiple spatial units develops until 13 to 15 years. More complex processing of information in which the individual must organize and structure information develops until ages 16 to 17 years (Luciana et al., 2005). Complex processing of information in working memory has also been found to develop into early adulthood (20–29 years) with age related declines becoming apparent in the 50–64 years range (De Luca et al., 2003).

Measurement of Executive Functions

Information about the typical trajectory for executive function abilities in younger children has been limited by the absence of measures appropriate for longitudinal use. Although there are a number of effective measures of executive functions for preschool children, variation in performance on these measures is usually restricted to a relatively narrow age range with pronounced floor and ceiling effects outside of that range. Carlson (2005) reviewed several widely used measures in early childhood research and found that most are adequate within a relatively narrow age range. Similarly, Espy and collaborators have shown that an attention shifting and inhibitory control task known as the Shape School tracks age related changes in abilities in a cross sectional sample of 3 to 6 year olds (Espy et al., 2006). Noting the need for measures that can be used longitudinally to examine within person change in executive function and that address the tripartite division of executive function into working memory, inhibitory control, and cognitive flexibility domains, Willoughby and Blair (2010) developed a battery of six executive function tasks appropriate for 3–5-year-olds. This battery, similar to analysis of other executive function batteries (Wiebe, Espy, & Charak, 2008), was found to indicate a single underlying factor of executive function. It also demonstrated longitudinal measurement invariance across the age range studied and good test–retest reliability (Willoughby et al., 2011). Notably, findings in a large longitudinal sample ($N = 1{,}292$) indicated rapid and substantial development in early childhood of 2.8 SD on average in executive function between ages 3 and 5 years (Willoughby et al., 2012).

The aforementioned studies provide some indication of the typical course of the development of executive function and indicate that the ability to process complex information continues to develop into young adulthood. There currently is not a complete normative picture of executive function development, however, against which atypical trajectories can be identified. Obtaining this information is a priority for research in psychopathology and for research on human development in the context of risk, generally. Deficits in executive function are one mechanism through which early adversity affects lifetime risk for mental as well as physical health disorders (Blair & Raver, 2012).

Atypical trajectories for executive function development in early childhood may provide some early indication of risk. An important step in obtaining normative information on executive function development has been the creation of what is known as the NIH Toolbox, which includes computerized versions of two widely used measures of executive function, the Dimensional Change Card Sort task and the Eriksen Flanker Task (Zelazo et al., 2013). Presumably normative information on these measures will be forthcoming and will provide a valuable resource for examining executive function deficits as potential indicators of risk for developing psychopathology.

In developing longitudinal measures of executive functions, however, it is important to note that executive function abilities may be highly vulnerable to a variety of insults and therefore less informative as a definitive indicator of risk for psychopathology. Executive functions can be affected by a variety of things, from the mundane (lack of sleep and lack of exercise; Chadock-Heyman et al., 2013; Davis et al., 2011) to the catastrophic (structural and functional damage to PFC and related circuitry; Duncan, Burgess, & Emslie, 1995). Unlike, for example, semantic memory or speed of information processing, aspects of cognition that are more stable, executive functions can be relatively variable within person. The openness of executive functions to insult small and large means that within person change and the stability of between person differences may be great. To a considerable extent, this aspect of executive functioning is a manifestation of the relation of these cognitive abilities to the lower level processes in the model in Figure 13.1. As noted by Luu and Tucker (2004, p. 125), "Disembodied concepts of executive functions may be particularly inappropriate when dysfunctions of executive control are invoked to explain pathologies of mood and motivation. Rather than a disorder of an external supervisory control, these pathologies suggest fundamental alterations in the internal goals and set-points guiding self-regulation." Executive functions are understood to be predictably variable due to influences on attention and emotion and stress physiology as a manifestation of self-regulation development.

Notably, the inherent variability in executive functions creates problems for traditional psychometric analyses by which the validity of psychological assessments is typically established. Test–retest reliability may tend to be low and correlations among assessments of putatively the same construct administered concurrently may correlate weakly or even not at all (Rabbitt, 1997; Willoughby & Blair, 2011). These measurement concerns and considerations in executive function research are seen most clearly in latent variable model analyses of executive function test batteries (Willoughby, Pek, Blair, & FLP Investigators, 2013). Latent variable modeling is an appropriate and widely used strategy for estimating and analyzing the common variance among a set of measures of ostensibly the same construct. Analyses of general mental ability and academic achievement are well-known examples of the utility of latent variable modeling to derive a single underlying construct. Task batteries of these constructs produce robust latent factors that account for upward of 70% of the variance in each of the individual measures (observed indicator variables) used to create the latent variable. Unlike test batteries for these constructs, however, executive function assessments in most latent variable analyses (e.g., Miyake et al., 2000; Willoughby et al., 2012) present low to moderate correlations among the observed indicators and as a result executive function latent variables usually account for only small amounts of variance in each of the indicator variables. This aspect of the task batteries places an upward limit on the reliability of the latent variables, referred to as maximal reliability, despite typically excellent global model fit (Willoughby, Pek, Blair, & the FLP Investigators, 2013). Excellent model fit in this instance cannot be taken as an indicator of the quality of the measurement of the underlying construct, raising questions about conclusions of the literature on executive function abilities using latent variable modeling.

The foregoing characteristics of executive function measures highlight the inherent weaknesses as well as strengths of the construct. On one hand, traditional psychometric standards for establishing reliability and validity indicate that the construct is somewhat problematic. On the other hand, part of the value of executive functions lies in their inherent instability. Here, theory and empirical evidence indicate that the construct may be most valuable because of its potential malleability and suggest novel methodologies to study it. To this end, executive function research could benefit from the application of innovative but underutilized methods focusing on within person change (Molenaar, 2008; Nesselroade & Jones, 1990). The application of what is referred to as a multivariate, replicated, single-subject, repeated measures design focusing on intraindividual variability as opposed to interindividual variability could provide the basis for a more accurate estimate of the typical course of the development of executive functions and the relation of this development to risk for psychopathology. Such idiographic research methods were developed to address the fact that traditional analytical approaches that address inter-individual variation cannot provide accurate information about within person change.

To appropriately model the complexity of development, for current purposes relations among various aspects of the self-regulation system as they relate to within person change, it is necessary to measure individuals, as many as possible, as repeatedly as possible, and to analyze the data to examine how variables combine within persons (Ram, Brose, & Molenaar, 2013). This approach allows for conclusions about trajectories and processes of change within an individual as well as identification of patterns of similarity among groups of individuals, empirically capturing the reciprocal, dynamic nature of development so forcefully outlined by Magnusson and Cairns (1996) and by an experiential canalization framework.

Executive Functions and Developmental Psychopathology

Issues relating to the measurement of executive function abilities and appropriate methods for the study of change are heightened by the fact that developmental studies have indicated deficits in executive functions across a variety of disorders including attention-deficit/hyperactivity disorder (ADHD; Biederman et al., 2007; Willcutt et al., 2010) and autism (Ozonoff & McEvoy, 1994). Studies have also established that executive function deficits are characteristic of major depression and schizophrenia (Tan, Callicott, & Weinberger, 2009). Although executive function deficits are neither necessary nor sufficient for the diagnosis of any psychiatric disorder, knowledge of executive function development and its biological and experiential determinants can likely provide valuable information to further understand psychiatric disorders and their pathogenesis. Consistent with the framework of the experiential canalization model in Figure 13.1, however, executive function deficits across various disorders or within a single diagnostic category could originate from multiple different sources of influence. Executive function deficits in and of themselves are perhaps too general to be of use on their own in identifying risk for and potential course of a given disorder. Knowledge of the processes that underlie the development of typical executive function abilities, however, will likely prove to be useful in diagnosing and treating subsets of individuals with a given disorder.

The specific etiology and course of psychopathology generally might be more readily discerned by considering the various levels in the model in Figure 13.1. Two examples are useful here: schizophrenia and ADHD. Both are characterized by executive function deficits and executive functions have been extensively studied in individuals with these disorders. More specifically, for present purposes, the COMT gene has figured largely in research on schizophrenia. Given the role of this gene in the activity of dopamine in PFC, it serves as a logical candidate for understanding the etiology of schizophrenia. The association of COMT with schizophrenia is, however, weak at best (Fan et al., 2005). This is not surprising given the complexity of processes affecting executive function as well as risk for schizophrenia, among which dopamine availability associated with the activity of a single gene is one small influence. Research on the COMT polymorphism, which has been voluminous, has revealed, however, the centrality of taking into account the background physiological state of the individual. Given the inverted U shape curve defining the relation between neurotransmitter levels and neural activity in PFC, it may be advantageous under conditions of stress or threat, or even moderately elevated stress, to break dopamine down more efficiently, as do individuals with one or two copies of the val allele of COMT. Therefore, research on one aspect of the individual, such as COMT genotype, might prove to be a risk factor or a protective factor in the case of schizophrenia or other disorders affecting executive functions, depending on a host of other characteristics of the individual. Although relations among this host of factors is undoubtedly complex, the experiential canalization approach provides a framework for incorporating this complexity and for discerning relations among levels of influence that lead to the disorder or to its absence despite substantial risk. Here, the principles of developmental science articulated by Magnusson and Cairns (1996) listed at the beginning of the chapter suggest the importance of focusing on the timing of individual experience and variation in rates of development of the various components of the self-regulation system. Application of single-subject, repeated measures designs to the well-established relations among COMT, catecholamine levels, and executive function abilities can address complex relations among influences on an intermediate phenotype associated with risk for psychopathology.

ADHD is also a complex disorder for which the experiential canalization approach is useful in discerning multiple etiologies and subtypes of the disorder. Prior models of ADHD have focused primarily on executive function deficits as its defining feature (Barkley, 1997; Nigg, 2001). Given the inherent complexity of executive functions and multiple pathways to problems with executive functions, however, identification of ADHD as a disorder of executive functions is too general and has required a focus on heterogeneity of subtypes and on bottom-up as well as top-down influences on cognitive ability and behavior. As outlined in the model of self-regulation, the bottom-up influences can affect top-down executive

control abilities. In ADHD research, this has been noted in a focus on sensitivity to reward and approach behavior (Nigg & Casey, 2005) as processes at the emotional and physiological levels that can override or subvert executive function abilities. Furthermore, the recognition of the multiplicity of influences and pathways in ADHD has resulted in a focus on the identification of heterogeneity in the disorder. That is, rather than taking a core deficit such as executive dysfunction as the sole focus of research on etiology, diagnosis, and treatment, investigators have turned to heterogeneity of psychological functioning in typically developing populations as a backdrop against which to understand heterogeneity in ADHD. This effort has pursued what is known as community detection, an approach to define clusters or communities of similarity among relevant measures of cognitive ability among a sample of children meeting criteria for ADHD and typically developing controls. Notably, the approach has yielded the insight that heterogeneity in ADHD is embedded in heterogeneity in typically developing children (Fair, Bathula, et al., 2012). As well, the heterogeneity in subtypes identified by community detection was observed in variation in functional connectivity in the brain for two of the most common ADHD subtypes (Fair, Nigg, et al., 2012). These results confirm to some extent the value of a focus in developmental psychopathology on both multi and equifinality and on the mutually informative relation between typical and atypical development. As well, these findings suggest the value of a developmental analysis as outlined in the seven principles enumerated in the introduction. It may be that distinct pathways to the disorder can be discerned early in development and that the timing and type of experience associated with each yield insights into its etiology and potential preventive intervention.

Application to the Study of Anxiety and Mood Disorders

A further illustrative example of the way in which an understanding of the hierarchical organization of influences on self-regulation is related to the study of psychopathology is found in its application to anxiety and mood disorders. Anxiety is an essential aspect of human functioning that has been conserved throughout evolution for its value in detecting and responding to threat. Executive functions, which enable the higher order processing of potentially threatening information, expands the link between detection and response, projecting it into the future and building upon past experience (Luu, Tucker, & Derryberry, 1998). For present purposes in the experiential canalization framework of self-regulation, this understanding of executive control, as one that is intimately connected with threat detection (emotional, reactive) highlights the reciprocal relation between bottom-up and top-down processes for understanding anxiety and mood disorders. Specifically, bottom-up pathways linking amygdala and anterior cingulate cortex (ACC) have been identified as critical components of individuals' regulation of fear and anxiety. Individuals prone to high levels of anxiety demonstrate clear differences in amygdala function, processing threatening versus nonthreatening stimuli differently than non-anxious controls in a bottom-up model of attention and emotion processing (Debiec, Diax-Mataiz, Bush, Doyere, & LeDoux, 2010; Dolan & Vuilleumier, 2003; Mogg & Bradley, 1998). Processing biases in depressed individuals' perception of emotionally negative stimuli have also been found to be associated with heightened activation throughout additional ventral components of the network linking amygdala, insula, ventral striatum, and ventral ACC (Mayberg, 2003; Phillips et al., 2003). Findings extend to pediatric samples of nonmedicated children and adolescents experiencing high levels of depressive symptoms (Roberson-Nay, et al., 2006; Yang et al., 2010).

These bottom-up processes of emotion regulation (ER) involved in responses to fear-evoking or threatening stimuli are, of course, tied to top-down processes involving PFC function (see Dolcos, Iordan & Dolcos 2011 for review). Specifically, executive functions can aid in modulating negative arousal as well as in interpreting and responding to emotionally negative stimuli (Ochsner, Bunge, Gross & Gabrieli, 2006; Ochsner & Gross, 2005; Posner & Peterson, 1990; Wang et al., 2008). Highly anxious individuals, however, have been found to show reduced executive functions, and consequently, difficulty in managing competing or conflicting cognitive demands relative to nonanxious controls (Bishop, 2009; Bishop, Duncan, & Lawrence, 2004: Rueda, et al. 2004). These differences have been hypothesized to play critical roles in anxious individuals' difficulty in accurately appraising both the emotional states and intentions of others, in socially positive as well as socially negative situations. While past work has largely focused on elucidating the links between greater proneness to reactive versus reflective profiles of self-regulation and profiles of behavioral disinhibition (e.g., higher risk taking behavior, higher delinquency and higher risk of substance use problems), newer research considers the ways that top-down processes are implicated as symptom (as much or more so than cause) in the development of anxiety, depressive disorders and broader-band internalizing difficulty (Buckner, Mezzacappa & Beardsley, 2003; Zucker, Heitzeg & Nigg, 2012).

Recent reviews examining the neural circuitry implicated in processing of emotional stimuli for individuals with depressive disorders suggest support for a dual systems model emphasizing bottom-up and top-down processes. Automatic responding to emotional stimuli primarily draws upon amygdala and ventral and medial prefrontal cortex including subgenual ACC. In contrast, voluntary behavioral and attentional processing of emotional stimuli has been found to involve dorsal regions, including dorsal ACC and dorsal lateral PFC (Rive et al., 2013). Neuroimaging studies of adults with depression diagnoses suggest that effective connectivity from the subgenual ACC and amygdala is increased, with depressed individuals needing to deploy greater medial PFC activation to maintain automatic attentional control relative to their non-depressed counterparts. This hypothesis has been supported by findings indicating increased activity in dorsal medial PFC and dorsal ACC in depressed participants relative to healthy controls during tasks requiring automatic emotion regulation such as facial matching and Stroop-like tasks where emotional stimuli are embedded. In short, activation of neural circuitry underlying executive functions appears to be increased in a compensatory fashion in individuals with depression to redirect attention away from emotionally negative and distracting stimuli (Etkin & Schatzberg, 2011; Rive et al., 2013). This added demand on executive cognitive abilities may indicate that deficits in executive cognitive ability are secondary to increased demand on attention to emotional processing. Patterns of hypoactive function in lateral prefrontal areas across a number of studies examining depressed participants' performance on tasks involving voluntary cognitive control of negative emotions may indicate typical depletion of executive abilities in the face of repeated demands. Such findings are aligned with results suggesting the individuals with major depressive disorder have difficulty voluntarily stopping or inhibiting the processing of negative information (Gotlib & Joorman, 2010). Treatment studies using fMRI to examine the impact of pharmacological treatment using SSRIs such as paroxetine, sertraline and fluoxetine highlight the joint roles of amygdala, rostral ACC and the lateral PFC in emotion processing. In one recent study, decreases in amygdala activation as well as increased dorsal cortical activation (including increased rostral cingulate and DLPFC) were found as a function of antidepressant treatment, with evidence argued to support indirect pathways of influence (e.g., SSRI treatment leading to improved dorsal prefrontal control over dysregulated limbic activity; Ruhe et al., 2013).

Parallel to these findings, investigators focusing on HPA axis function among depressed individuals have highlighted corresponding patterns of disrupted neuroendocrine function that align well with our model of self-regulation. Specifically, depression has been found to be associated with higher cortisol and increased CRF activity. Importantly, melancholic depression characterized by hyperarousal of negative emotion, higher anxiety, and greater focus on the self is associated with a pattern of hyperfunction of the HPA axis (Struber, Struber & Roth, 2014)

THE EXPERIENTIAL CANALIZATION MODEL OF SELF-REGULATION IN THE STUDY OF EMOTIONAL DEVELOPMENT AND RISK FOR THE DEVELOPMENT OF PSYCHOPATHOLOGY

In previous sections, we have outlined a case for the multiple ways that chronic exposure to adversity disrupts self-regulation through both top-down and bottom-up processes. In the sections that follow, we focus more specifically on the bottom-up processes of emotion regulation, through which stressors impact higher order cognitive functions and increase risk for poor longer term mental health outcomes. In the next section, we build on the idea that this model of emotion regulation can be productively understood through the lens of experiential canalization, and can be characterized as the emergence of specific and well ordered forms and behaviors that represent a progressive narrowing of developmental paths taken and foreclosed.

Three domains of emotion regulation (ER) may be particularly relevant to the experiential canalization of psychopathology including (1) the individual's attention to emotional information, (2) the capacity to comprehend and categorize that emotional information, and (3) the individual's capacity to make sense of emotional information within the self, including subjectively experienced anxiety, fear, anger, and frustration. Following the basic principle that understanding of normal development must serve as the foundation for our understanding of psychopathology, we first outline a schematic or thumbnail representation of some of the basic neurobiological and developmental processes that underlie each of these three domains of ER (see Cicchetti, 1984, 2002; Werner, 1948). We then go on to review ways that these domains are shaped by adversity, drawing from a theoretical model of experiential

canalization to highlight the ways that children's emotion regulation is shaped by chronic exposure to environmental stressors.

Attention to Emotional Information

Attention represents the gate to engagement, the key, early step to detecting, processing, and optimally responding to emotionally salient stimuli (Petersen & Posner, 2012; Posner, 1994). As noted earlier, attention processes (to both emotionally negative and neutral stimuli) are understood to be composed of three key components (see Petersen & Posner, 2012; Posner & Petersen, 1990). These include a first alerting phase (i.e., the brain's effort to handle the when of the presentation of a stimulus through vigilance), and involve key cholinergic neurotransmitters ascending through the basal forebrain (Stormer et al., 2012). The second component involves attentional orienting, where the brain focuses on location (or the where of the stimulus), involving the deployment of the parietal cortex. Finally, the third component of attention is composed of the executive network, where the DLPF and dorsal ACC are recruited in distinguishing the target stimulus from multiple competing stimuli with the involvement of multiple neuromodulators including serotonin and dopamine (Desimone & Duncan, 1995; Stormer, et al, 2012).

Humans are clearly neurobiologically and behaviorally wired to attend to stimuli that have an emotional valence, with extensive laboratory studies demonstrating that adults and children orient to emotional stimuli more quickly than to non-emotional stimuli within a given visual array (LeDoux, Mogg, & Bradley, 1997; LoBue & DeLoache, 2008; Ohman et al., 2001). These findings have been offered as evidence for ways that human attention is evolutionarily tuned to the rapid detection of threatening stimuli. Similarly, emotional information captures attention making it harder for individuals to disengage from emotionally valenced stimuli than nonemotional stimuli (Steinmetz & Kensinger, 2013).

Research demonstrates these forms of attention bias through the use of several laboratory paradigms including visual search, where the individual has to locate targets with emotionally salient vs. emotionally neutral distractors, and the dot probe paradigm, where individual has to locate targets after presentation of paired neutral-neutral versus neutral-emotional stimuli. Using these paradigms, researchers highlight the ways that emotion and attention are bidirectionally linked: For example, individuals with mood disorders (e.g., high anxiety) consistently demonstrate increased attentional bias for emotionally negative stimuli (Bar-Haim et al 2007; Waters et al., 2011). These processes emerge in early infancy, are complex and extend over a relatively long time course, with cognitive theories of anxiety suggesting initially faster orientation to threat followed by later avoidance, or suppression of attention to threat in an effort to modulate anxious mood (Nakagawa & Sukigara, 2012). Faster initial orientation to threat suggests that individuals prone to high levels of anxiety are demonstrating differences in amygdala function, processing percepts differently than non-anxious controls at the preattentive stage, that is, early in the bottom-up model of attention and emotion processing (Debiec, Diax-Mataiz, Bush, Doyere, & LeDoux, 2010; Dolan & Vuilleumier, 2003; Mogg & Bradley, 1998). This body of research on individual differences in attention bias has also highlighted the roles of rostral ACC and the lateral PFC in postattentive phase of emotion processing, where highly anxious individuals show reduced functioning of the DLPFC and consequently, in managing and shifting attention across multiple competing, or conflicting cognitive demands relative to nonanxious controls (Bishop, 2009; Bishop, Duncan, & Lawrence, 2004: Pesoa, 2009; Rueda et al., 2004).

This level of complexity across multiple components of attention (and respective activation of multiple corresponding brain regions) is important to keep in mind when mapping the development of individual differences in attention to threat. As outlined earlier, emerging research suggests that individual differences in both early facilitation of attention and later difficulty managing and shifting attention may be powerfully shaped by chronic exposure to a range of environmental stressors. Given the key role of the multiple neuromodulators listed earlier, molecular genetic processes (involving multiple polymorphisms of several candidate genes such as COMT and CHRNA4) are also likely to be involved in driving individual differences in both the early and late phases of attention bias (Posner, Rothbart, Sheese & Voelker, 2012; Vuilleumier & Pourtois, 2007). In the following section, we review ways that environmental and genetic processes may work additively and interactively to support or constrain individual differences in attention to threat.

Past research on the link between trauma exposure and later symptomatology (across diverse conditions of war, community violence, and parental maltreatment) highlight the role of the environment in altering children's development of attention, with well-replicated evidence of higher levels of difficulty shifting and maintaining

attention on clinical measures (Husain, Allwood, & Bell, 2008). Functional neuroimaging research with adults with PTSD yields consistent evidence of heightened amygdala response to rapidly presented emotional stimuli, and correspondingly, behavioral hypervigilance and exaggerated startle response (Bruce et al, 2013; Shinn et al, 2007). These findings are indicative of alterations in the early preattentive period where the "rapid and automatic alerting mechanism for responding to nonconscious signals of fear" are altered by exposure to trauma (Bryant et al., 2008, p. 518). Importantly, several studies have also yielded evidence for increased connectivity between the amygdala and other brain regions associated with the assessment of emotional stimuli and difficulties with the redirection of attention, including left and ventral anterior cingulate and medial PFC, and for hyporesponsiveness in the ventral medial PFC (Bryant et al, 2008; Liddell, et al, 2005). In short, trauma may have negative sequalae in both heightening the system responsible for initial alerting to threat and in lowering capacity for disengagement (including shifting and executive processing) occurring in the late or phase of attention deployment. These findings regarding fear circuitry from the PTSD literature are helpful in demonstrating that it may be that disruptions in both early and late phases of attention processes are at work when trauma-exposed individuals manifest tremendous difficulty in downregulating fear, once it has been triggered (Bryant et al, 2008).

For example, some previous studies using behavioral and attentional paradigms (including dot-probe tasks) demonstrate that chronic exposure to both parents' and peers' anger and aggression tunes children's attention for heightened vigilance to emotionally negative stimuli (Pollak, Messner, Kistler & Cohen, 2009; Pollak, Vardi, Bechner, & Curtin, 2005). Functional neuroimaging research with adults who experienced childhood maltreatment has also found evidence for reduced medial PFC volume, relative to nonmaltreated controls (Van Harmelen et al, 2013). Emerging work on attention bias among young children who have experienced maltreatment relative to controls has replicated some of these findings.

Higher Order Cognitive Processing of Emotional Information

A second key component of emotional self-regulation is the extent to which children appraise stimuli as angering, upsetting, or fear-inducing, that is, children's capacity to cognitively control emotionally salient conditions through top-down cognitive processing (McRae, Ochsner, & Gross, 2011). The capacity to read others' emotions is thought to have species-wide benefit, allowing individual members of a group to communicate signals of fear, anger, threat, nurturance, and appetitive desire with conspecifics in ways that promote survival and reduce the risk of predation (Damasio, 2004). Children's appraisal of others' signals (including facial expressions, vocal tone and posture) as capable of communicating emotional information has been a key area of past research: Past work has focused both on children's discrete ability to label others' facial expressions (termed declarative emotion knowledge) and to individual differences in their tendency to attribute particular emotions (such as anger) to others' intent, termed emotion processing patterns (Schultz, Izard & Abe, 2005). Not surprisingly, children's ability to identify others' emotions relies heavily, but not exclusively on the attention processes described earlier. In addition, exposure to facial stimuli produces activation in the face-selective fusiform face area (FFA) of the fusiform gyrus (see Kawasaki et al., 2012) with concomitant orienting and attending to this specific type of emotional cue. Amygdala activation also plays a central role in cognitive processing of expressions of anger and fear, with studies of lesion to the amygdala demonstrating striking deficit in the ability to interpret emotion from others' facial expression and tone of voice (Adolphs, Tranel, Damasio & Damasio, 1995; LeDoux, 1996; Vuiellemier et al, 2004).

As children transition from infancy through middle childhood, they develop increasing skill in identifying and labeling others' emotions using appropriate emotion language. Children's also demonstrate increasingly strong tendencies to read sadness, anger, or fear into emotionally ambiguous social situations and into others' intentions as they transition through early and middle childhood (Ackerman, Izard & Schultz, 2000). Children's accurate perception of emotional information has consistently been associated with adaptive social responses to peers, for example, while inaccurate perceptions of others' emotions has been predictive of children's negative attributional biases regarding others as well as feeling of failure in social situations, social isolation and loneliness (Denham et al, 1990; Fine et al, 2003; Garner, Jones & Miner, 1994: Schultz et al., 2010). Difficulty or deficits in accurately labeling emotions in others as well as heightened tendencies to attribute anger in others has consistently been found to serve as a major stumbling block for some children as they struggle to make friends and attempt to navigate emotionally intense interactions in classrooms and on playgrounds (Arsenio, Cooper & Lover, 2000; Blair & Coles, 2000; Schultz, Izard, Ackerman & Youngstrom, 2001).

Individual differences in children's cognitive processing of emotional cues (both in terms of their declarative knowledge and their proneness to attributional bias) are clearly shaped by environment. Past correlational studies of family socialization and randomized control studies of emotions curricula have implicated adults' use of emotion language, the quality of adults' care, and broader emotional climate as key contributors in shaping children's ability to accurately perceive, encode, and label others' emotions (Durlak, Weissberg, Dymnicki, Taylor, & Schellinger, 2011). Findings also clearly highlight the extent to which chronic exposure to violence within and outside the home is associated with deficits in children's cognitive processing of emotional information. Children exposed to higher levels of interparental conflict demonstrate compromised, less fully formed cognitive schema about emotions and relationships as a central feature of profiles of maladjustment (McCoy, Cummings, & Davies, 2009). Importantly, though children from high-conflict households show greater physiological arousal as well as greater behavioral distress, they perceive lower levels of angry affect when overhearing a simulated argument between adults than do children who live in low-conflict households (Cummings, Pellegrini, Notarius, & Cummings, 1989; El-Sheikh, 1994).

Consistent with the theoretical model of self-regulation in Figure 13.1 and using the lens of experiential canalization, we and others have argued that this disruption in children's perception of and response to others' emotion is undergirded by environmentally shaped neuroendocrine and neurocognitive processes: Higher exposure to the acute and chronic dimensions of threat associated with parental fighting, aggression, and violence may lead to alterations in the adrenocortical and neurocognitive response among conflict-exposed children (Blair & Raver, 2012; Davies, Sturge-Apple, & Cicchetti, 2012). Prior research suggests that, for children exposed to high levels of parental harshness and aggression, prolonged exposure to threat increases children's arousal to such a great extent that they are less able to make accurate attributions about their own and others' emotions (Kim & Cicchetti, 2010; Sullivan, Carmody & Lewis, 2009). These effects may be exacerbated by exposure to neighborhood stressors: Recent research suggests that low-income children's higher exposure to neighborhood violence is clearly associated with compromised ability to marshal attention at chronometrically slower, molar levels (as assessed by observer report) and with maladaptive patterns of attention to negative stimuli at the chronometrically faster, micro level (using neuropsychological assessments such as the dot probe) (McCoy, Raver, & Sharkey, in press; Sharkey et al., 2012). Importantly, violent crime exposure was found to be differentially related to the risk of manifesting hypervigilant versus avoidant patterns of attention depending on children's profiles of high versus low trait-based negative affectivity, illustrating the ways that these regulatory subsystems are complex, integrated, and recursive rather than independent (McCoy et al., in press; see also Solomon, O'Toole, Hong, & Dennis, 2014).

The Body as a Source of Emotional Information: Subjective Feelings of Negative Affect

Finally, children vary greatly in their struggles and successes with felt experiences of negative emotion, as indicated through large research literatures on self-reported negative affectivity (Ronan, Kendall & Rowe, 1994), negative affect regulation, self-reported state and trait anxiety, and subjective distress. The neurocognitive and affective substrata for children's emerging understanding of their own feeling states is remarkably complex, including somatosensory changes in striated musculature, and first- and second-order changes that range across several major brain regions including the amygdala, thalamic regions, and left prefrontal, as well as medial PFC and dACC regions (McKrae et al., 2011). Additional research focusing the somatic marker hypothesis underscores the role of the vmPFC in linking somatosensory information and feeling states, with individuals with lesion to that area unable to access emotionally relevant internal cues and also less able to predict the emotional consequences (whether positive or negative) of their actions (Bechara, 2004; Damasio et al., 1996). In other studies, higher levels of vmPFC have been associated with self-awareness, higher levels of processing of self-relevant emotion words, and rumination, supporting its role in individuals' ability to identify and think about their own internal states (termed interoceptive awareness; Struber et al., 2014).

Across all these literatures, the individual's conscious appraisal of his or her own affective state yields evidence that individuals can either perceive those emotions are well-managed versus overwhelming and out of control, with a sense of themselves as reasonably good at regulating emotion, or less so. Early in development, children may be less aware of their own emotional states, but by middle childhood, children can reliably report both on dispositional negative affectivity and on transient emotional states. Recent experimental evidence from studies with adults highlights ways emotional states can be internally generated through thoughts or internally evoked images, and that those emotional states are accompanied by

matching physiological responses (such as changes in eye blink startle) that support the veridicality of subjective report (Ray, McRae, Ochner, & Gross, 2010). High levels of dispositional negative affectivity have consistently been found to relate to higher levels of attention bias to threat, particularly when children have lower levels of behavioral self-control (Lonigan & Vasey, 2004).

Subjective experiences of distress (including feelings of sadness, fear, and worry) that are chronic, overwhelming, or debilitating represent hallmark symptoms of mood disorder, particularly when accompanied by the attentional and cognitive biases previously described. Bidirectional relationships between these three components of ER have been established at neuroanatomical and behavioral levels, with evidence that fear circuitry is self-reinforcing, becoming increasingly canalized over time. For children diagnosed with social phobia, for example, reported subjective experience of symptoms of physiological arousal such as blushing and elevated heart rate are not only more easily triggered and more acute than subjectively experienced by controls, but also accompanied by faulty attributional biases (e.g., that others can see their nervousness) and by heightened or excessive self-focused attention (Kramer et al., 2011). Those cognitive biases are accompanied by heightened autonomic and neuroendocrine reactivity, including disrupted patterns of sAA, HR and cortisol levels across both basal and stressor conditions (e.g., social evaluative threat tasks such as the Trier Social Stress Test) and across multiple pediatric samples (van Veen et al., 2008). Our own and others' work highlights the ways that bottom-up processes such as dysregulated feelings of self-reported trait anxiety can interfere with EF performance on standardized assessments such as Stroop and Hearts and Flowers tasks (Ursache & Raver, 2014). Additional research on the role of experienced anxiety, lower EF performance, and heightened attention to error suggests that as children get older, they not only perform less well on cognitively demanding tasks when experiencing high levels of anxiety, but their subjectively experienced difficulties with working memory and heightened attention to failure may magnify their experiences of negative emotions as overwhelming and spiraling out of control (Ramirez, Gunderson, Levine, & Beilock, 2013).

Exposure to chronic adversity has consistently been found to be predictive of earlier onset, steeper trajectories, and more acute symptomatology for a wide range of internalizing mood disorders including anxiety, depression, across multiple developmental periods from early toddlerhood through adolescence and early adulthood (Grant et al., 2003). Certainly, mood disorders such as depression and anxiety are understood to have multiple etiologies: There is a wealth of empirical emphasis for the direct and indirect pathways by which parents with genetic vulnerability to mood disorders may transmit that risk to their offspring. However, our model of experiential canalization provides a complementary neurobiologically and environmentally mediated mechanism by which conditions of high versus low adversity may substantially increase individuals' risk. That model is well aligned with developmental cascades models suggesting that cumulative exposure to high levels of poverty-related adversity is jointly predictive of profiles of externalizing behavior problems and high risk of comorbid internalizing problems from childhood through early adulthood (Herrenkohl et al., 20011; Jaffee et al., 2003; McCarty et al., 2009).

As outlined earlier, models of mood disorder and neurocognitive function have highlighted the extent to which disrupted or compromised limbic function and attention bias represent hallmarks of anxiety and depression and that those changes in neurocognitive function have been argued to reinforce individuals' dysphoria over time. Importantly, cognitive processing in the context of mood disorder has been understood as a two-way street. That is, a large number of observational and experimental studies in developmental and clinical areas of research highlight the importance of higher order cognitive processing, considered through the lenses of cognitive appraisal and coping, as a mechanism through which some individuals are able to ward off depression and anxiety and as a powerful approach to ameliorating elevated symptomatology (Lazarus & Folkman, 1984; Moos & Holahan, 2003).

Past work on rumination versus cognitive avoidance provides good examples of styles of cognitive appraisal (or coping) that have been identified as placing some individuals at greater risk for long-term trajectories of mental health difficulty relative to others. Individuals who ruminate extensively about situations and events as negative, unmanageable and uncontrollable and about themselves as less capable in handling those situations are at substantially greater risk of higher levels of depressive symptoms and more frequent bouts of depression over time, even after controlling for symptomatology at baseline (Lyubomirsky, Tucker, Caldwell, & Berg, 1999; Nolen-Hoeksema, 2000; 1999) Alternately, individuals struggling with high levels of distress and fear may resort to cognitive styles of coping that involve cognitive avoidance, characterized by high mental effort not to think about the problems, events, or situations that are understood as sources of worry or sadness. In contrast, individuals able to maintain shift and persist involving realistic appraisal of obstacles and

challenge with long-term positive outlook or confidence in long-term persistence or success in overcoming of those obstacles strategies of cognitive appraisal have been found to weather major stressors with lower vulnerability to health and mental health problems, than other individuals facing similar psychosocial challenges (Chen & Miller, 2012). Importantly, treatment involving shifts in cognitive appraisal serve as the foundation of much cognitive behavioral therapy (CBT) and have been found consistently in meta-analyses of randomized control trials to be effective in lowering the odds of mild and moderate depressive symptomatology in childhood adolescence, and adolescence (Harrington, Whittaker, Shoebridge, & Campbell, 1998; Jakobsen et al., 2012) as well as in reducing the risk of relapse after pharmacological treatment of depression (Paykel, 2007).

Recent work integrating interpersonal and psychobiological perspectives highlights the ways that multiple systems can interact to alter individuals' HPA axis reactivity and chances of long-term mental health problems in the face of chronic exposure to stress (Cacciopo et al., 2002; Gianaros & Hackman, 2013). Specifically, emerging work on the stress-buffering role of social support in both animal and human models suggests that social interactions suppress stress-responsive HPA reactivity through direct and indirect mechanisms. For example, the presence of socially supportive conspecific or romantic partner during stressful conditions such as the TSST has been associated with increased release of the neuropeptide oxytocin, which in turn has been found in both rat and human randomized controlled trials to significantly lower HPA axis activity in the face of experimentally induced stress (Heinrichs et al., 2009; Struber at al., 2014). Research in this area has been complicated by difficulty of measuring oxytocin peripherally: in several recent studies, positive tactile contact from a socially supportive partner has been found to substantially reduce cortisol levels and heart rate for adults during stressful lab procedures but not to reduce plasma levels of oxytocin (Ditzen et al., 2007). Additional work on the salutary effects of parents' provision of positive caregiving on lowering HPA reactivity through mediating mechanisms of oxytocin in children is promising and is reviewed now. Across this range of social interactions, theoretical and empirical perspectives have emphasized the need to consider both transitory and longer term consequences of positive provisioning of care: results yielded from longer term studies of individuals exposed to early trauma and prolonged periods of deprivation suggest the likelihood of inhibition of oxytocin receptor expression. In contrast, supportive caregiving during early periods in the context of adversity may facilitate long-term patterns of adaptive HPA axis response mediated through longer term changes in serotonin and oxytocin expression (Struber et al., 2014).

Theoretical and Methodological Challenges and Innovations

One strength of the model that we have outlined is that it underscores developmental plasticity and malleability, for good or for ill, rather than trait-like fixity in considering the dynamic attentional, cognitive, and neuroendocrine processes involved in making sense of one's emotional world. On the other hand, one grave implication of this model consistent with the developmental science principle of correlated constraint is that individuals undoubtedly contribute to the reinforcement or canalization of their own emotion regulatory trajectory by selecting, structuring and reappraising emotional information from social interaction and by subsequent patterns of approach versus withdrawal from those social interactions (Cicchetti, 2002). The implications of this theoretical shift are immense: Through this lens, for example, feedforward models of fear circuitry would need to be reexamined across both neurobiological and biobehavioral strata. How does the responsiveness of those early components of the alerting and orienting mechanism develop, over time, increasingly constrained by prior development and experience, as an anxious child, for example, increasingly opts out of new and potentially frightening social contexts? At the neuroendocrine level, we also know less about ways that individuals who experience higher levels of anxiety in socially ambiguous situations may effectively reduce opportunities to learn to entrain HPA axis regulation of high arousal by avoiding social engagement. In short, models of canalization underscore the extent to which processes of self-regulation are self-organizing. Yet we have only just begun to consider ways that those systems are interrelated, along multiple neurobiological, representational, and behavioral strata.

A major problem in research on self-regulation and psychological development in the area of emotions research is the failure to replicate across samples facing varying levels of environmental risk, varying types of stimuli, and varying age groups. For example, studies that have explored attention bias have often used stimuli that are of human faces, with depressed and anxious individuals more prone to attend to emotionally threatening stimuli (see for example, Waters et al, 2011 where children ages 9 to 12 and high though not clinical levels of anxiety showed clear attentional bias for angry versus neutral faces on

dot-probe, with stimulus duration ranging from 500 to 1250 ms). Yet other studies find that children with high levels of anxiety may be more prone to demonstrate avoidance of threat, rather than bias toward (or hypervigilance for) threatening stimuli. This may be because higher acuity in detecting negative stimuli may arise from multiple sources that are themselves nonlinear—exposure to moderate levels of conflict or threat, for example, may tune the attentional system to be more alert, more vigilant, and the PFC to be more actively mobilized to resolve conflicting system in order to promote the capacity to act. On the other hand, exposure to high levels of threat may lead the system to a pattern of blunted, avoidant, or hyporesponsive profile.

Second, the process of attention, interpretation, and somatosensory response to threat occurs over a time course that is rarely accounted for in extant emotion regulation research. Temporally early bottom-up attention processes in handling threatening, emotionally arousing information may be facilitated (as reflected in behavioral measures) for individuals chronically exposed to threat, while top-down, temporally late-breaking processes (such as memory, retrieval, and labeling of emotion terms) may be disrupted by high levels of stress and among individuals experiencing high threat. Those individuals exposed to very high levels of anxiety may show correspondingly lower performance on behavioral measures that tap complex processes involved in recognizing, identifying, and correctly naming facial emotions (Henckens, van Wingen, Joels, & Fernandez, 2012). Research in this area is still nascent: we are not yet able to carefully parse neurobiological, neuroendocrine, and behavioral responses across a microanalytic time course in ways that yield consistency in our findings.

Thirdly, with respect to developmental time course, the model of self-regulation indicates the need to identify and track processes that are occurring very early in development, at conception and over the first year, and to consider self-regulation intergenerationally. Emotion and attention in infancy have been studied extensively in their own right, but few studies, with the exception of the research on temperament of Rothbart, Posner, and colleagues (Posner & Rothbart, 2000) have studied relations between the constructs developmentally. As well, although the role of caregiving in early development has been the primary stock in trade of child development researchers, few programs of research have focused on the psychobiology of caregiving and the way processes of self-regulation in caregivers influences both the biological and experiential environment in which child development takes place.

THE ROLE OF EARLY CAREGIVING IN THE EXPERIENTIAL CANALIZATION MODEL OF SELF-REGULATION: IMPLICATIONS FOR RISK AND RESILIENCE IN DEVELOPMENTAL PSYCHOPATHOLOGY

In the foregoing sections we have outlined processes of self-regulation development as a function of multiple levels of influence, focusing primarily on the internal processes of the experiential canalization model of self-regulation. In the following sections we turn to external influences that are presumed to shape development through experiential input. As noted in the earlier sections, a primary shaper and canalizer early in development is thought to be stress hormones and a primary environmental influence on hormone levels is thought to be experience with caregivers. Information about the environment is transmitted to developing offspring, prenatally and postnatally through maternal experience and behavior. As such, in the experiential canalization model, parenting behavior is presumed to be a central if not the central mechanism through which information about the quality of the environment is communicated to the developing child. Notably, the psychobiological system is multigenerational and recursive. The primary caregiver is itself a self-regulating psychobiological system and caregiving a product of the caregiver's psychobiological makeup and developmental history. The model in Figure 13.1 applies as readily to the parent as to the offspring. Here, inheritance must be understood broadly—that what is passed on from parents to offspring is not only a biological inheritance or an environmental inheritance but an interactive psychobiological system, an interacting manifold of biology and experience (Gottlieb, 1997).

The Neuroendocrinology of Maternal Behavior

Given the psychobiological nature of parental behavior and influence (Corter & Fleming, 2002; Rosenblatt, 1994), the experiential canalization model provides one framework for understanding the intergenerational transmission of risk for the development of psychopathology. In the parent as in the offspring, stress hormones are a primary influence on maternal behavior with implications for child physiology and behavior. A number of key hormones are involved in the maternal response to infant stimuli including cortisol, oxytocin, dopamine, and endogenous opioids, which facilitate and regulate typical maternal behaviors (for review see Swain et al., 2011). In their review of the literature, Swain and colleagues (2011) used the example of

the maternal behavioral response to a baby cry to illustrate how multiple hormonal influences come online to facilitate maternal behavior in the course of a typical interaction between mother and child. In this example, dopamine and oxytocin are the first to engage in response to baby cry, and promote maternal action by focusing attention and decision making on the part of the mother. In response to infant suckling, oxytocin is involved in milk ejection during lactation. Subsequent to the initial response of dopamine and oxytocin, the HPA axis regulates maternal behavior in ways that vary as a function of life stressors, postpartum time, age, and parity status. Once resolution is reached, endogenous opioids promote relaxation, and in addition, reinforce maternal behaviors via reward circuitry. Importantly, each step in this behavioral and psychobiological cascade must be situated in context; each step is a point of inquiry and intervention.

The relation between the HPA axis and maternal thoughts and actions is complex, however, given that it varies as a function of the personal history of the mother, her parity status, and time since parturition (Barrett & Fleming, 2011). For instance, resting levels of cortisol measured within the first four postpartum days are positively associated with increases in affectionate behaviors in mothers (Fleming, Steiner, & Anderson, 1987) as well as with a mother's increased attraction to her infant's odors (Fleming, Steiner, & Corter, 1997). These findings suggest that maternal HPA axis activity during the first postpartum days may enhance the salience of infant cues and in turn increases sensitive caregiving by mothers (Fleming et al., 1997). The direction of association changes between cortisol levels and maternal behavior in the months after parturition, however. Specifically, heightened cortisol levels at 3 months postpartum are associated with negative mood and fatigue in middle-aged mothers (Krpan, Coombs, Zinga, Steiner, & Fleming, 2005), and cortisol reactivity at this time has been related to less synchronous or sensitive behaviors with infants (Thompson & Trevathan, 2008). Increases in basal cortisol levels at 6 months postpartum are associated with increases in negative and intrusive behaviors with infants (Mills-Koonce et al., 2009).

It is also critical to keep in mind the environmental and social origins of maternal physiological dysregulation and parenting behaviors. As an example, interparental avoidance in marital relationships is positively related to cortisol reactivity in mothers, which, in turn, is related to increases in psychologically controlling parenting behaviors and inconsistent discipline of children (Sturge-Apple, Davies, Cicchetti, & Cummings (2009). In addition, experiencing adversity in early life, including experiencing inconsistent care or maltreatment by past caregivers, is related to higher levels of diurnal cortisol in mothers as well as with decreases in maternal executive functions (Gonzalez, Jenkins, Steiner, & Fleming, 2012), both of which mediated the relation between early life adversity and maternal sensitivity in adult mothers. Thus, the context of physiological stress is an important component of the psychobiological relation between maternal physiology and behavior. It is clear that biological as well as experiential influences critically shape maternal behaviors that have powerful downstream implications for child development.

Development of the Caregiving System

Typical and atypical development of the caregiving system is mutually informative. The early parent–child relationship provides a foundation upon which child development proceeds, from early influences on emotion and attention and the stress response, with implications for gene expression, brain growth and development, and emerging higher order cognitive abilities (Blair & Raver, 2012). As described in a previous section, the canonical example of the experiential canalization model of development is found in the effect of maternal behavior in the rat on stress physiology and behavior in offspring (Francis, Diorio, Liu, & Meaney, 1999; Liu et al., 1997; Weaver et al., 2004). Cross-fostering studies highlight the psychobiological factors accounting for the intergenerational transmission of the stress response in rats. Specifically, the adult biological offspring of low licking and grooming (LG) and low arched back nursing (ABN) mothers who were fostered by high LG-ABN mothers show significantly reduced fear response to novelty and additionally, exhibit increased LG-ABN behaviors themselves compared with adult offspring from high LG-ABN mothers who were fostered by low LG-ABN mothers (Francis, Diorio, Liu, & Meaney, 1999). Thus, rearing experiences with caregivers in very early life contribute to the intergenerational transmission of both stress response and maternal behaviors later in adulthood. Indeed, this multilevel epigenetic process from maternal behavior down to the genetic level and back again to the behavioral, presents both a top-down and bottom-up process of the shaping of biology by experience—the central tenet of the experiential canalization model.

The example of cross fostering is very interesting in that it highlights the potential plasticity of the developing self-regulation system early in life. Alterations to experience can shape the developing system in ways that are likely to lead to a prototypically well-regulated profile or to a more reactive and less well regulated behavioral

profile that can predispose to psychopathology. An important point here, however, is the rapidity with which this developmental process unfolds. The influence of maternal behavior on the outcomes of adult offspring in the rat model unfolds over the first 8 postnatal days. This is a remarkably short period that is presumably specific to rats. The historical emphasis on early experience in child development, however, perhaps extending over the first year or more, is consistent with such a rapid effect. The presence of such an early occurring effect, however, does not preclude the possibility of later malleability. Indeed, in the developmental psychobiological model, earlier occurring processes shape later processes, propagating an essentially conservative nature of development, referred to in the principle of correlated constraint. Reorganization of the system is possible, however, and has been demonstrated in the LG-ABN rat model through environmental manipulations occurring in the immediate post-weaning period (Meaney, 2001). In the cross-fostering example, pups of low LG-ABN mothers reared by high LG-ABN mothers exhibited behavior similar to the biological offspring of the high LG-ABN mothers (Francis et al., 1999a). In another example, low LG-ABN mothers increased LG and ABN when their pups were briefly handled, an expected result, and these animals exhibited high LG-ABN themselves as mothers, providing evidence of the causal role of experience in shaping later behavior (Francis et al., 1999b).

While the effects of maternal behavior on development in the rat model have been shown to persist into adulthood, these effects have been shown to be functionally reversible. Specifically, Francis and colleagues (Francis, Diorio, Plotsky, & Meaney 2002) have shown that the effects of maternal separation on HPA-axis reactivity and behavioral responses to stress are attenuated in maternally separated rat offspring reared in enriched environments during the peripubertal period. The authors highlight, however, that this reversal in stress response physiology and behavioral response associated with enriched environments is not mediated by the reversal of underlying neural mechanisms (i.e., gene expression) but rather, that activity of brain areas including the PFC and hippocampus may play a role in compensating for earlier life stress (i.e., maternal separation). Similarly, Bredy, Humpartzoomian, Cain, and Meaney (2003) demonstrated that the effects of low maternal caregiving competence on hippocampally dependent learning and memory could be reversed at the behavioral level through environmental enrichment, but that the physiological function of the hippocampus was not altered in expected ways. Thus, the effects of environmental enrichment in functionally reversing the negative effects of maternal separation and low maternal caregiving competence occur on some levels of analysis but not others. This is consistent with the psychobiological perspective on the development of self-regulation, which not only highlights the considerable plasticity of the developing self-regulation systems at the neural and behavioral levels, but also the idea that these systems, in and of themselves, should not be considered at isolated levels of analysis, but rather, at multiple levels of analysis ranging from the genetic, to the neural and physiological, to the behavioral.

The Prenatal Period

Given the emphasis on malleability but also concerning the essentially conservative nature of development, it is important to consider how influences on the maternal psychobiological state may shape the developing psychobiological state of the offspring from conception onward. The prenatal environment influences both offspring embryological development as well as postnatal development through the influence of the HPA axis (Barbazanges, Piazza, Le Moal, & Maccari, 1996a; O'Donnell, O'Connor, & Glover, 2009). The fetal programming hypothesis suggests that during sensitive periods in utero, the placenta affects fetal development in ways that are adaptive for future environments, as it is a proximal indicator of the external environment. In the case of low-resource, stressful environments, the evolutionary significance of the fetus' interaction with proximal (placental) and distal (external) environments is that insults to the fetus may adaptively prepare offspring for potential harsh external environmental conditions. Research on maternal stress during the prenatal period in humans and non-human animals indicates effects on behavioral and physiological aspects of the development of the stress response in offspring with substantial implications for the development of psychopathology. One pivotal mechanism by which prenatal stress is passed on to offspring is via secretion of corticosterone from mother to fetus through the placenta. Indeed, blocking maternal secretion of corticosterone prenatally resulted in no difference between offspring of prenatally stressed and nonstressed mothers, suggesting a mechanism of stress transmission via corticosterone placental transfer (Barbazanges, Piazza, Le Moal, & Maccari, 1996b). Neurophysiologically,, high prenatal maternal stress is associated with decreased glucocorticoid receptor (GR) density in the hippocampus (Maccari et al., 2003), which may compromise negative feedback regulation of glucocorticoids (Sapolsky, Meaney, & McEwen, 1985). Behaviorally, prenatally stressed rats display abnormalities

in social behavior and dysregulation of the HPA axis and these outcomes are mediated by heightened levels of corticotrophin-releasing hormone (CRH) in the amygdala, reduced hippocampal GR density, and attenuated endogenous opioid GABA/BZ inhibition (Weinstock, 1997). Maternal stress in both the prenatal and early postnatal environment is associated with physiological and behavioral outcomes in rat offspring, and in both scenarios, the influences of biology and environment are intertwined in an irreducible way.

Research on the effects of maternal stress in the prenatal period in humans suggests processes similar to those seen in animal models. Buss and colleagues have shown that prenatal maternal anxiety specifically regarding pregnancy is related to both decreased gray matter density in the PFC (Buss, Davis, Muftuler, Head, & Sandman, 2010) as well as to diminished executive function abilities (Buss, Davis, Hobel, & Sandman, 2011) in child offspring at 6- to 9-year longitudinal follow-up. Maternal prenatal psychological distress and anxiety have been associated with infant temperament (Huizink, Robles de Medina, Pascale, Mulder, Visser, & Buitelaar, 2002) cognitive impairment (Mennes, Stiers, Lagae, & Van den Bergh, 2006), ADHD, anxiety, and externalizing problems in children (Van den Bergh & Marcoen, 2004) and with flattened diurnal cortisol patterns associated with depression in females (Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2007).

Motivational Model of Maternal Behavior

In addition to the mechanism of transmission associated with stress physiology and effects of glucocorticoids on the developing brain, the shaping of self-regulation development in offspring postnatally is of course predominantly shaped by caregiving behavior. In addition to passing on elevated stress levels and an HPA axis that may be less effective in regulating stress hormones within an optimal zone, caregivers under stress shape offspring behavior through caregiving behaviors that may provide limited support for the development of prototypically optimal self-regulation. Caregiving behavior is itself shaped by an underlying neurobiology that influences offspring development for good or for ill.

As reviewed by Numan (2006), animal models support a motivational model of maternal behavior, whereby the medial preoptic area (MPOA) of the hypothalamus and the neighboring ventral bed nucleus of the stria terminalis (vBST) regulate maternal behavior in the presence of infant stimuli by inhibiting competitive avoidance motivations and increasing approach–response motivations, via downstream projections inhibiting a competitive medial amygdala (MeA) to periaqueductal gray (PAG) circuit and activating dopaminergic mesolimbic circuitry involving the ventral tegmental area (VTA) and nucleus accumbens (NA), respectively (Numan, 2006).

Here, as with the experiential canalization model of self-regulation in children, hormones are the essential mechanisms through which the development of the maternal response is understood to be shaped. Maternal behavior in rats is exhibited directly after parturition (Numan, 2006) and in contrast virgin rats do not immediately display maternal behavior in the presence of pups (Fleming & Luebke, 1981; Fleming, Vaccarino, & Luebke, 1980) due to their lacking the necessary hormonal shift occurring in the late prepartum period. Thus, the experience of giving birth to offspring critically primes the mother for childrearing. The hormonal mix during the peripartum period includes a dramatic decrease in the hormone progesterone and simultaneous increase in estradiol and lactogen hormones, responsible for the regulation of maternal behavior (Numan, 2006; Numan & Insel, 2003). As evidence for this, injection of the hormones at levels similar to those found during the peripartum period induces maternal behavior in virgin rats, suggesting the integral role that neurohormones play in the transition to parenthood (Numan, 2006).

Similar to the above mechanisms of motivation and attachment in mothers, attachment and odor preferences on the part of offspring can be formed even in the instance of very low quality care and abuse. Specifically, Sullivan and colleagues have shown that infant rats learn preferences for maternal odor that are accompanied by a neurobiological mechanism in which the locus coeruleus is hyperfunctioning, sending large amounts of norepinephrine (NE) to the olfactory cortex to ensure that a preference for the odor of the mother is formed (Landers & Sullivan, 2012). For rats, this is a primary means by which attachment to the mother is formed. As a consequence of this neurobiological cascade, infant rats have a reduced ability to acquire learned aversions during this time and do not regularly learn aversions until post weaning age. At that age, corticosterone increases and begins regulating amygdala function, which is useful at an age that is characterized by life in and out of a nest. Notably, attachment is formed in infants regardless of the quality of the care received; even maltreated infants successfully form attachments. These findings are significant within the lens of experiential canalization, where early experiences shape expectations of future environments. That the process of attachment is robust enough to persist

even in contexts of pain or adversity—where instead of avoiding the mother, the infant remains in close proximity to, and learns from the mother—is consistent with what is known as the maternal provision model (Cameron et al., 2005). This neurobiological mechanism of attachment is therefore essential for learning in early life.

Animal and human models illustrate a critical multisystem psychobiological shift during the peripartum period in neuroendocrine and neural architecture that set the stage for the initiation of maternal behavior with consequences for offspring development. This maternal behavior is guided by the motivation to perceive infant stimuli and to provide necessary care. However, parenthood in humans is qualitatively more complex than in animal models. Research on the neural substrates of parenting in humans is beginning to expand upon what is already known about the transition to parenthood in animal models (Kim, Leckman, Mayes, Feldman, et al., 2010; Lambert & Kinsley, 2012; Swain, 2011). In humans, structural maternal brain changes occur over the postpartum period. Specifically, Kim and colleagues (2010) compared magnetic resonance images of brain volumes during the early postpartum (2–4 postpartum weeks) and in the later postpartum (3–4 postpartum months) and found increases in gray matter in prefrontal cortex (PFC), parietal lobes, and midbrain. Moreover, the authors show that increases in gray matter volumes in hypothalamus, substantia nigra, and amygdala were related to positive perceptions of infants (Kim et al., 2010). These neural and behavioral developments taking place over the first postpartum year in mothers are thus the result of a combination of neurobiological and experiential input, consistent with the psychobiological model.

Research highlights specific neural circuits involved in typically occurring maternal behavior in response to experience with implications for ways this circuitry might result in atypical maternal behavior (Champagne & Meaney, 2006; Jans & Woodside, 1990; Nephew & Bridges, 2011; Terkel & Rosenblatt, 1971). Gestational stress is associated with decreases in maternal licking and grooming behaviors in high LG-ABN dams, but not in low LG-ABN dams (Champagne & Meaney, 2006). Additionally, after a gestational stress condition, oxytocin receptor binding (OTR), which is typically increased in high LG-ABN dams, decreases to levels comparable to that of low LG-ABN dams (Champagne & Meaney, 2006). Additionally, thermal factors, access to resources, and social stressors disrupt maternal behaviors including nest building and time spent with pups and also affect the growth of dams and pups (Jans & Woodside, 1990; Nephew & Bridges, 2011; Terkel & Rosenblatt, 1971).

In humans, studies have begun to investigate the maternal brain response to infant cues such as pictures or baby cries (Lorberbaum et al., 2002; Swain, Lorberbaum, Kose, & Strathearn, 2007; Swain, 2011). The canalization process, through which maternal behavior and child behavior are reciprocal and mutually reinforcing, suggests that maternal sensitivity in perceiving infant stimuli will be shaped by the combined action of experience and biology. Using fMRI, the typical response to standard baby cry versus white noise is associated with activity in the medial thalamus, medial prefrontal cortex and right orbitofrontal cortices, hypothalamus, midbrain, dorsal and ventral striatum (Lorberbaum et al., 2002). These areas are broadly involved in key decision-making, planning, reward/punishment circuits, and are likely critically involved in the motivation circuitry defined earlier in rodent models (Numan, 2006).

Importantly, infants' neuroendocrine and behavioral response has been found to be altered dramatically by the presence or absence of supportive maternal caregiving. Just as mothers' olfactory sensitivity to infant odors likely increases provisioning of care, infants are sensitive to odors expressed from the nipple, with increased suckling following exposure to maternal odors, and with memory for odors regulated by oxytocin released in the infant's brain while suckling (Nagasawa et al., 2012). Theoretical and empirical traditions that highlight dyadic synchrony at behavioral levels have been extended to examine psychobiological attunement during the course of social interaction between caregivers and offspring (Feldman et al., 2010; Laurent, Ablow, & Measelle, 2012). Among a sample of 86 low-income mothers and their 18-month-old infants for example, increases in mothers' cortisol/sAA predicted increases in infants' cortisol/sAA across two different stressors (e.g., separation episode or LabTab fear/frustration tasks; Laurent et al., 2012).

It is important to note that evidence for attunement (i.e., a moderate to strong correlation between maternal and infant trajectories of cortisol) has been found for some but not all studies (note Hibel et al., 2009, with reported correlation of $r = .01$ versus Atkinson et al., 2012 with reported correlations in the $r = .40$ to .62 range). One reason for this variability in findings may be due to the moderating role of maternal sensitivity, with significantly higher values for cortisol and sAA attunement found among highly sensitive caregivers as relative to their less sensitive counterparts (Atkinson et al., 2013). Another source of difference across these studies may be the use of alternate stress paradigms to assess child and maternal reactivity. In exploring the possible role of stressor type and the extent of stability across contexts, Atkinson et al. (2013)

report greater intraindividual variability in child HPA axis activity across multiple stressor paradigms (separation and frustration) for children of more sensitive caregivers, while children of less sensitive caregivers demonstrated weaker and less variable responses to both stressors, over time. Building on these findings, Hibel and colleagues (in press) found in a predominantly low-income prospective longitudinal sample that mother–child adrenocortical attunement is disrupted in response to a child stress task and that both maternal sensitivity during free play and child emotional reactivity elicited during a stress task moderate the strength of attunement. Whereas reductions in attunement in response to the stress task were evidenced by dyads in which mothers engaged in low amounts of sensitivity, attunement in dyads of highly sensitive mothers was moderate and stable across the stress task. This finding provides evidence that maternal sensitivity may buffer the otherwise disruptive effects of stress on attunement.

LONGITUDINAL EVIDENCE IN SUPPORT OF THE EXPERIENTIAL CANALIZATION OF SELF-REGULATION AND RISK FOR THE DEVELOPMENT OF PSYCHOPATHOLOGY

Given the wide variety of influences and levels of analysis that self-regulation encompasses, it is not surprising that there are numerous research literatures related to the topic, particularly in adults (e.g., Vohs & Baumeister, 2011). We have focused on relevant literatures on the early development of emotion, attention, executive functions, and stress physiology, relying on correlational and experimental work, much in nonhuman animal models. We now turn to three prospective longitudinal examples that provide some empirical evidence in humans in support of the experiential canalization model. We conclude with examples from prevention research in which efforts to foster self-regulation development and prevent the development of psychopathology provide key tests of the theory of the experiential canalization of self-regulation development.

Longitudinal studies highlight the value of looking across levels of analysis and suggest the extent to which change in experience through typically occurring variation can alter developmental trajectories in specific ways. Our own work on the experiential canalization of self-regulation has been conducted through a project funded by the National Institute of Child Health and Human Development of the U.S. National Institutes of Health, known as the Family Life Project (FLP). Through the FLP, we have been following a population-based sample of 1,292 children and families recruited at birth. The sample is located in predominantly rural and low-income communities in the United States (in Northern Appalachia and the Southern Black Belt) and the participating children and families have been seen in home visits for data collection at approximately annual intervals between the ages of 7 and 60 months. Children have also been seen at school from prekindergarten through the second grade.

One component of the FLP is designed to assess the development of emotion, attention, and executive functions in early childhood. During home visits for data collection when children were 7, 15, and 24 months of age, data collectors implemented protocols to assess emotional reactivity and regulation in response to fear and frustration evoking challenges and collected saliva samples from the children before and after the emotion challenge procedures. The samples were later assayed for cortisol and alpha amylase in order to examine physiological reactions to stress. Cortisol, as noted above, is a glucocorticoid hormone and indicator of activity in the HPA axis. Alpha amylase is a surrogate marker of norepinephrine, and as such an indicator of the faster acting sympathetic adrenal system.

With these data, we first examined the idea that the quality of early experience would shape the development of stress response physiology in ways that are consistent with the experiential canalization model. Here we focused on the quality of parenting that children received as a proximal indicator of the quality of the environment. In one analysis (Blair et al., 2008), we found a relation between the mother's style of parenting and the infant's cortisol levels at 7 months of age. Here, we found that infants whose mothers supported and scaffolded their child's play, meaning that that they were neither too intrusive nor too detached, had lower levels of cortisol than infants whose primary caregivers exhibited less scaffolding and support for the child's play. Importantly, we also found that 7-month-old infants whose mothers displayed the positive parenting style were more likely to exhibit a cortisol response to the emotion challenges. Children of mothers with the more supportive parenting style exhibited a larger increase followed by a decrease in cortisol, indicating a flexible and prototypically healthy response to the stress of the emotion challenge. As well, the amount of increase and decrease was associated with the level of emotional reactivity observed behaviorally. The physiological and behavioral responses are presumed to be one in which the organism prepares itself to deal with the challenge of the emotion inducing contingency but then returns to baseline following this challenge. In contrast, children whose mothers did not show the sensitive pattern had higher initial cortisol levels and tended to exhibit either a flat or blunted

response to the emotion challenge despite high levels of emotional reactivity to the challenge.

Following the sample longitudinally, we found that at age 15 months, children receiving higher levels of positive parenting in infancy at age 7 months, maintained lower cortisol levels and were more likely to exhibit lower overall cortisol levels in response to the same emotion challenges implemented again at this later time point. These results demonstrated that typical aspects of the parenting that children receive, namely, positive scaffolding and active encouragement of children's play behavior, are shaping or canalizing the development of the stress response system as indicated by levels of cortisol.

Given expectations for relations between the regulation of cortisol and executive functioning, we next sought to chart the complete path in environmental disadvantage in the context of poverty from parenting to stress regulation to executive functions. In this analysis we examined whether the development of executive function abilities in the sample was consistent with the predictions of the experiential canalization model. That is, we examined executive function at age 3 years in relation to demographic characteristics associated with poverty (income, race, maternal education, crowding and safety in the home) as well as parenting behavior and baseline cortisol levels measured at 7, 15, and 24 months of age. Using covariance structure modeling, we found that the effects of poverty on executive function ability were mediated through both parenting and cortisol, over the child's first two years (Blair et al., 2011). Notably, in support of the experiential canalization model of self-regulation development, we found that the effects of poverty on cortisol levels, and by extension executive function abilities, were mediated through positive aspects of parenting behavior. Primary caregivers (in almost all cases the child's mother) living in poverty were less likely than their more affluent counterparts to exhibit the positive parenting style characterized by support for and scaffolding of their child's play. In turn, lower levels of the positive parenting style were associated with a higher level of cortisol, which was in turn inversely related to child executive function at age 3. Positive parenting was also directly related to executive function in children. These results indicated that in addition to directly affecting child executive function, sensitive parenting also influenced the development of children's executive function abilities through child cortisol.

In a subsequent analysis with the Family Life Project data, we examined further the relation between stress physiology and executive function and also between stress physiology and early academic abilities, such as knowledge and reasoning ability in mathematics as well as knowledge of letters, sounds and early reading ability. In the examination of stress physiology we expanded our analysis to include sAA as an indicator of activity in the sympathetic adrenal system. Consequently, we expected that baseline levels of cortisol and sAA might show an interactive pattern in relation to executive function. That is, lower cortisol levels but higher sAA levels, indicating an attentive and prepared orientation to experience might be a more optimal physiological state conducive to executive function. Conversely, simultaneously high or low levels of both cortisol and sAA might reflect an over or under aroused state. As expected, again using covariance structure analysis, we found that high levels of sAA and low levels of cortisol at each time point of measurement in infancy and early childhood, 7, 15, and 24 months of age, were associated with a higher level of executive function ability as measured by our test battery. Conversely, simultaneously high or low levels of these stress markers were associated with poor performance. There was also some indication that higher cortisol but lower sAA was also associated with a higher level of executive function than simultaneously low levels. Finally, we found that cortisol and sAA were also related to the indicator of academic ability but that this relation was fully mediated through executive function abilities (Berry et al., 2012).

In the realm of emotion recognition and emotion regulation, analyses of Family Life Project data suggest that higher levels of physical aggression between parents during the period from infancy through early childhood, chronic exposure to chaos in the household and income poverty, could each be empirically distinguished as additive and statistically significant contributors to 58-month-olds' ability to recognize, interpret, and modulate negative emotion (Raver, Blair, Garrett-Peters, and FLP Investigators, in press).

Although the model of experiential canalization and self-regulation development emphasizes development early in life, from conception onward, notable longitudinal examples of the combined action of biology and experience are also seen in young adolescent high-risk samples. Analyses from these samples indicate the ways that the environment of poverty shapes physiological processes with implications for physical and mental wellbeing. For example, in a rural poverty sample, elevated stress physiology as assessed by a cumulative index of allostatic load composed of overnight levels of catecholamines (dopamine, norepinephrine) and cortisol from urine and body mass index at ages 9 and 13 years was positively related to an index of psychosocial risk in poverty in

childhood and negatively related to a measure of working memory at age 17 years (Evans & Schamberg, 2009). Findings from this sample also indicated, however, the extent to which sensitive maternal behavior can influence development. At child age 13 years, it was shown that the relation between risk from poverty and allostatic load was moderated by maternal sensitivity. In adolescent children of mothers rated as sensitively responsive, no association between risk and allostatic load was observed. It was only among children of mothers low in sensitivity that the relation between cumulative risk and allostatic load was observed (Evans, Kim, Ting, Tesher, & Shannis, 2007).

Similar findings have been observed for an adolescent sample of African American youth in rural communities. Here, however, relations between risk factors associated with poverty and mental and physical health outcomes were moderated by genetic variation. Combinations of high life stress and specific genes associated with dopamine and serotonin function (e.g., DRD4, 5-HTTP) act to increase or decrease the likelihood that stress will lead to mental health problems (Simons et al., 2011). Several general findings of analyses from this sample are notable from the perspective of experiential canalization. One is that in the analysis of the moderation of life stress by DRD4 in the prediction of aggression, effects were mediated by individual's cognitive schemas and subjective experience of emotion (hostile attribution, anger). This provides some evidence for the shaping of psychological state through the combined action of biology and experience with implications for behavior and risk for psychopathology. This finding also suggests that alterations of cognitive schemas and emotional states might act as an effective intervention for the prevention of aggression and its attendant consequences and that effects would be greatest for those with greater genetic susceptibility. Indeed, in intervention trials with this sample, the investigators demonstrated such genetic moderation of intervention effects in evaluations of programs to reduce aggression and substance use by fostering positive parent-child interaction (Brody, Chen & Beach, 2013; Brody et al., 2013). Finally, also of relevance in this sample is the indication that genetic susceptibility can also affect resilience. That is, in the sample, despite high risk, relatively few individuals exhibited high levels of behavior and substance use problems, denoting a high level of resilience. Among the proportion of the sample exhibiting resilience, however, those with the short allele of the serotonin transporter gene (associated with lower serotonin transporter availability) also tended to exhibit elevated indicators of stress physiology (high allostatic load) and high levels of health problems (Brody, Yu, Chen, et al., 2013) despite healthy psychological functioning.

CONCLUSIONS AND IMPLICATIONS FOR FUTURE RESEARCH AND INTERVENTION

In the previous sections of this chapter, we have drawn upon several examples from human and animal models of self-regulation that underscore the idea that individuals develop though combined biological, maturational, experiential, behavioral and cultural strands that are fused in ontogeny. Biology is found in these examples to influence and be influenced by behavior through complex interactions and pathways that have only recently become clear. In some ways, the complex integration of biology, behavior, and interpersonal interaction implies constraints on the range of developmental pathways taken. Caregivers' provisioning for infants, and infants' subsequent development of self-regulation, is clearly shaped not only by the best of parents' intentions, but also by neuroendocrine processes that are breathtaking in the directness and precision of the mechanisms involved. Overall, however, we find across numerous examples that developmental paths are far more complex, circuitous, and open to environmental forces both for good and for ill than is generally assumed. That is, we have dramatically diverged from simpler arguments regarding whether nature or nurture has the upper hand in shaping development. Instead we find that exposure to multiple forms of experience shapes development through complex and conditional relations among variables at multiple levels of analysis. This complexity and conditionality signals four key conclusions.

First, we are only at the beginning of the path to multidisciplinary scientific discovery needed to understand human developmental processes. At various moments it is easy to become daunted by the forest of research literatures covering the neurobiological and behavioral mechanisms related to self-regulation, across animal, infant, child, and adult literatures emphasizing development in typical, at risk, and atypical populations. To find a way through the wilderness, we will need collaborative teams of scholars from disciplines as diverse as neuroscience, biological anthropology, epidemiology, and behavioral health research among many others, united under the conceptual framework of developmental science. We will need appropriate, population-based samples of research participants that can be followed longitudinally to appropriately model processes and trajectories as they

unfold. Much can be learned from such data sets, particularly when they include comprehensive biobehavioral and psychiatric epidemiological data on adolescent and adult outcomes. Population-based data sets with a rich array of data over the life course offer opportunities to test the role of self-regulation not only for adult risk of psychopathology but also for different trajectories of both biological and economic inheritance. For example, in the Dunedin Multidisciplinary Heath Study, a birth-cohort study, self-control before age 10 predicted not only a range of better health, economic, and demographic outcomes by age 32, but also whether participants were parenting their own children in one- versus two-person households, signaling tremendous dynamic complexity on both theoretical and empirical fronts (Moffitt et al., 2011). To match this focus on development will likely require idiographic methods that explicitly model processes within the individual as well as across individuals. In the absence of an idiographic approach, multifinality and equifinality can be described conceptually but are less likely to be convincingly demonstrated empirically.

Second, we conclude that our success in pursuing this ambitious intellectual course will in some ways be pinned to the clarity and precision of the key constructs in our models. To date, the term *stress* has been used widely and less precisely. The many disciplinary perspectives represented in this chapter will not be able to speak effectively to one another until environmentally linked terms such as stress, adversity, and neuropsychologically linked terms such as reactivity and executive attention are clearly provided and justified. Recent discussion by Odgers and Jaffee (2013) has highlighted this concern regarding the distinction between adversity and daily hassles, finding that daily hassles can actually serve to both mediate and moderate the role of adversity on child health outcomes. Here, a further implication of the approach is the need to focus on persons more so than on variables. A focus on the principles of development noted in the introduction makes clear that a given variable may take on different meanings depending on the configuration of variables with which it is embedded.

Third, we conclude that we must find new ways of leveraging experience; of using interventions designed to support mental health and well being as an experimental basis from which to draw strong causal inferences regarding developmental mechanisms outlined earlier. A central point of research in the tradition of developmental psychopathology concerns the way developmental theory and preventive intervention are mutually informative. Theory informs the development of efforts to reduce or prevent the occurrence of psychopathology in individuals at risk and in turn experimental evaluations of these preventive interventions serve as key tests of developmental theory (Cicchetti & Hinshaw, 2002). Just as pharmacological studies have manipulated doses of cortisol and oxytocin to yield evidence of neuroanatomical, behavioral, and cognitive mechanisms underlying risk for psychopathology, increased attention to the measurement of neuroanatomical, neuroendocrine, genetic, cognitive, and emotional processes in the design and evaluation of prevention trials can yield highly valuable information on processes of experiential canalization and the malleability of the multiple, interrelated processes involved.

There are relatively few extant examples of prevention trials that focus on the early development of self-regulation that provide insight into experiential canalization and processes of malleability and change in self-regulation development. In infancy and toddlerhood, prevention science research has recently expanded from targeting molar dimensions of parenting, more broadly, to improving specific caregiving practices that are theorized to scaffold early regulation of attention and emotion (see, e.g., Dozier et al., 2006; Fisher et al., 2007; Neville et al., 2013). These experimental tests build upon theoretical and empirical insights provided by Izard and collaborators over a decade ago (Izard et al., 2002), outlining the ways emotion theory can inform prevention efforts. The recent generation of prevention science studies targeting processes of self-regulation provides compelling evidence of biological mediating mechanisms that have profound interpersonal consequences. In one natural experiment, for example, foster mothers' peripheral oxytocin levels were found to become increasingly attuned, or related to ERP indicators of their brain activity in response to images of their own child versus other children over the first 2 months of caring for a foster child, providing fascinating evidence of experiential canalization processes involved in optimizing the provision of care (Bick, Dozier, Bernard, Simmons & Grazzo, 2010). There are also strong implications for the reduction of risk of psychopathology among both adults and children from this new generation of research: As another example, the Family Check-Up intervention yielded significant reductions in mothers' depressive symptoms along with reductions in very young children's risk of externalizing and emotional dysregulation problems (Shaw et al., 2009). In our own lab (as well as in projects recently launched by colleagues funded by the Administration for Children and Families' Buffering Toxic Stress Consortium) we increasingly capitalize on randomized control trials that target both maternal and child indicators of physiological, emotional, and cognitive regulation

to examine processes of self-regulation development and to test models of experiential canalization.

Experimental tests of the role of experience can extend to classroom contexts—one such example is a preschool-based intervention known as the Chicago School Readiness Project (CSRP). The CSRP is notable in that it focused on the early prevention of behavior problems in children by focusing on emotion regulation and did so in community-based educational settings for children in poverty, namely Head Start programs. Most notably for present purposes, it was developed within the developmental science framework, explicitly acknowledging connections among levels of analysis and the need to intervene across levels to bring about comprehensive behavior change (Raver et al., 2009, 2011). Recent results from CSRP analyses suggest that experimentally induced benefits to self-regulation gained in the context of classroom-based intervention can be undermined by later exposure to traumatic stressors such as unsafe school settings and neighborhoods with high levels of violent crime, (Sharkey et al., 2012; Raver, et al., 2013). Following children who were initially enrolled in early interventions like Family Check-Up or CSRP through early adulthood (using both biobehaviorally and psychologically anchored measures of self-regulation) will provide the empirical basis we need to test key models of experiential canalization, allowing us to use developmental theory to design preventive intervention and to use evaluation of the intervention to test developmental theory. Doing so will help to fill an important gap in research in early childhood in which knowledge of emotional development can play a central role in efforts to comprehensively foster child well-being and reduce early indicators for psychopathology.

A related example of the value of preventive intervention as a test of developmental theory, also in a classroom context, is found in a program based on emotions theory. The Promoting Alternative Thinking Skills (PATHS) program is a developmental science-informed approach to reducing behavior problems in young children. It does so by focusing on emotion knowledge and emotion regulation strategies with the understanding that promoting these abilities in children will be associated with benefits to executive functions. Evaluations of PATHS have shown that it is effective at reducing behavior problems and that change in executive function abilities is associated with program effects (Riggs, Greenberg, Kusche, & Pentz, 2006). Extension of the PATHS approach to other areas of behavior management and self-regulation provide further evidence of the efficacy of the approach. Altering the focus in PATHS on emotion regulation and impulse control to encompass healthy dietary choices, Riggs Sakuma, and Pentz, (2007) demonstrated changes in attitudes toward self-regulation and in choices relating to food and to physical activity.

Another example of the potential for change through experience in school-based settings is our evaluation of the educational approach known as Tools of the Mind with children in kindergarten. The Tools approach is explicitly designed to provide support for child self-regulation and the development of executive functions through structured child-directed, teacher-scaffolded activities (Bodrova & Leong, 2007). We found that children in schools randomly assigned to implement the approach had moderately higher levels of executive function abilities as well as mathematics and reading achievement (ES = .10). The effects were particularly large (ES = .30–.80), however, in high poverty schools and extended to measures of children's ability to control attention in the face of fear evoking stimuli in addition to reasoning and vocabulary ability (Blair & Raver, 2014). Notably, this demonstration of the effect of the Tools of the Mind approach followed two prior evaluations of the prekindergarten version of the curriculum, one of which demonstrated effects of the approach on children's executive function abilities (Diamond et al., 2007), and the second of which found no effects on any aspect of children's executive functioning or academic abilities (Wilson & Farran, 2012). Clearly, additional research is needed school-based approaches to the comprehensive promotion of self-regulation in school-based settings. In combination with the CSRP and the Tools of the Mind evaluation, longitudinal follow-ups of the Perry Preschool (Heckman et al., 2009) and Abecedarian (Campbell et al., 2014) programs, and findings from a recent meta-analysis of 213 school-based, universal social-emotional learning (SEL) programs involving 270,034 children indicating significant social-emotional and academic gains resulting from SEL (Durlak et al., 2011), provide clear empirical evidence of the potential to structure educational experiences for children in ways that comprehensively foster self-regulation development at multiple levels of analysis with the possibility of pronounced benefits into adulthood.

As illustrated by CSRP, Tools of the Mind, and classic early intervention studies, capitalizing on efficacy trials of preventive intervention extends our understanding of socioeconomic adversity's impact on self-regulation abilities. Many neuroscientists focusing on the recently established SES gradient in self-regulation may think that we can't experimentally manipulate poverty, but experts in policy analysis know that we can and we have

experimented with populations' experiences of material deprivation through anti-poverty programs. Were biological, neuropsychological and behavioral assays and assessments to be built into those and other experiments, we would gain additional purchase on ways that environments shape cognitions and mood states through both bottom-up and top-down processes, in ways that we can now speculate are plausible and have pieced-together empirical support. Moreover, attention to economic and demographic outcomes within efficacy trials of clinical intervention would allow us to test ways that those processes are bidirectional: Treatment of depression or other mood disorders would be expected to substantially shift not only individuals' executive functions but also their ability to navigate key life-course decisions in areas such as employment, housing, partnership, and risk taking. In short, we might learn not only about adversity's impact on self-regulation, but self-regulation's impact on exposure to adversity, over the long term.

There is also a host of what can be considered more proximal attempts to increase self-regulation and its consequences through interventions focusing on training working memory, modifying attention, and altering the ways individuals frame goals and intentions. Attempts to improve working memory through repeated practice reflect the top-down approach to self-regulation and represent the theory that strengthening executive control will lead to behavior change. Evaluations of this training, with children as well adults, indicate that it very clearly improves working memory abilities. Evidence to date that these improvements transfer or generalize to other aspects of behavior, however, has been limited (Melby-Lervag & Hulme, 2013; Shinaver et al., 2014). Notable examples of the effects of working memory training for children with ADHD indicate improvements in working memory tasks but limited evidence of improvements in ADHD symptoms (Klingberg et al., 2005; van Dongen-Boomsma et al., 2014). Similar to working memory training, efforts to modify attention bias to threatening, anxiety provoking, or highly appetitive, addictive stimuli indicate that the training is effective in altering the capture of attention by relevant stimuli. Effects on behavior from attention modification, however, are limited (Beard et al., 2012; Mogose et al., 2014). In contrast to limited effects on behavior from effective change at the attentional and working memory/executive cognitive levels, a relatively straightforward approach to changing problem behavior by mentally contrasting a desired goal state with one's current condition and developing a simple action plan to implement steps to attain the goal state, referred to as mental contrasting with implementation intentions, has demonstrated that it is effective at changing unwanted behavior (Stadler, Oettigen, & Gollwitzer, 2009) and improving academic performance (Duckworth, Kirby, Gollwitzer, & Oettigen, 2013).

In planning and executing preventive intervention experiments as tests of developmental theory, investigators can remain vigilant for the ways that individuals' responsiveness to treatment may vary as a function of genetic, cognitive, and interpersonal context. Put another way, interventions that have heretofore been understood to have relatively small average causal impact could be reexamined for large impacts in small but theoretically indicated subgroups. An interesting example concerns an analysis of the effect of working memory training on behavior among alcoholics in which problem drinkers were randomly assigned to receive working memory training or not (Houben et al., 2011). Results indicated that the training was associated with reduced alcohol intake over a 1 month period post-training for participants with strong automatic preferences for alcohol as indicated by an implicit attitudes task.

The foregoing brings us to our fourth and final conclusion; namely, the way in which the experiential canalization model of self-regulation development illustrates what is in many ways the most revolutionary of the central tenets of developmental science, namely the idea that behavior is the leading edge of development (Cairns, 1991). This phrase highlights the importance of a continued focus on experience, on behavior as a dynamic rather than fixed process that represents and can itself bring about change at multiple levels of analysis in a developmental system. Recognition of this central point can orient scientific inquiry in ways that are at once both familiar and new. On the one hand, it builds on well-established traditions of the study of behavior, particularly social behavior, and the potential of a host of techniques, practices, interventions, and programs to bring about behavior change. On the other hand, it challenges our understanding of the goals of these techniques, practices, interventions, and programs to move beyond the establishment of a fixed behavioral endpoint or outcome, to an understanding of process; of behavior as the representation of an organized state of relations among variables across levels of analysis, and also as a dynamic entity that can bring about change in that organized state. Comprehensive analysis of multiple influences on behavior at multiple levels over time is not merely a scientifically interesting if daunting endeavor, it is essential for understanding human development and preventing psychopathology.

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CHAPTER 14

Anxiety Regulation: A Developmental Psychopathology Perspective

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INTRODUCTION

It has been roughly 20 years since Ross A. Thompson (1994) published a highly influential monograph outlining the challenges associated with defining emotion regulation and embedding the construct accurately in the broader matrix of knowledge about social behavior and cognition. This work synthesized and expanded on converging strands of research about a topic that had received a growing amount of attention in academic journals and books in the preceding years, including a widely cited special section of *Developmental Psychology* on development of emotion regulation that Kenneth A. Dodge edited in 1989. Around the same time, Gross and Muñoz (1995) clearly laid out various ways emotion regulation and dysregulation contribute to changes in mental health.

During the intervening decades since these works appeared, the phrase emotion regulation has become a central component in our definitions of most psychopathology (Dillon, Deveney, & Pizzagalli, 2011), and researchers have made great strides in clarifying the processes by which we modulate our emotional experiences across the life span in both adaptive and maladaptive ways (e.g., Tamir, 2011; Thompson, 2011). Not surprisingly, however, given that the term emotion regulation comprises a complex, nuanced, and dynamically interactive range of functions and concepts, questions remain regarding how it is best conceptualized and the ways it develops, evolves, and manifests across contexts (Aldao, 2013; Thompson & Goodman, 2010; Thompson, Lewis, & Calkins, 2008). Indeed, some researchers and theorists even debate its fundamental validity as a distinct entity that can stand independently from other facets of emotion (e.g., Gross & Feldman, 2011; Kappas, 2011).

Notably, although Thompson's (1994) framework emphasized processes involved in modulating emotions in general, recently burgeoning literatures also examine the biological and psychological processes involved in the regulation of specific emotions, including happiness (Quoidbach et al., 2010; Urry et al., 2012), sadness (e.g., Cassano & Zeman, 2010; Sheppes & Meiran, 2007), anger (e.g., Kim & Deater-Deckard, 2011; Novin et al., 2011), and anxiety/fear (e.g., Bowers, Choi, & Ressler, 2012; Cisler et al., 2010; Hartley & Phelps, 2010). These emotion types share multiple regulatory commonalities; indeed, findings regarding shared mechanisms have driven interest in transdiagnostic approaches to treating psychopathology (Aldao & Nolen-Hoeksema, 2010; Kring & Sloan, 2010). However, across the life span there also appear to be distinctive cognitive and neural patterns associated with the modulation of individual emotions (e.g., Amstadter, 2008; Kovacs, Joormann, & Gotlib, 2008), which provide

striking evidence of the complexity, flexibility, and nuanced functioning of our emotion regulation systems. Together, these patterns of overlapping and discrete functions serve to support a broad range of responses to emotional experience and expression.

Many recent reviews cogently summarize the literature on the umbrella construct of emotion regulation as it develops and changes across the life span (e.g., Denham, 2010; Jacob et al., 2011; Nolen-Hoeksema, 2012; Webb, Miles, & Sheeran, 2012). These works approach the topic from behavioral, cognitive, and psychophysiological perspectives and reflect in particular our growing understanding of the ways the brain mediates the experience and modulation of emotions. To extend and complement this body of research, the present chapter aims to describe and critically review the literature that focuses specifically on the regulation of anxiety from infancy through older adulthood.

We use the developmental psychopathology perspective, which emphasizes several core tenets, as a guiding framework for this chapter (Cicchetti & Cohen, 1995). Our review of the literature thus carries within it a number of implicit assumptions about the ways psychopathology emerges and evolves over the life span. First among these is the idea that multiple factors interact in a dynamic, transactional fashion to affect the ways a disorder might initially manifest, how it changes over time, and whether and how it resolves. Consistent with this idea, clinically significant anxiety can emerge as an endpoint of an array of developmental pathways, in accordance with the principle of equifinality (Ollendick & Hirshfeld-Becker, 2002). For example, varied combinations of genetic and environmental risk factors can precipitate the development of a particular anxiety disorder (McGrath et al., 2012). However, in keeping with the related principle of multifinality, none of those pathways is necessarily guaranteed to result in that condition, or, for that matter, in any anxiety disorder. Indeed a given etiological factor (e.g., genetic vulnerability) can produce any of several different effects depending on the system or context in which it operates. Findings that genetic characteristics, such as serotonin transporter polymorphisms, interact with stressful life events to differentially predict anxious symptoms (along with depressive and other symptom types) nicely illustrate this principle (Caspi et al., 2003; Petersen et al., 2012). Thus, the probability that an anxiety disorder will emerge at a given point in development varies depending on the evolving interplay among vulnerabilities and protective factors for any particular child, adolescent, or adult.

Based on the idea that an accurate understanding of dysfunction necessitates a comparable understanding of normal or successfully adaptive developmental paths, an additional core assumption of the developmental psychopathology perspective is that typical and atypical development must be studied in concert. This assumption is particularly salient to anxiety, which constitutes an integral, adaptive, and normative part of human existence throughout the life span (Barlow, 2002). Indeed, the absence of anxiety, a goal that clinically anxious adults in one qualitative study articulated with some regularity, has been aptly conceptualized as mythical normativity (Lloyd & Moreau, 2011).

It is only under certain circumstances that anxiety shifts from a normative to a dysfunctional response; considerable evidence suggests that convergence of salient biological and environmental factors leads to neural hypersensitivity that manifests behaviorally as hypervigilance and overresponsiveness to stimuli perceived as threats, or pathological anxiety (Rosen & Schulkin, 1998). Precisely how and why this transition occurs in some individuals, but not others, is a focus of considerable research attention; if we are to obtain accurate answers to these questions, it is critical that we comprehensively map the terrain that surrounds the transition.

An additional core tenet of the developmental psychopathology perspective informing this chapter is that the developmental context must be considered when evaluating whether or not a disorder is emerging or subsiding. Symptoms vary in their meaning and import at different points in development. A sizable proportion of children between the ages of 4 and 12 years, for example, report nighttime fears (i.e., realistic or unrealistic fears that something bad will happen during the night), with prevalence reaching its peak between seven and nine years (Muris et al., 2001). In contrast, such fears are less common among adolescents (Gordon et al., 2007). Nighttime fears thus appear more likely to be pathological, at least in terms of deviance from typical developmental patterns, at some points than at others. Similarly, whereas being separated from primary caregivers commonly provokes fear among infants and toddlers (Thompson & Limber, 1990), comparable separation-related distress is less typical among older children and adolescents (Compton, Nelson, & March, 2000). Its occurrence among older youths may thus indicate the presence of pathology.

Taking these tenets as a guiding structure, we aim in this chapter to examine the mechanisms and methods by which humans regulate anxiety over the course of the life span. In the first section, we define salient terms and concepts that are at the heart of our review. We clarify the models we rely on to describe emotion and anxiety regulation, and

we then offer a short overview of common manifestations of anxiety across development. In the second section, we shift focus to the regulation of anxiety and fear per se. In particular, we examine whether and how cognitive and neural mechanisms underlying the regulation of anxiety vary across development. The third section of this chapter turns to the contexts, both intrapersonal and interpersonal, that may facilitate or inhibit the use of different regulatory mechanisms and strategies among individuals experiencing acute or chronic anxiety across the life span.

DEFINITIONS OF TERMS

Emotion Regulation, Emotion, and Feelings

The human capacity to modulate emotional experience and expression in intentional ways has been a topic of scholarly interest for centuries. Physicians, philosophers, and psychologists have long acknowledged both the power of emotions to both elevate and disrupt human experience and the many ways people try variously to rein in or amplify these internal states. In a succinct review of influential ideas on these topics, Cicchetti, Ackerman, and Izard (1995) traced the path along which our understanding of emotion and emotional control has evolved from the time of Hippocrates and Aristotle to the late twentieth century. In particular, they highlighted two core themes that pervade thinking on these topics throughout history: first, that uncontrolled emotion is a key player in the development of psychopathology; and second, that reason is necessary to keep the emotions under control.

As early as the mid- to late 1800s and the early 1900s, while some continued to explore these themes by delving into the relationship between emotion and the broad constructs of reason, sensibility, and will (e.g., Bain, 1859; Jastrow, 1915; Moore, 1852), other researchers and theorists moved away from treating these constructs as unitary forces that one could willfully exercise to keep emotions in line. These scholars instead, or concomitantly, examined specific cognitive mechanisms that might participate in or facilitate the regulation of emotion. In his book on principles of mental physiology, for instance, the prominent British physiologist William B. Carpenter (1876) speculated about the fundamental role that attention plays in the regulatory process, noting that until our attention is drawn to our emotional reactions, we are unable to intentionally direct those reactions; indeed, we may not even be aware of whether and how they are changing. Motoric inhibition of emotional displays, if not experiences, also received mention in the literature (e.g., Bain, 1859), as did executive functions, such as cognitive or mental inhibition (e.g., Clouston & Folson, 1884).

Early in the twentieth century, references to emotional regulation or control also began to appear in the educational literature, reflecting a surging interest in expanding the role of schools in the processes of behavioral and characterological development, in concert with their ongoing efforts to encourage intellectual growth and achievement (Henry, 1917). Further, educators were acknowledging with increasing frequency the impact of emotional factors on academic performance, which appeared to heighten interest in helping children acquire self-regulatory skills (e.g., Arthur, 1922; Johnson, 1928). This theme recurred in the education and child-rearing literatures through the mid-twentieth century (e.g., Arlitt, 1938; Stendler, 1950), and it continued to translate more broadly, particularly to developmental psychology outlets, in the latter decades of the twentieth century.

By the late 1980s and early 1990's, the term *emotion regulation* appeared regularly in the general psychological and psychiatric literatures; recent searches of online databases (PsycINFO, PubMed) yield nearly 2,000 publications since 1980 that list it as a key search term or phrase, and thousands of additional articles and chapters reference the topic. In these many publications, emotion regulation has been used to label a diverse array of clinical and psychological phenomena, some very broad and others more narrow in scope. For example, as Grolnick, McMenamy, and Kurowski (2006) summarized, some definitions focus on general changes in emotions, which involve altering or maintaining patterns of emotional valence, intensity, or course in the context of interpersonal transactions or salient cultural norms (Campos, Mumme, Kermoian & Campos, 1994; Cole, Martin, & Dennis, 2004, Fox, 1994). Others, however, maintain that emotion regulation encompasses a broader set of processes; Campos, Frankel, and Camras (2004), for example, defined it as "the modification of any process in the system that generates emotion or its manifestation in behavior" (p. 380).

For the purposes of this chapter, we rely primarily on Thompson's (1994) definition of emotion regulation. More precisely, we use the term specifically to describe "processes responsible for monitoring, evaluating, and modifying emotional reactions . . . to accomplish one's goals" (pp. 27–28). Of note, our chosen definition identifies emotional reactions as the target of regulatory processes. These reactions are multifaceted and may manifest in one or more different ways, both within and out of awareness. Indeed, as Jacob and colleagues (2011) underscore,

emotion regulation involves an array of dynamic processes; while inhibition or suppression are the processes most often intuitively linked to emotion regulation, other regulatory processes, including exaggeration, substitution, avoidance, or neutralization of affective responses, warrant attention.

We consider affectively valenced states that one experiences subjectively and can describe reliably to be feelings, consistent with Damasio's writings (Damasio, 2001; Damasio et al., 2000). Feelings may or may not be associated with emotions, which we define as patterns of neural response (along with their broader physiological or information processing correlates) associated with the experience of rewards (any stimuli that animals or humans work to procure) or punishments (any stimuli that animals or humans make effort to avoid; Rolls, 1999). Changes in emotion are thus necessarily reflected in neurophysiological and, in many cases, information-processing measures; they can be, but do not have to be, reflected in measures of subjectively reported experience. As such, the relationship between feeling and emotion is unclear, and will remain so until a suitable theory of consciousness exists to define subjective feeling states in the same types of neuroscience-based terminology used currently to define emotions. Nevertheless, theorists and researchers have articulated ways the two may interact. For example, scholars who approach the topic from developmental, neuroscience, and translational perspectives contend that feelings act to influence emotional states, both by monitoring variations that occur at the level of emotions and by feeding information back to higher cognitive processes, which in turn modulate the ongoing stream of emotion (e.g., Damasio, 2000; Hoeksma, Oosterlaan, & Schipper, 2004; Panksepp, 1998; Scherer, 2000).

Carefully distinguishing feelings from emotions is important; although the terms are often used interchangeably in lay language, the psychological/psychiatric literatures specify subtle distinctions between the two and use them in slightly different contexts. In particular, feelings are at the core of many currently conceptualized psychiatric disorders included in the fifth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual for Mental Disorders* (*DSM-5*; APA, 2013) in that subjectively reported changes in emotional states (e.g., depressed mood most of the day, nearly every day) or behaviors (e.g., distractibility) form the basis for a variety of diagnostic criteria. Objectively measured behaviors that are putatively associated with emotional states (e.g., pressured speech; avoidance) also constitute a handful of criteria. Notably, no current diagnostic criteria incorporate data from directly measured changes in brain states, although research under the auspices of the National Institute of Mental Health's Research Domain Criteria (RDoC) initiative aims to reorganize our understanding of psychopathology and its diagnostic classification according to a neuroscience-based framework (Insel & Wang, 2010; Morris & Cuthbert, 2012). This initiative, if successful, will facilitate the use of biomarkers in addition to or in place of phenomenological observations for diagnostic purposes; it already played an influential role in shaping the fifth edition of the *DSM* (Kupfer & Regier, 2011).

Until the literature better supports a biomarker-driven method for identifying and classifying psychopathology, however, a continued focus on feelings in our efforts to understand and distinguish among most psychiatric diagnoses will be necessary. This reliance on subjective data is problematic at a number of levels. First, correlations between subjective reports and performance on objective measures tapping the same domain are often relatively weak, even for cognitive and behavioral functions that observers can readily assess with high reliability (e.g., Burdick, Endick, & Goldberg, 2005; Gosling, John, Craik, & Robins, 1998; Svendsen et al., 2012). It thus remains unclear how well and how consistently self-reports regarding internal, affective states, which are currently hard to evaluate objectively, describe lived experience. Notably, some evidence suggests that even very young children are able to provide valid and meaningful information regarding their feelings, based on findings of convergence between 3- and 6-year-old youths' self-reports and objective coding of their facial expressions during affectively evocative tasks (Durbin, 2010). However, the magnitude of convergence between these measures was small to moderate across emotions, with self-report accounting for no more than 15% of the variance in objective coding scores.

Second, reliance on subjective reports of feelings in our conceptualizations of mental disorders introduces marked challenges into the conduct of translational work that integrates research across human and nonhuman species. Even though many mammalian species show evidence of consistencies and continuities in terms of experienced emotion (Davis & Whalen, 2001; LeDoux, 1994, 1998, 2000), it is difficult to measure the presence of feelings in nonhuman organisms. This difficulty, at least in part, reflects our almost exclusive reliance on verbal reports of feelings, which we cannot obtain from nonhuman species. It is further confounded by the lack of an accepted model of consciousness and subjective reports, which could support cross-species investigations of feelings. Panksepp (2011; 2012), however, argued that the current approach is unnecessarily limiting; instead, he contends that by

directly stimulating brain networks that have consistently been shown to mediate emotional behavior, it is possible to access at least some types of emotional experience without need for verbal report. His ideas suggest a path out of the current impasse, in which nonhuman species' lack of verbal language appears to prohibit insight into their mental and emotional processes. However, until empirical data point us toward a broadly accepted and widely used, reliable, and valid approach to accessing mental and emotional states in the absence of language, translational studies will continue to grapple with the interface between feelings and emotions, which remains imprecisely specified across species.

Our understanding of regulatory mechanisms is similarly complicated by the challenges inherent in identifying boundaries between emotions and feelings. Indeed, in light of our emphasis on the distinction between emotions and feelings, one could argue that in addition to attention to emotion regulation, a parallel focus on feeling regulation is warranted. However, despite the availability of cogent hypotheses about the dynamic interplay between feelings and emotions (e.g., Hoeksma et al., 2004), the term emotion regulation is broadly operationally defined, so that it encompasses the processes that serve to modulate both constructs. Thus, in the interest of simplicity and consistency with much of the literature that we review, and in recognition of the inextricable links between emotions and feelings, we have adopted a comparably broad and inclusive use of the term emotion regulation.

Fear and Anxiety

Just as we tend to conflate emotions and feelings in popular discourse, we also commonly treat fear and anxiety as indistinguishable. Notably, however, as far back as 45 BC, Cicero wrote about the divergence between *anxietas*, a state of general fearfulness, and *angor*, a passing state of fear provoked by a specific stimulus (Cicero, 1927). Consistent with Cicero's ideas, the scientific literature has come to recognize anxiety and fear as representing different constructs (e.g., Sylvers, Lilienfeld, & LaPrairie, 2011), and in this chapter, accordingly, we treat them distinctly. For our purposes, the term *anxiety* denotes a frequently enduring phenomenon that may arise in response to a range of nonspecific, overt, or covert stimuli that an individual perceives as representing potential threat (Dias, Banerjee, Goodman, & Ressler, 2013). The perception of possible impending threat is commonly accompanied by feelings of apprehension, as well as increased arousal and vigilance. The term fear, in contrast, represents a transient state that typically evokes defensive responses in the presence of specific overt stimuli and subsides when those stimuli are gone (Dias et al., 2013). Thus, whereas fear is tied to relatively clear, unambiguous threats, the dangers that give rise to anxiety are less clearly demarcated.

Such a conceptualization of anxiety and fear as distinct constructs finds support in empirical work on the structure of mental disorders. Krueger (1999) analyzed comorbidity patterns in a large epidemiological sample of adults and found that the best fitting factor structure included distinct, although highly correlated, first-order anxious-misery and fear factors that loaded on a higher order internalizing factor. This pattern of findings has been widely replicated in adult samples (e.g., Slade & Watson, 2006; Vollebergh et al., 2001; Watson, 2005). In a recent effort to extend Krueger's (1999) work to an adolescent and young adult sample, however, Beesdo-Baum and colleagues (2009) found a slightly different factor structure to yield the best fit. Like Krueger's (1999), their data were consistent with the presence of anxious-misery and fear first-order factors; notably, however, the correlation between the two factors was much weaker, and a model including the higher order internalizing factor yielded a weak fit. This structural variation raises questions about the developmental stability of anxiety and fear constructs and points to the need for more research in this area, ideally with developmentally sensitive methods that permit examination of within-subject changes over time.

Neurobiological studies in both nonhuman and human species also point to clear distinctions between anxiety and fear. As Sylvers and colleagues (2011) summarized, research on varied rodent species, as well as on nonhuman primates, converges to suggest that discrete neural structures play key roles in fear and anxiety. Whereas the lateral and central nuclei of the amygdala (LA and CeA) appear to be critical players in the acquisition of fear and the emergence and expression of fear-conditioned responses (Kalin, Shelton, & Davidson, 2004; Ledoux et al., 1988, 1990; Wilensky, Schafe, Kristensen, & Ledoux, 2006), additional regions, including the bed nucleus of the stria terminalis, the septum, and hippocampus may figure in the emergence of anxious responses (e.g., Degroot & Nomikos, 2005; Edinger & Frye, 2006; Gray & McNaughton, 2000).

Of note, despite their distinctions, anxiety and fear share a number of common features, which fuels the common tendency to treat them as interchangeable. Both, for example, can be categorized as either emotions or feeling states that humans experience when they encounter stimuli that they perceive as threatening or as capable of producing harm and that elicit avoidance. Although both

can manifest in atypical or dysfunctional ways, neither necessarily connotes a pathological state, as we discuss below in further detail in our overview of anxiety disorders. In addition, both anxiety and fear elicit a number of common physiological responses including autonomic arousal (Cook, Hawk, Davis, & Stevenson, 1991), as well as activation from a number of overlapping neural structures that include the amygdala and areas within the medial prefrontal cortex in human and nonhuman species (Blair, 2003).

Regulation of Fear and Anxiety

When applied to fear and anxiety, our definition of emotion regulation demands attention to two distinct, but related, processes. First, anxiety/fear regulation is initiated by stimuli and circumstances that elicit fearful or anxious reactions, due to their real or perceived capacity to harm the organism. Second, the individual enacts a range of behavioral, cognitive, and neural response that serve to monitor, evaluate, and modify the elicited fearful or anxious reactions that the stimulus elicits. The sequence as a whole thus necessitates a triggering stimulus or circumstance and a regulatory response to it. Taken together with the increasing tendency in the developmental and general psychopathology literatures to conceptualize anxiety disorders as centrally characterized by maladaptive emotion regulation (e.g., Cisler, Olatunji, Feldner, & Forsyth, 2010; Esbjørn, Bender, Reinholdt-Dunne, Munck, & Ollendick, 2012; Jacob, Thomassin, Morelen, & Suveg, 2011; Rodebaugh & Heimberg, 2008), our definition suggests that anxious pathology lies less in the circumstances that elicit emotion or the magnitude of an initial emotional reaction and more in the degree to which an individual can engage resources to regulate this reaction once it emerges.

Within the course of the regulatory process, however, there are also nuances that warrant attention. Davidson (1998) laid some of these out clearly in his description of a model of emotion regulation that emphasizes affective chronometry, referring to the time course of emotional responding. According to this model, it is important to view the processing of emotionally evocative stimuli in the context of their temporal dynamics rather than as a unitary block. In other words, the processes that are engaged as an affective reaction rises to its peak may differ from those engaged as the reaction subsides and disruption of processes during either period may contribute to the emergence of different forms of pathology. Further, the trajectory of the rise and fall of a response is likely to vary considerably both across individuals and across biological and cognitive systems within an individual. We thus risk inadequately characterizing a regulatory response if we fail to consider its temporal course along with its content. A range of such temporal features, including the continuity of a feeling or emotion from one moment to the next (Koval & Kuppens, 2012) and the process of transition within an emotional response (Filipowicz, Barsade, & Melwani, 2011), have received increasing research attention since Davidson's (1998) article first appeared.

From an affective chronometry perspective then, conceptual distinctions between emotional reactions and emotion regulation may be arbitrary. Instead, it may be more useful to consider the two constructs as representing conceptually unified, but temporally distinct phases within an individual's response to an emotional stimulus at behavioral, cognitive, and neural levels. Such a perspective gives rise to the possibility that some disorders may relate to perturbations that occur early in the course of a response, while others may relate to perturbations that are evident later during the processing of emotional stimuli. Davidson (1998) reviewed data, for example, that suggest that differences between anxiety and depression, which share many features and often emerge comorbidly (Angold & Costello, 1993; Brown, Campbell, Lehman, Grisham, & Mancill, 2001), may, in part, reflect variability in the functioning of neural regions that participate in regulatory processes (e.g., prefrontal cortices) that leads to differential influences on the dynamic unfolding of the emotion regulation sequence. For example, in a later publication focused explicitly on anxiety, Davidson (2002) underscored the important roles that ventromedial and orbital regions of the prefrontal cortex play in modulating the time course of responses in subcortical neural structures such as the amygdala, which converging data have shown to function atypically in the context of anxiety disorders.

Taken together, both content- and process-oriented perspectives provide a broad range of intersecting hypotheses about how abnormalities in either emotional reactions or emotion regulation, as they are measured in the laboratory, may relate to the emergence and maintenance of developmental psychopathologies, including anxiety disorders. Research over the past few decades has made advances in testing these hypotheses and we review, in subsequent sections of this chapter, the findings that are emerging within this growing literature and their interpretation through a developmental psychopathology lens. Many questions in this domain, however, remain unanswered and we attempt to point out gaps in the existing body of work on the regulation of anxiety that merit further attention, particularly in the context of anxiety that is severe or pervasive enough to qualify as pathological.

Pathological Anxiety

As a group, anxiety disorders represent the most severe and extreme manifestations of anxiety. These conditions are common throughout development, with recent lifetime prevalence estimates for any anxiety disorder in the United States appearing as high as 32.4% for adolescents to 33.7% for adults (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). The same study also found twelve-month prevalence rates for individual anxiety disorders to be high in adolescent and adult populations, with, for example, up to 7.4% of individuals meeting criteria for social phobia and 12.1% meeting criteria for a specific phobia in a given year. Prevalence rates for 12 months among children under 12 also appear high; a review of epidemiological research using both *DSM-III-R* and *DSM-IV* criteria found 12-month estimates of the presence of any anxiety disorder to range from a low of 3.05% to a high of 20.2%, with a median of 4.02% (Cartwright-Hatton, McNicol, & Doubleday, 2006). Evidence also suggests that at least some anxiety disorders are stable over time; one study, for example, found 56.7% of adolescents and adults diagnosed with social anxiety disorder to continue to meet criteria 10 years later (Beesdo-Baum et al., 2012). Stability rates appear particularly high in individuals with comorbid anxiety and depressive disorders (Fichter, Quadflieg, Fischer, & Kohlboeck, 2010). Surprisingly, however, in light of their frequent occurrence and persistence, anxiety disorders received relatively little research attention until the past few decades, perhaps because they have historically been perceived as less severe than other forms of psychopathology.

Research since the late 1980s indicates decisively that perceptions of anxiety as minimally impairing and rarely associated with adverse outcomes are inaccurate. Anxiety disorders are associated with a variety of adverse outcomes, including development of other psychiatric problems such as major depression and suicidality (Fehm, Beesdo, Jacobi, & Fiedler, 2008; Fichter et al., 2010; Pine, Cohen, Gurley, Brook, & Ma, 1998). Indeed, most adults who suffer from a mood or anxiety disorder will have first developed signs of their illness, manifest as an anxiety disorder, during childhood or adolescence (e.g., Costello et al., 2002; Pine et al., 1998; Ramsawh, Weisberg, Dyck, Stout, & Keller, 2011).

Anxiety disorders are also costly to society in terms of both financial and social consequences. Medical costs and utilization rates associated with this diagnostic category are high (Berger et al., 2011; Martin & Leslie, 2003), especially when treatment is concordant with practice guidelines (Prins et al., 2011). School dropout rates are also elevated among adolescents who meet criteria for anxiety disorders (Leach & Butterworth, 2012), and affected adults have also been found to miss work more frequently and to show decreased output when they do attend work (Erickson et al., 2009; Revicki et al., 2012).

Finally, anxiety disorders are a source of impairment in multiple domains for children, particularly those who meet criteria for more than one diagnosis (Alfano, 2012; Klein & Pine, 2002; Langley, Bergman, McCracken, & Piacentini, 2004). Research has found evidence, for example, that sleep-related problems (Alfano, Ginsburg, Kingery, & Newman, 2007), interpersonal difficulties (Weeks, Coplan, & Kingsbury, 2009), and school absenteeism (Dube & Orpinas, 2009) are associated with the presence of anxiety, particularly when it manifests at clinically significant levels. In light of their negative impact on individuals across the course of development, it is critically important that we understand what the anxiety disorders are, how they emerge and evolve across the course of development, and how they converge with and diverge from normal manifestations of anxiety.

CLASSIFICATION OF ANXIETY DISORDERS ACROSS DEVELOPMENT

In May 2013, the American Psychiatric Association published the fifth edition of its *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (*DSM-5*; American Psychiatric Association, 2013) with the aim of updating the diagnostic nosology based on changes in the research base since the fourth edition of the manual (*DSM-IV*; APA, 1994) was published in the mid-1990s and revised in 2000 (*DSM-IV-TR*; APA, 2000). The authors' intensive attention to the integration of novel research findings with solidly supported older data resulted in a number of changes to diagnostic criteria and, in some cases, disorder definitions (American Psychiatric Association, 2013). However, the magnitude of change in the anxiety disorders is relatively minimal, particularly when compared with the changes that occurred more than 30 years ago with the publication of *DSM-III* (APA, 1980), where anxiety classification was radically transformed. Given that the *DSM-5* was not yet published when this chapter was in preparation, the research data on anxiety disorders that we cite come from studies that used the nosology of the *DSM-IV* or earlier editions of the DSM. These editions recognized eight distinct anxiety disorders: separation anxiety disorder (SAD), social phobia, generalized anxiety disorder (GAD), specific phobia, posttraumatic stress disorder (PTSD), acute stress disorder (ASD), panic disorder/agoraphobia,

and obsessive-compulsive disorder (OCD), along with a less specific diagnosis, anxiety disorder not otherwise specified (NOS), for clinically significant conditions that did not fully meet criteria for other disorders.

With the transition to the fifth edition of the *DSM*, however, this grouping changed in two key ways. First, PTSD and ASD were moved to a separate section on trauma- and stressor-related disorders; this section also includes two forms of attachment disorder that were both classified in *DSM-IV* under the rubric of reactive attachment disorder (RAD). Second, OCD was shifted to a section centered on obsessive-compulsive and related disorders (*DSM-5*; APA, 2013). These changes reflect ample evidence, described below, that the longitudinal outcomes, comorbidities, familial aggregation patterns, and biological correlates of these conditions are distinct from those of other disorders traditionally considered to be anxiety disorders. In this chapter, accordingly, we focus only on conditions classified in the *DSM-5* as anxiety disorders; we further limit our focus to three that commonly aggregate and are often treated as a cluster (RUPP, 2003), especially in the developmental literature: SAD, social phobia/social anxiety disorder, and GAD. Notably, although social anxiety disorder and GAD were previously classified as anxiety disorders in *DSM-IV*, SAD was identified as a child-specific disorder along with such conditions as attention-deficit/hyperactivity disorder (ADHD). The section devoted exclusively to childhood disorders was eliminated from *DSM-5* due to evidence that it encompassed conditions that manifested in adults as well as youths and thus set artificial age-related boundaries. In place of a section devoted explicitly to children and adolescents, a developmentally influenced perspective helped shape the diagnostic criteria and considerations for all of the anxiety disorders. Nevertheless, SAD was placed in the anxiety disorders section for *DSM-5*, as opposed to the neurodevelopmental disorders, and readers were informed that it was suitable to apply the diagnosis of SAD to adults.

Although the importance of a developmental mindset is overtly recognized with the publication of *DSM-5*, developmental considerations have been important, if subtler, components of the DSM diagnostic process for the past two decades. With the *DSM-IV*, the American Psychiatric Association adopted a nosological convention in which identical diagnostic criteria were to be applied to individuals across the life span, in the absence of strong data that supported using a developmentally tailored approach. Thus, as noted already, in the *DSM-IV*, all anxiety disorders but one (SAD—which was conceptualized as occurring exclusively in childhood) were diagnosed using the same criteria for children, adolescents, and adults. In addition, although the GAD criterion items were identical for youths and adults, juveniles had to show fewer symptoms than adults to cross the threshold for the disorder. In the *DSM-5*, however, based on data suggesting that some elements of this developmental tailoring lacked empirical support, SAD is recognized as a condition that can manifest after the age of 18 (Marnane & Silove, 2013).

To meet criteria for any anxiety disorder, individuals must exhibit a specific set of symptoms; in the third and fourth editions of the DSM, they were also required to show signs of either functional impairment or significant distress. The latter requirement, commonly termed the impairment/distress criterion, was initially added to diagnoses that had first appeared in the *DSM-III* in 1980, with the aim of ensuring that individuals who experienced normal fluctuations in psychiatric symptoms were not inappropriately diagnosed with and treated for categorically distinct disorders. However, despite the intuitive appeal of this conceptual distinction, it has proved difficult to apply in practice. First, many core symptoms of anxiety disorders consist of variants of distress, which Rapee and colleagues (2012) define as "a personal and subjective sense of malaise and negativity" (p. 455). Second, it is simply easier to disentangle symptoms and the impairment associated with them in some conditions than in others (Rapee et al., 2012). For example, even highly anxious individuals can function adequately or even well in many domains (Keyes, 2005), unlike most individuals with some other forms of severe psychopathology, such as psychosis or dementia, particularly at advanced stages. Indeed, given the long-noted lack of specific functional impairment criteria for the anxiety disorders (e.g., Beidel, Silverman, & Hammond-Laurence, 1996), it is remarkably challenging to determine reliably where the line is between adequate and problematic adaptation to a given environment.

This challenge is compounded by the fact that diagnostic decisions about the presence or absence of anxiety disorders, especially those made regarding youths, must often be made against the background of normative developmental changes in behavior, cognition, and affect. As we noted earlier, some anxious thoughts, feelings, and behaviors are normal at different stages of development—fears of negative evaluation from others, for example, become increasingly common as children transition into adolescence (Vasey, Crnic, & Carter, 1994). Such fears, in contrast, are relatively unusual among three year olds (Spence, Rapee, McDonald, & Ingram, 2001); thus, the presence of negative evaluation fears might be considered normal in adolescents but atypical in young children.

Because of this narrow and constantly moving line between typical and atypical anxiety across the life span, as well as the fact that symptoms that lead to impairment at one age may not do so at others, the developmental psychopathology perspective's emphasis on considering normal and deviant processes in conjunction is particularly appropriate to the study of anxiety disorders.

In recognition of these and other related issues, the authors of the *DSM-5* considered removing the impairment/distress criterion from individual disorders, thus shifting from a view in which impairment/distress are integral features of different conditions to one in which they are consequences of psychopathology. Ultimately, however, they retained this criterion for most of the anxiety disorders, while electing to provide on the *DSM-5* Web site (http://www.psychiatry.org/practice/dsm/dsm5/online-assessment-measures#Disorder) dimensional disorder-specific scales that can be used to describe severity.

The subtlety of the distress/impairment threshold for anxiety disorders clearly poses problems for clinicians, who are charged with distinguishing between normal range and clinically significant conditions. It also creates issues in the epidemiological literature, in that it complicates the determination of population-level prevalence rates. This set of problems is particularly salient for anxiety-related conditions; indeed, studies that set different impairment thresholds tend to find dramatically different prevalence rates for anxiety disorders, for which many symptoms are internal and accessible only by self-report. In contrast, the threshold for impairment has a much smaller influence on rates for other psychiatric conditions, such as depression or conduct disorder, whose symptoms may be more readily observable to others (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Shaffer et al., 1996).

The challenges associated with differentiating normal from abnormal anxiety, in terms of both impairment and distress, reflect the limitations of our current approach to identifying and categorizing most psychopathology primarily via clinical evaluation (e.g., interview, self-report). Alternate, more objective approaches, such as assessments of physiology, genetics, or brain function have generated considerable excitement among researchers and enjoy some empirical support (e.g., Siegle et al., 2012). They have only been used to date clinically, however, for the diagnosis of mental disorders that result from underlying nonpsychiatric medical illnesses (e.g., genetic disorders such as Fragile X syndrome, disorders such as AIDS that can be associated with dementia). Thus until we can move beyond a reliance on clinical evaluation and incorporate a broader range of converging measures in our diagnostic decisions, consistent with the NIMH's RDoC initiative (Insel & Wang, 2010; Morris & Cuthbert, 2012), our definitions of most mental disorders must be regarded as preliminary.

Identification of reliable and effective biological predictors of mental illness may also contribute to the already active shift away from an exclusively categorical nosology for mental disorders and toward the incorporation of dimensional models that help more precisely capture the multifaceted and complex nature of most psychiatric illness (Morris & Cuthbert, 2012). Indeed, by clarifying the ways observable behaviors and neurobiological characteristics relate to the presence or absence of psychopathology, we may ultimately alter the criteria we use to distinguish health from disease broadly and normal from abnormal anxiety more specifically. Moreover, some psychiatric conditions, including certain anxiety disorders, may eventually be recognized as extremes on continua with normality, just as some forms of hypertension are thought to represent the extreme end of the blood pressure continuum. Indeed, efforts have been under way for several years to develop dimensional measures for use in diagnostic assessments for anxiety (e.g., LeBeau et al., 2012; Niles, Lebeau, Liao, Glenn, & Craske, 2012) disorders and many of these are now accessible on the *DSM-5* Web site (http://www.psychiatry.org/practice/dsm/dsm5/online-assessment-measures).

Evidence for Anxiety Disorder Specificity

The conditions classified as anxiety disorders, both historically and currently, are broadly related, in that each has anxiety of some sort as a core feature. Moreover, virtually all of the individual anxiety disorders have been linked in longitudinal studies to later onset of another anxiety disorder. However, these conditions do not form a neatly unified group; indeed, as noted earlier, in recognition of their marked distinctions, several (PTSD, acute stress disorder, OCD) were removed from the anxiety disorders cluster with the transition to the *DSM-5*. These decisions were based in part on five sets of standards that researchers have used to distinguish among the anxiety disorders; notably, relatively few data are available that use these criteria to validate specific anxiety disorders in children and adolescents and most of the research base is thus focused on adults.

First, both the *DSM-IV* and the *DSM-5* define anxiety-related conditions as distinct by setting forth different sets of diagnostic criteria for each disorder. These criterion sets identify symptoms that most frequently cluster in patients

TABLE 14.1 Social Anxiety Disorder, Generalized Anxiety Disorder, and Separation Anxiety Disorder: Changes From *DSM-IV-TR* to *DSM-5*

	DSM-IV-TR	*DSM-5*
Disorder name	Social phobia	Social anxiety disorder
Cardinal symptoms	Marked and persistent fear of one or more social or performance situations involving potential scrutiny or exposure to unfamiliar people.	Marked fear or anxiety about one or more social situations involving potential scrutiny.
Differences between Editions	Adults (but not children) must recognize that their fear of social situations is excessive or unreasonable. Recognized two forms of the disorder—isolated fear of public speaking versus anxiety in a range of social situations.	Recognition that fear is unreasonable or excessive is no longer required for individuals aged 18 years or older. Anxiety must be out of proportion to actual risks, after cultural contextual factors are taken into account. Most cases treated as generalized, with specifiers added to cases restricted to public speaking or involving selective mutism.
Disorder name	**Generalized anxiety disorder**	**Generalized anxiety disorder**
Cardinal symptoms	Excessive and hard-to-control anxiety and worry about a number of events or activities.	Excessive and hard-to-control anxiety and worry about a number of events or activities.
Differences between Editions	—	No substantive changes from *DSM-IV-TR*.
Disorder name	**Separation anxiety disorder**	**Separation anxiety disorder**
Cardinal symptoms	Developmentally inappropriate and excessive anxiety concerning separation from home or from attachment figures.	Developmentally inappropriate and excessive fear or anxiety concerning separation from those to whom an individual is attached.
Differences between Editions	Classified as a disorder usually first diagnosed in infancy, childhood, or adolescence. Onset before the age of 18. Symptoms last at least 4 weeks.	Classified as an anxiety disorder. No cutoff set for age of onset. Symptoms last at least 4 weeks in children and adolescents and, typically, 6 months or more in adults.

with one or another condition. Although there is considerable consistency in the diagnostic criteria that the *DSM-IV* and *DSM-5* use for the disorders on which this chapter focuses (SAD, social anxiety disorder, GAD), there have also been several changes, as summarized in Table 14.1.

The remaining four standards focus on characteristics that can vary across condition types. Thus, the second standard centers on clarifying distinctions in the specific longitudinal trajectories and associated pattern of comorbidities for the anxiety disorders, and the third takes into account variations in familial patterns of aggregation within families for different anxiety-related conditions and their comorbidities. The fourth standard shifts focus to the specific risk factors or perturbations in biological systems reflective of underlying pathophysiology that research has shown to relate to individual disorders. Treatment response is at the heart of the fifth standard, which has led to evidence that at least some adult anxiety disorders show differential patterns of improvement following specific psychotherapeutic or psychopharmacologic interventions.

OCD and PTSD

Within the *DSM-IV* anxiety disorders, the strongest evidence for specificity based on these five standards derives from studies of disorders that were moved, due to cumulating findings suggesting that they were better classified elsewhere, to new sections of the *DSM-5*. The case is particularly clear for OCD, which is characterized by recurrent, time-consuming, and impairing compulsions or obsessions. With respect to longitudinal trajectory and associated comorbidity, OCD exhibits relatively strong cross sectional and longitudinal associations with disorders of impulse control, including tic disorders and ADHD (Grados et al., 2001; Peterson, Pine, Cohen, & Brook, 2001). Similarly, OCD that occurs early in development predicts an increased risk for further OCD either later in adolescence or during adulthood (Peterson et al., 2001). Family-genetic studies show similar patterns of coaggregation, with associations among OCD, tics, and ADHD emerging frequently within families (Pauls, Alsobrook, Goodman, Rasmussen, & Leckman, 1995; Pauls, Leckman, Towbin, Zahner, & Cohen, 1986; Peterson et al., 2001) and work is also under way to identify gene variants associated with the condition (Grados, 2010). Such patterns of comorbidity are thought to reflect dysfunction in a common neural circuit encompassing the prefrontal cortex, striatum, and thalamus, forming so-called cortico-striato-thalamo-cortical (CSTC) loops (Saxena & Rauch, 2000).

Relatively consistent findings also differentiate PTSD and acute stress disorder (ASD) from other anxiety disorders (but see Zoellner, Rothbaum, & Feeny, 2011, for a dissenting view); in particular, both conditions stand out from most other DSM disorders, in that a specific causal factor, in the form of a frightening event or stressor, is explicitly tied to their onset. The pattern of associated symptoms and comorbidities is also distinctive in PTSD (e.g., Brett, 1997; Sullivan & Gorman, 2002), and a few studies show associations between PTSD in children and signs of stress-related psychopathology in their parents (Yehuda, Halligan, & Bierer, 2001; Yehuda, Halligan, & Grossman, 2001). A growing body of research provides evidence that PTSD is characterized in adults by a specific pattern of neural dysfunction, with excessive activation evident in the amygdala and hippocampus and underactivation apparent in medial prefrontal regions (see Patel, Spreng, Shin, & Girard, 2012 for a review). Less evidence exists to distinguish childhood PTSD from other childhood conditions at a neurobiological level, although some findings suggest that youths with PTSD show structural anomalies in a set of brain regions (corpus callosum, prefrontal cortical areas) that is distinct from areas documented as functioning atypically in adults (Jackowski, de Araújo, de Lacerda, Mari, & Kaufman, 2009). Trauma exposure itself, however, has been associated in a number of pediatric studies with a range of neurodevelopmental consequences, and further work is needed to disentangle these from sequelae or correlates of PTSD (Watts-English, Fortson, Gibler, Hooper, & DeBellis, 2006). Finally, optimal psychotherapeutic treatment of PTSD also differs from that for other anxiety disorders, in that it often involves a heavy focus on repeated exposure to traumatic events (Smith et al., 2013).

Evidence for the specificity of the three conditions on which we focus in this chapter—separation anxiety disorder, GAD, and social anxiety disorder—is weaker than for OCD and PTSD. Indeed, these three conditions are frequently, particularly in pediatric research, treated as a cluster, given their frequent comorbidity (RUPP, 2001). Nonetheless, for each of the three disorders, data suggest that at least some of the five standards are met, including distinct patterns of symptoms.

Separation Anxiety Disorder

Investigators have adopted conflicting conceptualizations of separation anxiety disorder (SAD) during the past few decades and only recently have they begun to recognize it as a condition that can manifest across the life span (Marnane & Silove, 2013). For many years, the prevailing view has held that this condition is closely related to panic disorder, as defined in the *DSM-IV*, and recent findings support a genetic link (Roberson-Nay, Eaves, Hettema, Kendler, & Silberg, 2012). Panic disorder is characterized by sudden, unexpected paroxysms of extreme anxiety or terror. While panic attacks can occur at any point during the life span, the experience of spontaneous, recurrent panic attacks rarely begins before adolescence. In severe cases, the disorder typically follows a developmental course in which isolated, spontaneous panic attacks begin during adolescence and are followed later in life by multiple, recurrent panic attacks that meet criteria for panic disorder (e.g., Pine, Cohen, Gurley, Brook, & Ma, 1998). Agoraphobia, or anxiety about being in places or circumstances from which escape would be difficult or embarrassing in the case of a panic attack, is a common ensuing complication.

The conceptualization of SAD as related to panic disorder arose largely from clinical data in adults with panic disorder, who report high rates of SAD during childhood (Bandelow et al., 2001; Silove, Manicavasagar, Curtis, & Blaszczynski, 1996). Such data are problematic, however, in that they are vulnerable to referral biases and retrospective distortions. In general, data from family and longitudinal studies provide some support for the view that SAD relates to panic disorder; however, the data are not unequivocal (Biederman et al., 2007; Pine et al., 1998; Roberson-Nay et al., 2010). The strongest support for the link between SAD and panic disorder comes from studies of respiratory function, where panic attacks and SAD have been tied to similar breathing perturbations (e.g., Atli, Bayin, & Alkin, 2012; Goodwin & Pine, 2002; Pine, Klein, et al., 2000).

Notably, however, high rates of SAD are also found in offspring of parents with major depression (Biederman et al., 2001), in individuals who have experienced traumatic stress (Goenjian et al., 1995; Pine & Cohen, 2002), and even in the context of streptococcal infection (Swedo et al., 1998). In light of these findings, as well as evidence that childhood SAD is a strong predictor not only of adult panic disorder, but also of adult depression (Lewinsohn, Holm-Denoma, Small, Seeley, & Joiner, 2008), there may be utility in alternate models that conceptualize SAD as a specific pattern of responses to general distress (Lipsitz et al., 1994).

Generalized Anxiety Disorder

GAD, which is characterized by a pattern of pervasive and recurrent worries about a range of topics, along with avoidance of emotional experience or processing, has also been conceptualized as a set of responses to real or anticipated distress (Newman & Llera, 2011). The diagnosis of GAD

has evolved since its initial appearance in the *DSM-III* (APA, 1980). In its first incarnation, the diagnosis was assigned only to adults who presented with a pattern of recurrent worries; children with similar symptoms were instead diagnosed with overanxious disorder (OAD). With the publication of *DSM-IV*, despite mixed evidence regarding the overlap of GAD and OAD (Beesdo-Baum et al., 2011), the GAD diagnosis subsumed overanxious disorder and age was eliminated as a defining diagnostic criterion, although lower symptom thresholds were still used for youths than for adults (Andrews et al., 2010). The *DSM-5* conceptualization of GAD, which emerged after substantive debate regarding multiple issues, including the relative merits of dropping some associated symptoms (Comer, Pincus, & Hofmann, 2012) and the most appropriate minimum duration of symptoms and appropriate symptom thresholds (Beesdo-Baum et al., 2011), continues to allow youths to display fewer symptoms than adults to cross the diagnostic threshold.

Of the conditions classified in *DSM-5* as anxiety disorders, GAD has generated perhaps the most debate, because it virtually always presents with another concurrent anxiety disorder (Klein & Pine, 2002; RUPP, 2001). Indeed, some have contended that GAD represents a complication of other anxiety disorders rather than an independent disorder in its own right (Klein & Pine, 2002). Further, GAD shows unusually tight links with major depressive disorder (MDD), in children as well as adults (Kendler, 2001; Pine et al., 1998; Silberg, Rutter, & Eaves, 2001), leading some prominent theorists to suggest that GAD be grouped conceptually with other distress disorders marked by high levels of negative affectivity, including MDD and PTSD (Watson, 2005).

Social Anxiety Disorder

In individuals with social phobia or social anxiety disorder, anxiety symptoms emerge in anticipation of embarrassment in social or performance situations. Although this construct was historically labeled social phobia, evidence that social anxiety disorder differs dramatically from specific phobias on several fronts (impairment, treatment-seeking behavior, longitudinal outcome, and familial aggregation; e.g., Fyer, 1998; Fyer, Mannuzza, Chapman, Martin, & Klein, 1995; Pine et al., 1998) led to a preference for a new label: social anxiety disorder.

Whereas *DSM-IV* recognized two forms of social anxiety disorder, one characterized by an isolated fear of public speaking and the other characterized by high levels of anxiety in a range of social situations, *DSM-5* treats most cases as generalized, with a specifier assigned to those cases that are restricted to public speaking fears. This change reflects considerable evidence that although individuals with exclusive performance/speaking fears share other socially anxious individuals' core concern about being negatively evaluated, they show distinctive etiological and treatment response profiles (Bögels et al., 2010).

Of note, prior to the publication of *DSM-IV*, children who showed severe avoidance of social situations could be diagnosed with avoidant disorder of childhood instead of social phobia/social anxiety disorder. In light of evidence, however, that the distinction between the two conditions was minimal (e.g., Francis, Last, & Strauss, 1992), the authors of the *DSM-IV* elected to fold avoidant disorder of childhood into the social anxiety disorder category, just as they decided that GAD would subsume overanxious disorder of childhood. This change not only eliminated age as a diagnostic criterion, but it also decreased redundancy among diagnoses, given that avoidant disorder appeared to be rare and to overlap considerably with social anxiety disorder.

Shared Characteristics Among the Anxiety Disorders

A large and growing body of evidence identifies distinctive symptom and familial aggregation patterns as well as markers of neurophysiological dysfunction, within individual anxiety diagnoses. As interpreted most recently by the *DSM-5*'s authors, this literature supports the view that anxiety disorders can be defined as a family of related, but discrete, conditions. However, although individual disorders clearly show specific profiles, there is also ample and comparably strong evidence of commonalities among at least some conditions. For example, common to virtually all of the anxiety disorders is a persistent tendency to experience any of a wide range of anxious symptoms. These can be somatic (e.g., racing heart, sweating, nausea, trembling), cognitive (e.g., worry, fear), or behavioral (e.g., avoidance, tearfulness).

These symptoms may occur discretely or in clusters; when four or more somatic or cognitive symptoms suddenly co-occur and rapidly peak in the context of intense fear, they constitute a panic attack. In individuals with panic disorder, another condition classified as an anxiety disorder (but not a focus of this chapter), panic attacks occur spontaneously and without apparent provocation. In this context, such attacks sometimes lead to agoraphobia, or a fear of experiencing panic symptoms or attacks in a public setting. However, in the presence of specific feared stressors, individuals with other anxiety disorders can also experience panic attacks. For example, individuals with

social anxiety disorder may experience panic when they must speak to a group or mingle at a party. Children with separation anxiety disorder may experience panic when leaving for school in the morning, and adults with the disorder may have such attacks while heading to work.

Worry also represents a core feature of most anxiety disorders for youths and adults alike (Borkovec, 1994; Fialko, Bolton, & Perrin, 2012). Conceptualized as hard-to-control repetitive thoughts or images about future events perceived as uncertain and likely negative, worry represents an effort to reduce the likelihood that those future events will occur (Borkovec, Robinson, Pruzinski, & DePree, 1983). As we discuss later in this chapter, it can function as a type of emotion regulation strategy, albeit one that is less adaptive than others.

Worry can be observed in children as young as preschoolers and it appears to become an increasingly central factor in anxiety disorders over the course of development. This pattern of repetitive thinking appears to emerge as a function of multiple processes—cognitive avoidance, proclivity to interpret problems as difficult to address, beliefs that the process of worry has value, and intolerance of uncertainty (Fialko, Bolton, & Perrin, 2012). Because the process of worry differs minimally across disorders, it is the content and precipitating environmental cues that serve as distinctive characteristics. In GAD, for example, worry and excessive anxiety develop about a variety of events or circumstances and can float from target to target. Objects of worry may also be circumscribed items or situations, as in SAD or social anxiety disorder.

Thus, although SAD, GAD, and social anxiety disorder each demonstrate distinctive profiles in numerous ways, they also share a number of core features. Further, because these three disorders commonly co-occur, particularly in childhood and adolescence, it is difficult to disentangle and study individual disorders in isolation. For these reasons, our review of the literature on mechanisms of anxiety regulation will focus largely on research that encompasses one or more of these three conditions. Recent findings from both developmental psychology and cognitive neuroscience studies of these disorders and of normal-range anxiety converge to provide an increasingly clear picture of the mechanisms of anxiety regulation, at behavioral, cognitive, and neural levels.

ANXIETY REGULATION

The relevance of the construct emotion regulation to our understanding of anxiety, in both clinical and normative manifestations, has been a topic of intense interest in the past several years, leading to the publication of numerous reviews and analytical papers. These put forth a number of ideas about how emotion regulation processes may figure in the onset and maintenance of anxiety disorders in childhood and adulthood (e.g., Cisler, Olatunji, Feldner, & Forsyth, 2010; Rodebaugh & Heimberg, 2008; Suveg et al., 2010). Models vary in the degree to which they emphasize cognitive versus neural versus behavioral processes, but most recognize the importance of all three to our management of anxiety. Further, theorists and researchers are acknowledging with increasing regularity the value of multilevel models for understanding the regulation of such constructs as anxiety; such models are designed to integrate knowledge regarding multiple constructs, processes, and modulatory factors, including genetics, neural function and structure, cognition, and context (e.g., Philippot et al., 2004). Finally, in recent years, more models of anxiety regulation have emerged that pay explicit attention to broad developmental processes and contexts and the ways they may figure in an individual's acquisition of skills for managing and responding to anxiety.

Cognitive-process-oriented models, such as Gross's widely cited (1998) process model of emotion regulation, emphasize the varied cognitive activities that people enact in the course of an emotional event with the aim of modulating their emotional responses. Gross distinguishes between antecedent-focused activities, which include selecting whether to enter given situations or contexts, modifying those situations, deploying attention toward or away from emotionally salient features, and changing one's appraisal of those features, and response-focused activities, which encompass attentional, evaluative, and behavioral processes that occur after an emotionally charged event has occurred. The adaptive value of these strategies varies—results of recent meta-analyses suggest that reappraisal strategies have the greatest impact on emotional responses or psychopathology, with weaker evidence available to support the use of attentionally centered strategies (e.g., distraction or concentration) or efforts to suppress or amplify emotions (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Webb, Miles, & Sheeran, 2012). Notably, however, some strategies within the attentional deployment and response modulation categories appeared more effective than others, which may have obscured significant effects. Specifically, active distraction and control of emotional expression were more closely associated with successful regulation than were concentration or effort to control emotional experience (Webb et al., 2012).

With respect to anxiety in particular, findings regarding cognitive regulatory strategy use are consistent with those from studies focused on emotion regulation more broadly. Reappraisal appears to be an especially effective strategy for modulating anxiety, and youths and adults who report elevated or clinically significant anxiety show atypically weak skill at implementing this strategy and make infrequent use of it (Carthy, Horesh, Apter, Edge, & Gross, 2010; Carthy, Horesh, Apter, & Gross, 2010; Werner et al., 2011). Further, recent findings suggest that even when anxious adults engage in cognitive reappraisal, it may not have the impact on daily life experiences that it appears to have for nonanxious peers (Farmer & Kashdan, 2012).

The process model's focus on cognitive activities aimed at modulating emotion is complemented by other perspectives that aim more specifically to understand how such activities, along with behavioral actions, may be put into use in the context of anxiety. Rodebaugh and Heimberg (2008), for example, framed their model of anxiety regulation in terms of Carver and Scheier's (1998) self-regulatory theory, in which both approach-related or appetitive systems and defensive or avoidant systems engage to facilitate attainment of goals. According to Rodebaugh and Heimberg, anxiety disorders are marked by an excessive focus on ensuring safety and avoidance of negative outcomes, which engages the prevention system, as well as relatively weak activation of the promotion system, which mediates the pursuit of positive or desired goals. Thus, anxious individuals preferentially enact behaviors and thoughts that presumably help them avoid negative outcomes; in the example that Rodebaugh and Heimberg used, individuals with GAD engage in worry behaviors to avoid experiencing negative affect, leaving few resources available for instead initiating behaviors that might help them reach goals that would reduce the negative affect that they are avoiding.

Models also differ in their focus on anxiety versus fear. Anxiety-focused models (e.g., Rodebaugh & Heimberg, 2008) emphasize the ways emotion regulation may modulate the cognitive and neural correlates of the anxious state. Fear-focused models (e.g., Cisler et al., 2010), in contrast, consider the ways emotion regulation may modulate the process of fear conditioning and its outcomes. Each model type informs our understanding in distinctive ways, and both hold value for helping us to better understand the role that emotion regulation plays in the emergence and resolution of both anxiety and fear.

Cisler and colleagues' (2010) proposed model suggests that capacity for emotion regulation influences one's range of response to fear cues after the fear conditioning process is complete. These authors contend that, first, an individual's access to and facility with different emotion regulation strategies will affect the ways that an individual responds in the moment when facing a fear cue. These online responses, in turn, can either weaken or strengthen the learned fear association; in the latter instance, they would increase risk for onset of an anxiety disorder. For example, two people who have been conditioned to fear public speaking are likely to employ different regulation strategies when they find themselves standing in front of an audience and experience the conditioned fear response. One may flexibly employ adaptive regulation strategies such as reappraisal, thus increasing the likelihood that she will be able to proceed with her talk and thus to gain exposure to experiences likely to weaken the learned association. In contrast, the other might use a less adaptive strategy, such as suppression, which paradoxically heightens her fear in the moment and leads her to leave the podium. She thus avoids the experiences that might have decreased her fear and instead chooses an experiential path that maintains or amplifies it.

In the models discussed so far, developmental considerations are implicit, if incorporated at all. In recent years, however, additional models of the anxiety regulation process have been proposed that explicitly assume a central role for developmental processes. Suveg and colleagues (e.g., Suveg, Morelen, Brewer, & Thomassin, 2010), for example, have described the emotion dysregulation model of anxiety (EDMA), in which child temperament and family emotional environment interact to predict capacity for emotion regulation and risk for anxiety. According to this model, youths who exhibit high emotional reactivity, manifested as a behaviorally inhibited temperamental style, and who also inhabit a family whose emotional environment is weighted toward the expression of negative affect rather than positive affect, are at risk for developing a maladaptive emotion regulation style. Consequent failure to manage arousal in the context of anxiety-provoking stimuli, in turn, is predicted to maintain anxiety. This model, which focuses primarily on factors that may contribute to poor emotion regulation skills, complements other models, which place emphasis instead on the cognitive, neural, or behavioral processes implemented in efforts to upregulate or downregulate emotional reactions.

Another recent developmentally informed model of anxiety regulation is embedded in attachment theory and underscores the key role that early attachment experiences may play in determining the emergence of adaptive or maladaptive approaches to managing stress and, by extension, the development of anxiety disorders (Nolte, Guiney, Fonagy, Mayes, & Luyten, 2011). This model is notable

in that its authors have made great effort to integrate data across multiple levels of analysis, with attention to the putative roles of genetic, neural/physiological, behavioral, cognitive, and contextual variables. In brief, Nolte and colleagues (2011) propose that children who encounter an early life environment that is characterized by inconsistent or unpredictable caregiving, particularly if they are temperamentally vulnerable to hyperarousal, may develop a hyperactive response style for coping with stress. While this style is initially adaptive, it begins to become problematic as the child generalizes it to circumstances outside the initial attachment relationship, eventually consolidating a maladaptive style marked by avoidance of threat cues and consequent failure to develop realistic expectations and perceptions of the environment. Consistent with the developmental psychopathology perspective, this model also takes into account the probability that salient variables interact in different ways at different points in development, and thus that multiple anxiety-related outcomes are possible. Recent reviews of the literature suggest that many elements of this model enjoy considerable empirical support (Esbjørn et al., 2012; Jacob et al., 2011); clearly there is value in a perspective regarding anxiety regulation that incorporates attention to developmental factors.

Further integrating this kind of developmentally informed model, which takes a wide-angle view of the big picture, with more elemental models that revolve around the discrete cognitive and neural processes involved in regulating anxiety and fear is a logical next step in the literature. Such broadly integrative efforts will need to take into account emerging data regarding the viability of different strategies and processes at different points in the life span, as well as the neural structures and functions and cognitive skills and capacities that must be in place to support them. In the next sections of this chapter, we summarize recent findings regarding the cognitive and neural processes and structures that support and facilitate the regulation of anxiety. Where possible, we also examine ways individual differences may influence the paths along which these factors evolve from childhood through the life span.

Cognitive Mechanisms of Anxiety Regulation

Much of the research on cognitive mechanisms of anxiety regulation as they emerge and evolve across the life span has focused on strategies that are commonly characterized as explicit or consciously and intentionally implemented. As Amstadter (2008) summarized in a recent review, the use and effectiveness of two strategies, reappraisal and suppression, have been especially common targets of study in samples across much of the life span. As we briefly noted earlier in this chapter, reappraisal, or cognitively reframing an anxiety-provoking situation in ways that are calming and constructive, enjoys perhaps the most empirical support as a useful approach to regulating anxiety in youths and adults (Webb et al., 2012). It is also a strategy that anxious individuals from middle childhood to early adolescence and onward appear to implement less often and less effectively than their less-anxious peers (Carthy, Horesh, Apter, Edge, & Gross, 2010; Carthy, Horesh, Apter, & Gross, 2010; Farmer & Kashdan, 2012; Legerstee, Garnefski, Jellesma, Verhulst, & Utens, 2010; Werner et al., 2011; but see Decker et al., 2008, and Tan et al., 2012, for conflicting findings), at least in part because they doubt the utility of this approach (Sung et al., 2012). In light of these findings, it is not surprising that quick mastery of cognitive reappraisal in the context of CBT shows promise as a predictor of positive treatment outcomes for anxious adults (Moscovitch et al., 2012).

Effective implementation of cognitive reappraisal places demands on a number of cognitive systems, some of which mature slowly. For example, cognitive control, or the ability to intentionally use effort to manipulate attention, memory, and other mental functions, appears to be a critical foundation for successful reappraisal (e.g., Vanderhasselt, Baeken, Van Schuerbeek, Luypaert, & De Raedt, 2013). This capacity does not appear to be fully developed until adulthood (Kar, Vijay, & Mishra, 2013), which is not surprising given that its neural substrates show a long, slow, and complex developmental trajectory that can extend into an individual's mid-twenties (Raznahan et al., 2011). Further, some evidence suggests that as the brain ages, the neural underpinnings of cognitive control show waning efficiency, as reflected in increased difficulty implementing reappraisal strategies (Opitz, Rauch, Terry, & Urry, 2012). Thus developmental status is an important consideration in evaluations of whether an individual shows deficits or strengths in capacity for cognitive control.

Ability to control and direct attention in the context of emotion appears to be particularly important for cognitive reappraisal, which demands that an individual move flexibly from one set of perceptions and interpretations to another. Anxious adults, for example, even those who do not cross diagnostic thresholds for any disorders, appear to have more difficulty than their less-anxious peers in consistently implementing this skill, even when they show typical ability to redirect attention to nonemotional cues (Johnson, 2009). Similar patterns of difficulty controlling attention to emotional stimuli characterize youths with

anxiety, which suggests that even rudimentary or immature capacity for attentional control may be critical to effective regulation of anxious thoughts and feelings (White, Helfinstein, Reeb-Sutherland, Degnan, & Fox, 2009).

Numerous approaches to treating anxiety disorders have begun to incorporate explicit training in cognitive reappraisal as a core component. In particular, cognitive reappraisal's compatibility with traditional cognitive behavioral therapy (CBT) for anxiety, which integrates techniques and approaches from cognitive and behavioral perspectives and has been successfully implemented with anxious children, adolescents, and adults, has generated considerable interest among researchers and clinicians. Traditional CBT focuses on exposure to anxiety-provoking stimuli and challenges to maladaptive thinking patterns; while a large proportion of individuals with anxiety disorders respond well, a sizable number (up to 30 or 40% in some studies) do not (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012). The merits of introducing cognitive reappraisal training to boost treatment effects, particularly in those who show weak responses to traditional CBT have received increasing attention, and some have even suggested making cognitive reappraisal and other emotion regulation techniques core elements of anxiety treatment for both adults (e.g., Mennin, 2006) and children (e.g., Hannesdottir & Ollendick, 2007). Although data are still emerging from studies that test the hypothesis that training in cognitive reappraisal and other adaptive emotion regulation techniques may augment treatment response among anxious individuals, findings to date are mixed and suggest that close attention to individual differences in patterns of response is warranted (Newman et al., 2011).

A second emotion regulation strategy that has received considerable attention in the context of research on anxiety is suppression of emotional experience or, more commonly, expression. Unlike cognitive reappraisal, suppression has been associated with a range of problematic consequences in anxious and healthy adults, including slowed reduction of negative emotion, decreased experience of positive affect and events, and, in some cases, heightened physiological arousal (Campbell-Sills et al., 2006; Farmer & Steger, 2006; Feldner, Zvolensky, Stickle, Bonn-Miller, & Leen-Feldner, 2006). In both adults and adolescent girls, use of suppression to regulate emotions has also been found to relate to a lack of emotional awareness (Eastabrook, Flynn, & Hollenstein, 2014; Gross & John, 2003).

A few studies have suggested that in both youths and adults, suppression is positively associated with the presence of anxiety, particularly social anxiety. For adolescent girls, for example, implementation of this emotion regulation strategy appears to mediate associations between limited emotional awareness and social anxiety (Eastabrook et al., 2014). Adults with social anxiety disorder, as well as those who endorse having avoidant attachment styles, which have been linked to a pattern of anxious and avoidant behavior, endorse more use of this strategy than do healthy controls, and avoidantly attached adults have been shown to evidence a distinctive neural profile when using suppression to regulate emotion (Vrtička, Bondolfi, Sander, & Vuilleumier, 2012; Werner et al., 2012).

Notably, in healthy youths, the use of suppression, which is more common among boys than girls, appears to decline with increasing age (Gullone, Hughes, King, & Tonge, 2010), which suggests that as complex cognitive skills emerge and mature, healthy individuals are likely to switch to the use of more adaptive strategies. John and Gross (2004) hypothesized that this normative developmental shift may also reflect the acquisition of life experience, which provides individuals with direct feedback about the pros and cons of using different emotion regulation strategies. Further, the rewards and negative consequences associated with the use of suppression may change across the life span, thus differentially reinforcing its use at different developmental stages.

Other emotion regulation strategies that are prominently associated with anxiety include worry and rumination, which constitute distinct, but related, patterns of repetitive negative thinking that an individual finds hard to control (McEvoy & Brans, 2013). Worry, which characterizes many anxiety disorders and serves as a core feature of GAD, is thought to function by helping individuals avoid negative affect. At least two ideas about how worry may facilitate emotional avoidance have received empirical support; first, it may constitute an effort to prevent or prepare for negative experiences, second, it may blunt bodily responses to stimuli that elicit fear. Thus, at both cognitive and physiological levels, worry prevents the processing that is critical for extinguishing anxious responses to perceived threats (Borkovec, 1994). Worry has also been conceptualized, on the basis of accumulating findings, as a means of maintaining a state of chronic distress in order to avoid having to shift from positive or neutral to negative emotional states in the face of negative events (Newman & Llera, 2011).

Tendencies to worry emerge early in life; however, although worries have been documented among preschoolers, they appear to increase in prevalence around the age of eight years (Vasey, Crnic, & Carter, 1994). The ability to worry depends on being able to anticipate future events

and to anticipate catastrophic outcomes, thus children are less likely to employ this as a primary regulatory strategy until these reasoning skills reach at least a rudimentary level of development. As early as elementary school, girls endorse more worrying than do boys (Silverman, LaGreca, & Wasserstein, 1995), and this pattern of sex difference appears to continue into adulthood (Zalta & Chambless, 2008).

Rumination, which differs from worry in that it focuses more heavily on past events than on the future and on content that is oriented toward issues of self-worth and loss rather than anticipated negative experiences, is also more common among women than among men (see Nolen-Hoeksema, 2012, for a review). Like worry, it also appears to account in part for sex differences in rates of anxiety symptoms and disorders from at least middle childhood onward (Bender et al., 2012; Zalta & Chambless, 2008; Zlomke & Hahn, 2010). As Nolen-Hoeksema (2012) pointed out, much less is known about the emotion regulation strategies that men, particularly anxious men, employ, than is known about women's preferred strategies. Further research is clearly needed across the life span to better characterize the male developmental trajectory for adaptive and maladaptive approaches to managing anxiety.

Research in both children and adults tends to find rumination to relate more strongly to depression than anxiety (McEvoy & Brans, 2013; Verstraeten, Bijttebier, Vasey, & Raes, 2011). Not surprisingly, however, given the high rates of comorbidity between anxious and depressive conditions, ruminative thinking also appears common in individuals identified as primarily anxious. Individuals with social anxiety, for example, frequently engage in postevent processing, which consists of repetitive reflection on negative aspects of a social interaction. Further, some evidence suggests that a ruminative response to anxiety may increase risk for depressive disorders and, conversely, rumination both in and outside of the context of depression may increase risk for anxiety (McLaughlin & Nolen-Hoeksema, 2011; Starr & Davila, 2012). These associations between rumination and psychopathology may stem, at least in part, from negative interpersonal correlates of rumination, such as excessive support or reassurance seeking (McLaughlin & Nolen-Hoeksema, 2012).

In adults with social anxiety, CBT appears to decrease tendencies for post-event processing or anxious rumination (Price & Anderson, 2011). Limited research has examined treatment effects on this emotion regulation strategy in youths; however, at least one influential theoretical model of child anxiety and its treatment explicitly identifies postevent attributions as a key element that warrants attention (Kendall, 2012). Further, CBT has been used successfully to target worry in children as young as 7 years of age (Suveg, Sood, Comer, & Kendall, 2009), which suggests that further efforts to modify repetitive negative thought patterns in youths are likely to yield positive results.

In addition to the anxiety regulation strategies outlined above, individuals may also use a range of other adaptive and maladaptive approaches to modulate their emotional state in the context of an anxiety-provoking circumstance. No one strategy is likely optimal in every situation; even those identified as typically maladaptive may sometimes be the best option an individual has available. Further, the range of accessible strategies is likely to vary across development, as will the contexts that demand their implementation; it is thus likely that strategies that are less effective at some developmental stages may hold more utility at others. In fact, rather than simply being skilled at a few adaptive regulation strategies, possession of a broad and flexible emotion regulation repertoire may serve as a stronger predictor of psychological health. In at least one study, individuals who reported using an array of regulatory strategies exhibited less internalizing psychopathology than did peers who endorsed a more limited range of strategies (Lougheed & Hellenstein, 2012).

A growing body of research also points to the value of mindfulness, or fostering awareness and acceptance of one's emotional experience, for regulating anxiety. Together with self-reported difficulties with emotion regulation, limited mindfulness predicts both anxiety symptoms and disorders in adults (Roemer et al., 2009). Treatment approaches that explicitly teach and encourage mindfulness have shown efficacy in reducing anxiety, along with its neural correlates, in adults (Goldin & Gross, 2010). Anxious children and adolescents, too, have been found to respond positively to mindfulness-based therapies in both open and randomized controlled treatment trials, and clinicians are incorporating mindfulness training into child treatment with increasing frequency (Semple & Burke, 2012). Notably, however, at least one study found the use of mindfulness or acceptance techniques to perpetuate, rather than mitigate negative affect in adults with GAD, which suggests that individual differences that predict a positive response to such approaches warrant further investigation (Aldao & Mennin, 2012).

Research into cognitive strategies for regulating emotion broadly and anxiety specifically has made great strides in the past few decades, with particularly notable advances made in understanding normative patterns of strategy

use across development. Integration of the cognitive, developmental, and clinical literatures has also yielded useful information about what strategies are most effective and whether and how such strategies, particularly cognitive reappraisal and mindfulness, can be efficiently incorporated into evidence-based treatment approaches. Perhaps the most striking developments in the knowledge base regarding anxiety regulation, however, come from translational work that spans neuroscience, clinical, and developmental domains. In the next section, we review recent research findings regarding the neural substrates of anxiety regulation as they evolve across the life span.

Neural Mechanisms of Anxiety Regulation

Research in neuroscience has made fundamental contributions to the conceptualization of the emotion regulation construct, broadly speaking. Moreover, due to cross-species conservation in brain-behavior relationships for fear and anxiety, neuroscience research in this area has provided a particularly influential perspective in shaping conceptualizations of both emotion and emotion regulation. This neuroscience perspective has clear advantages when it is assumed in attempts to understand emotion regulation in typically and atypically developing children and adolescents, as well as later in the life course; it also, however, holds several inherent disadvantages.

Because the brain is the ultimate arbiter of behavior and cognition, neuroscience research has the advantage of examining factors that may ultimately cause emotions and emotion regulation, providing a mechanistic understanding of the constructs. However, because considerable research in neuroscience is conducted using a cross-species approach, a certain degree of reduction is necessitated in the experimental approach if researchers are to maintain experimental control. The reductive aspects of neuroscience carry marked disadvantages for clinical application, in that findings from neuroscience-based research can be difficult to extrapolate to the complexities of the clinical scenario, particularly for children, where development adds additional complications and considerations. Again, research on anxiety has been at the forefront of attempts to integrate findings from neuroscience into current thinking about developmental psychopathology. Accordingly, research on the neuroscience of the regulation of normal and pathological anxiety is important not only to our understanding of anxiety per se, but also to our broader understanding of individual differences in other clinical domains and for emotion regulation more generally.

Consistent with the definitions that we outlined earlier in this chapter, the somewhat reductionist neuroscience perspective on emotion regulation considers emotion to constitute a brain state associated with stimuli, such as threat or rewards, that the organism will expend effort to approach or avoid. In this context, a threat is a dangerous stimulus, capable of harming the organism, which creates fear (the brain state created by an immediately present threat) or anxiety (the brain state created by a more distal or potential threat). For both sets of stimuli, the associated distinctive brain state can be identified in various species based on the organism's tendency to avoid the threatening stimulus. Of course, these definitions can be applied to both normal and abnormal forms of fear or anxiety, with the distinction hinging on the degree to which the brain state ultimately facilitates or hinders adaptation.

In the neuroscience perspective, emotion regulation refers to any attempt by the organism to alter or modulate this initial emotional response. For both fear and anxiety, regulation is viewed typically from this perspective as attempts to modulate levels of the emotion to facilitate ongoing adaptive behavior. In this context, normal emotion regulation can be differentiated from pathological regulation, based on the organism's ability to reduce the level of fear or anxiety that is expressed when signs of danger have dissipated. In some sense, this distinction between an emotion and the attempt to regulate it is arbitrary. This is because the attempt to regulate an emotion can begin virtually instantaneously with onset of the emotion. However, emotion and emotion regulation can be viewed as co-existing on a dimension. In this perspective, the term emotion refers most directly to the organism's immediate response, and the term emotion regulation becomes increasingly relevant in describing this response at later points in time. At these later points in time, regulation of emotion is expressed as the organism engages various cognitive and associated behavioral processes to alter the initial emotional reaction.

Considerable research has translated work in rodents and nonhuman primates to clinical contexts. Interest has focused particularly deeply on brain-imaging research examining the substrates of emotion regulation. This interest has emerged, at least in part, because such research extends to humans the considerable range of findings in other species regarding the brain substrates of emotion generation and the associated structures that regulate generated emotions. As is typical in many domains of brain imaging research, more studies of emotion regulation examine adults than children or adolescents. This state of affairs reflects the methodological and ethical

complexities of conducting brain imaging research in vulnerable individuals, especially children, who may find the scanning environment frightening and who may have difficulty monitoring and managing their own movement and distress (Bookheimer, 2000). These issues are particularly salient in studies focused on the experience of negative emotions, such as fear and anxiety, the induction of which may require the application of gentler stimuli than those that are used with adults (e.g., Pine, Fyer, et al., 2001). Nevertheless, after many years of successful application of imaging technology in research on adults, a growing brain imaging literature also has arisen that focuses on normal and abnormal child and adolescent development across multiple emotional and cognitive domains.

Over the past 10 years, imaging research on emotion regulation typically has adopted one of two experimental approaches, consistent with the dual-process framework that Gyurak and colleagues (2011) outlined. In one approach, the research participant is directly instructed to regulate any emotion that arises during a brain-imaging experiment. While regulatory acts could involve increases or decreases in either positive or negative emotions, the most consistent results have emerged in studies examining attempts to reduce fear, an observation that again follows from the cross-species conservation in brain-behavior relationships for this brain state. This first approach has been termed explicit emotion regulation, reflecting the fact that the research participant is explicitly told the goal of the experiment, which is to change an initial emotional response. Moreover, in some such experiments, the participants are directly taught methods for regulating their emotions. These methods vary across studies, but most research focuses on reappraisal, or changing the way in which one thinks about an emotionally charged situation or topic with the aim of increasing or decreasing its emotional impact. In other experiments, no instructions are provided regarding whether or how to employ particular regulatory strategies.

The other approach to emotion regulation does not provide any instructions to the participant regarding emotion; indeed, no reference is made to emotion at all. Rather, the participant is required to complete a neutral task, such as target identification or memory encoding. In this context, task-irrelevant emotional and neutral items are embedded, and emotion regulation is indexed based on the degree to which research participants can stay focused on and engaged in the neutral task when they are confronted by task-irrelevant emotional stimuli. Studies using this second approach are considered to be examining implicit emotion regulation, or regulatory processes that occur out of awareness.

A number of fMRI studies map the neural correlates of re-appraisal and other explicit emotion regulation strategies in healthy adults, with regulatory efforts focused on negative or positive emotions in general (e.g., McRae et al., 2012) or on anxiety in particular (e.g., Ball, Ramsawh, Campbell-Sills, Paulus, & Stein, 2012). This work in adults also has been extended to various anxiety states, including normal individual differences in healthy populations on anxiety rating scales and clinical diagnoses of social phobia or generalized anxiety disorder (Ball et al., 2012; Blair et al., 2012; Brühl et al., 2012). Moreover, studies of this type have examined differences in the neural correlates of emotion regulation between healthy adolescents and adults, and although fMRI studies of cognitive reappraisal in children are limited, researchers have successfully measured neural activity during reappraisal tasks using electroencephalographic (EEG) techniques in youths as young as 5 years (DeCicco, Solomon, & Dennis, 2012). The research base is thus growing and expanding in ways that will allow a more developmentally informed understanding of the neural substrates of emotion and anxiety regulation than was possible initially.

An additional factor renders a developmental approach to this area of study particularly challenging. Not only do researchers studying explicit emotion regulation face the general methodological and ethical issues inherent in neuroimaging work with youths, but they also must address one more specific set of complications. Because research participants are directed to attend to the study goals on each experimental trial, expectancies about what they should do can heavily influence their patterns of task responding. The relatively common use of self-report assessments of emotional change as the core measure of emotion regulation competency gives further weight to expectancies, and it remains unclear how tightly real life efforts to regulate emotion in the absence of instruction to do so or measurement of one's success map onto those produced during explicit emotion regulation tasks. In part because the effects of expectancy might vary among children, adolescents, and adults (Brenner, 2000), thus introducing a confound that is difficult to control for, relatively few studies compare the neural correlates of reappraisal in healthy adolescents and adults (but see McRae et al., 2012). None of these studies to date have made comparable comparisons across developmentally stratified groups with pathological forms of anxiety.

The most consistent findings from fMRI studies of explicit emotion regulation focus on the functioning of

areas within the association cortices, regions of the brain that are not directly involved in perception, motor execution, or even initial emotional responding, but instead support more integrative brain-based processes. Typically these areas operate in the context of brain networks known to support relatively complex forms of decision making, and include areas of the dorso-medial prefrontal cortex (PFC), the ventro-lateral PFC, and the dorsal parietal cortex. In healthy adults, these regions typically show enhanced activation during successful emotion regulation—both explicit and implicit, in tandem with reduced activation in brain regions such as the amygdala that are thought to support aspects of emotion reactions (e.g., Bush, Luu, & Posner, 2000; Somerville et al., 2013). Moreover, studies of adults with anxiety disorders, as well as those with temperamental or personality characteristics associated with anxiety generally find reduced activations in these parietal and PFC regions, suggesting that deficient emotion regulation in these individuals reflects an inability to engage regulatory neural structures (e.g., Ball et al., 2012; Vrtička et al., 2012).

Although the base of studies that take a developmental perspective to understanding the neural correlates of anxiety regulation is still growing, emerging evidence from comparisons of neural correlates of emotion regulation between healthy adolescents and adults suggests that the regions perturbed in adult anxiety disorders continue to mature through adolescence (e.g., McRae et al., 2012). Few studies have yet used neuroimaging to examine reappraisal in children prior to adolescence; one fMRI study, however, in which 5 to 10 year old children were asked to reappraise sad images, yielded evidence of bilateral activation in lateral and medial PFC regions, along with right-lateralized activity in the ACC and ventral lateral PFC (Levesque et al., 2004). Further, evidence from research that has measured evoked response potentials in preadolescent children during cognitive reappraisal of emotion also supports the hypothesis that the neural substrates of emotion and anxiety regulation are not yet functioning at an adult level (Dennis & Hajcak, 2009; DeCicco et al., 2012). Thus, maturation in these regions during development may explain why some forms of anxiety wane during adolescence.

Our understanding of the neural mechanisms of explicit anxiety regulation has become increasingly sophisticated in recent years, with a shift of focus from the activation of individual structures to the ways neural regions interact during an emotional event. This literature has yielded evidence that the degree to which prefrontal brain regions engage interactively and responsively with the amygdala is an important factor underlying variability in adult capacity to effectively down-regulate or decrease negative emotion. Lee and colleagues (2012) for example, recently found evidence that the PFC more effectively and efficiently modulates amygdala activity in adults who are more adept at using a reappraisal strategy than in those who show less skill at implementing this strategy.

Considerable fMRI research examines implicit emotion regulation in both healthy and anxious adults; this extensive database facilitates comparisons of the neural correlates of implicit and explicit forms of emotion regulation in such samples. Moreover, while relatively few studies examine developmental aspects of explicit emotion regulation (e.g., McRae et al., 2012), a more extensive database exists regarding implicit emotion regulation among children and adolescents. This body of research encompasses considerable work regarding the regulation of emotions in general, as well as the regulation of anxiety in particular. Research on implicit emotion regulation generally has relied on three different sets of processes, which can be characterized based on the neutral tasks that research participants complete. These tasks variously require participants to regulate emotion in the context of cognitive conflict, to orient attention, or to engage in stimulus-reinforcement learning.

In fMRI research on the brain response to conflict, participating individuals are presented with neutral stimuli that they are instructed to classify; for example, a subject may be asked to identify the direction in which an arrow is pointing or to label the gender of each model in a series of neutral faces. To make this classification more difficult, the neutral stimulus is surrounded with other, distracting stimuli, such as multiple task-irrelevant arrows pointing in opposite directions. The inclusion of task-irrelevant stimuli introduces cognitive conflict, in that the participant must stay focused on task-relevant stimuli and resist being derailed by the task-irrelevant distracters. Finally, to make the otherwise neutral task emotional, researchers embed features that connote threats and rewards in at least a subset of trials. For example, on neutral trials, a subject may be asked to perform difficult classifications of neutral faces, whereas on emotional trials, the subject must classify faces making emotional expressions. In these tasks, successful performance requires the subject to reduce responding to emotional stimuli in order to maintain task-relevant goals.

One particularly interesting example of such research examines the brain regions that implement both the monitoring and the control of cognitive conflict. Etkin and colleagues (2006) asked healthy adults undergoing fMRI scans to indicate the affect presented on fearful and happy faces; to introduce conflict, each face was overlaid with the word HAPPY or the word FEAR so that some face/word

combinations were congruent and others were incongruent. Their findings indicated that many of the brain regions involved in explicit emotion regulation, particularly prefrontal cortical areas and the anterior cingulate cortex (ACC), also play a role in conflict monitoring and control during performance of tasks that employ emotional stimuli. Further, taken together with the results of research focused on explicit processes, as well as those from additional studies that have found associations between state anxiety in healthy adults and patterns of function in prefrontal and ACC regions during cognitive conflict tasks (e.g., Bishop, Duncan, Brett, & Lawrence, 2004), these findings suggest that implicit and explicit forms of emotion regulation may draw on overlapping brain regions.

Moreover, the same group also implicates perturbed functions in these same regions in adults with GAD (Etkin et al., 2010; Etkin & Schatzberg, 2011). Using the same facial emotion conflict task, the authors of both studies found study participants with GAD to show difficulty engaging regulatory processes and their mediating neural structures that healthy individuals appear to activate spontaneously in the absence of explicit instruction. Blair and colleagues (2012) obtained strikingly similar findings in research directly comparing implicit and explicit forms of emotion regulation in patients with GAD and patients with social phobia. Notably, no significant differences in patterns of activation emerged between patient groups, suggesting that at least some shared neural substrates characterize the two disorders.

An important next step will be clarifying the neurochemistry of the anxiety regulation process as it is mediated in the PFC and other salient regions of the brain; studies that simultaneously probe neurochemical activity and neural function hold promise for advancing knowledge in this area. In one recent study, for example, Sripada and colleagues (2013) found evidence that by manipulating levels of allopregnalone, a neurosteroid that modulates the function of gamma-aminobutyric acid (GABA) type A receptors in healthy adults, they could enhance neural activity in the PFC and amygdala during an emotionally charged cognitive conflict task. When linked with the considerable data indicating that dysregulation of the GABA neurotransmitter system may play a key role in the development of anxiety (Kalueff & Nutt, 2007), these findings move us closer to understanding the anxiety regulation process as it plays out at multiple levels of analysis.

Because implicit emotion regulation tasks create different expectancies than explicit tasks, there has been interest in employing them in research that takes a developmental approach to understanding psychopathology, including anxiety. In healthy children as young as 9 years of age, evidence is emerging that suggests that prefrontal cortical activation, particularly dorsolateral regions, already differs between emotional and neutral task conditions (Lamm, White, McDermott, & Fox, 2012). Initial attempts to extend this work to individuals with or at risk for anxiety, however, have generated findings that are difficult to reconcile with the extensive research on normal and pathological emotion regulation, in the service of cognitive control. For example, two studies that have examined patterns of neural activation in adults or adolescents who were characterized during childhood as at high risk for anxiety due to a behaviorally inhibited (BI) temperamental style (Jarcho et al., 2013; McDermott et al., 2009), have yielded mixed findings. Whereas McDermott and colleagues (2009) found evidence that patterns of neural response to emotional cues presented within a conflict task moderated associations between childhood BI and adolescent anxiety disorders, Jarcho and colleagues' (2013) study of adults with and without a history of BI did not find brain activity patterns to function as either a moderator or a mediator in such associations (although BI history did predict atypical activation in prefrontal cortical regions).

Research on attention orienting, much like that on conflict, typically involves performance of a neutral task. However, participants tend to perform more quickly and accurately on orienting tasks than on cognitive conflict tasks, which suggests that the former are easier. In some orienting tasks, the participant is simply required to identify, as quickly as possible, the spatial locale of an easy-to-detect target. In others, participants might have to classify the target much as they might in cognitive conflict tasks; however, the classification is typically far easier due to the absence of explicitly conflicting cues. Orienting tasks present such stimuli in different contexts—some involving no other stimuli, others involving proximal neutral stimuli, and a third set involving proximal emotional stimuli. For example, in a hypothetical orienting task, a letter or symbol might serve as the target; in some trials it will appear alone (no other stimuli), in others it will appear with neutral faces (proximal neutral stimuli), and in still others it will appear with emotional faces (proximal emotional stimuli). In the context of this kind of task, emotion regulation is conceptualized as the capacity to rapidly orient across these different contexts at a consistent rate over time. Typically, orienting ability is quantified based on reaction time (difference scores are calculated for emotional vs. nonemotional trials), and various task arrays have been used.

The most frequently employed orienting paradigm in developmentally informed studies of normal and abnormal aspects of anxiety is the dot-probe task (e.g., Mogg & Bradley, 1998); numerous versions exist, which variously use emotional words, faces, and pictures as target stimuli. In healthy youths and adults, successful orienting to target cues in the context of the dot-probe task and other similar orienting tasks requires engagement of the ventro-lateral PFC, encompassing associated expanses of the anterior insular cortex (e.g., Monk et al., 2006) as well as parietal regions (Pourtois et al., 2006). Interestingly the ventro-lateral PFC region implicated in orienting processes overlaps with regions implicated in reappraisal (e.g., Campbell-Sills et al., 2011), which echoes evidence from conflict studies regarding parallels in neural correlates of explicit and implicit emotion regulation tasks.

The most consistent finding in studies of pathological anxiety, including trauma-related distress, is enhanced activation in this PFC region, which often correlates negatively with levels of anxiety (Fani et al., 2012; Monk et al., 2006). This pattern of results suggests that engagement of the ventro-lateral PFC facilitates maintenance of orienting, particularly in contexts where threats can disrupt it. Findings regarding both normal and abnormal variations in adolescent anxiety extend this framework to developmental psychopathology, representing a particularly broad application of the emotion regulatory framework.

The third area of fMRI research aimed at elucidating the neural correlates of implicit emotion regulation focuses on aspects of stimulus-reinforcement learning. Much as research on cognitive control and attention orienting does, studies of stimulus-reinforcement learning consider how responses to stimuli that initially are neutral change when those stimuli are linked to emotionally salient information. Of the three task types, those that involve stimulus-reinforcement learning place the fewest demands on research participants, whose learning can be assessed in the absence of any overt behavioral response.

The most basic form of stimulus-reinforcement learning examined in efforts to clarify the neural substrates of anxiety and its regulation focuses on fear conditioning (Dunsmoor & LaBar, 2013). In fear conditioning tasks, a neutral stimulus, such as a tone or a light, is paired with an aversive unconditioned stimulus (the UCS). Research with rodents, nonhuman primates, and adult humans typically uses electric shock, a highly potent stimulus, as the UCS; studies in children and adolescents, however, have relied for ethical and practical reasons on milder UCS, such as loud sounds or annoying air blasts (e.g., Monk et al., 2003; Pine et al., 2001). Following pairing of the neutral stimulus and UCS, the neutral stimulus acquires the capacity to evoke the same emotion as the UCS, in part because the participant learns to associate the two together. As a function of its newly acquired evocative capacity, the neutral stimulus is reclassified as a conditioned stimulus (CS+). In fMRI research, this initial form of learning is typically viewed as part of an emotional reaction that unfolds over time as the association between the UCS and the CS+ emerges, strengthens, and subsides.

In the context of most research on fear conditioning, emotion regulation is operationally defined in terms of changes that occur in this initial emotional reaction, following other experimental manipulations. Probably the most extensive body of research in this area considers changes in extinction, or the reduction or disappearance of a conditioned response. Extinction occurs when an organism repeatedly encounters a CS+ in the absence of the UCS, which appears to lead to a new learning process in which the CS+ is linked with safety, or the absence of threat (Bouton, 2004). This leads the organism to reappraise and reclassify the CS+ as an ambiguous stimulus, one that could evoke fear in one context, but not in others, including the UCS-free context in which the stimulus is currently encountered.

Many theories of anxiety, particularly those that emanate from the behaviorist tradition, emphasize the role of deficient extinction in sustaining individual differences in anxiety. Empirical data lend support to this notion; Lissek and colleagues (2005) found, in a meta-analysis of the fear conditioning literature, that not only does fear conditioning occur more rapidly in individuals with anxiety disorders, but extinction also occurs more slowly. Such impairment of extinction processes may reflect underlying genetic diatheses. Indeed, one study found that individuals with a particular genetic polymorphism (COMT met/met) that has been implicated in anxiety and other negative mood states were unable to extinguish conditioned responses at all (Lonsdorf et al., 2009). How these diatheses interact with experience and context to influence the developmental course of anxiety remains unclear; however, recent work takes a first step toward answering this question by suggesting that extinction failures may serve as a link between childhood anxiety (which is common but typically resolves) and the less common outcome of developing an adult anxiety disorder (Britton et al., 2011).

Some of the strongest support for these theories derives from research on the therapeutics of anxiety disorders, where CBT has emerged as one of the more effective treatments across the life span (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012). CBT for anxiety holds as central aims the modification of maladaptive thinking and the reduction of avoidance or facilitation of extinction via

exposure to feared or anxiety-provoking stimuli. Along with training in cognitive reappraisal, as discussed earlier, exposure has proven to be one of the most important elements in successful CBT treatment of a range of anxiety disorders (Moscovitch, Anthony, & Swenson, 2009), and neuroscience research into the mechanisms that underlie the exposure-mediated extinction process is yielding clues regarding both how extinction works and how it can be best achieved in the context of CBT.

In healthy adults, fMRI research has demonstrated that the amygdala is a primary mediator of fear learning and that the medial prefrontal cortex and the dorsal ACC play key roles in implementing extinction via inhibition of amygdala activation (Quirk, Garcia, & Gonzales-Lima, 2006; Sehlmeyer et al., 2009). There is some evidence that the ability to extinguish conditioned threats is still maturing during adolescence (Pattwell et al., 2012), with decreased capacity for extinction learning relative to children and adults observed both in adolescent humans and adolescent mice. Although the neuroimaging literature on fear conditioning and extinction in youths is still too limited to permit definitive statements about neural mechanisms, presumably this developmental pattern maps onto the maturation of relevant brain regions, particularly the PFC. Notably, however, related studies have yielded evidence of developmental changes in the fear conditioning process, as well as its psychophysiological correlates from age 3 years onward (e.g., Gao, Raine, Venables, Dawson, & Mednick, 2010), which suggests that similar attention to neural correlates across development may be fruitful.

Clearly our knowledge about the neural correlates and substrates of anxiety regulation has grown exponentially in the past several years and as researchers continue to find new ways to bridge neuroscience, clinical, and developmental domains, this literature is likely to continue to expand at a rapid pace. One particularly exciting direction that this work is taking builds on ideas that Tucker (1989) articulated many years ago by considering the interpersonal contexts in which emotion and anxiety regulation processes unfold. In the final section of this chapter, we describe recent advances in understanding how contexts, intrapersonal and interpersonal, may reciprocally influence the neural and cognitive processes involved in anxiety regulation across development.

The Role of Context in Anxiety Regulation

As Aldao (2013) astutely pointed out in a recent article, understanding contextual influences on emotion regulation in individuals with psychopathology is especially important, given that an inflexible set of responses to environmental cues serves as a core characteristic of many disorders. Many of the cognitive and behavioral biases that are commonly observed among individuals with anxiety disorders constitute precisely this kind of response set, and it will thus be critical to clarify how both intrapersonal and extrapersonal features may reinforce or discourage their implementation. A broad range of such features is likely to be relevant, with different contextual factors weighing more heavily into the anxiety regulation process at different points in development.

In infancy and early childhood, for example, interpersonal interactions with parents constitute a large proportion of an individual's daily life, and thus those interactions will typically play a large role shaping in the individual's responses to emotional cues. A large literature examines the ways parent–child interactions facilitate or interfere with healthy emotion regulation (Scaramella & Leve, 2004), and increasingly sophisticated research takes into account parent and child characteristics and the interplay between them as predictors of child responses to distressing circumstances (e.g., Aktar, Majdandžić, de Vente, & Bögels, 2013). In adolescence, in contrast, an individual's peer group assumes increasing salience for both adaptive and maladaptive responses to emotional cues, and while family relationships remain important, their patterns of influence on regulatory processes evolve (Adrian et al., 2009; Larsen et al., 2012).

Studying how these interaction patterns figure in the development of regulatory strategies and capacities is complicated, particularly if one aims to gather data at multiple levels (e.g., neural, cognitive, and behavioral). A number of recent neuroimaging studies focused on adolescents have addressed this challenge by incorporating clever behavioral paradigms that involve real or perceived social interchanges that carry varied affective charges (see Pfeifer & Blakemore, 2012 for a brief overview). For example, tasks that lead participants to believe that they are being rejected by peers tend to elicit activity consistently in ventral prefrontal regions (e.g., Guyer et al., 2012; Masten et al., 2009) that map onto those engaged during implicit and explicit emotion and anxiety regulation tasks. Such findings suggest that the neural activity associated with decontextualized experimental tasks parallels that evoked by real-life (or close to real-life) experiences. Other studies have begun to experiment with real-time interaction with an actual person during fMRI scanning (e.g., Redcay et al., 2010), an approach that may prove particularly fruitful for studying the neural correlates of efforts to regulate social anxiety.

Just as studies of the enactment of anxiety regulation and its neural correlates in the context of ecologically valid interpersonal interactions are important, research that

focuses on the process of selecting a regulatory strategy in response to environmental cues will be useful. Very little work to date has examined neural activity while an individual chooses among available regulatory approaches—typically, either participants are instructed to use a particular strategy or they are permitted to accomplish the regulatory task in any way they prefer to do so. Research that presents individuals with a range of regulatory options and then tracks patterns of choice and their correlates (e.g., neural, psychophysiological) may help elucidate optimal points of intervention for individuals who tend to rely inflexibly on maladaptive strategies. At least one study has found evidence that the ability to flexibly implement different regulatory strategies predicts later psychological health in college students (Bonnano, Papa, Lalande, Westphal, & Coifman, 2004); clarifying intrapersonal and situational factors that facilitate such flexibility and how those factors may or may not vary across development will help us better understand ways to encourage and support adaptive coping with anxiety.

At an even broader level, examining anxiety regulation in comparable interactions across varied interpersonal contexts (e.g., family, friends, romantic partners, unfamiliar peers) may provide clues about the ways specific patterns of interaction and different levels of intimacy may modulate both the available and the selected strategies for regulating anxiety. Engaging with a trusted person, for example, might facilitate more flexible use of regulatory approaches than would interaction with a novel individual, with whom a more circumscribed set of reactions might feel safer. Sociological approaches to the study of emotion, which provide useful insights into how we might better take into account the background against which anxiety and its subsequent regulation occurs may help inform work exploring such questions (e.g., Barbalet, 2011).

Translational Implications of Research on Anxiety Regulation

As the research we have described in this chapter illustrates, work conducted from multiple perspectives, at varied levels of analysis (e.g., genetic, neural, behavioral), and with a broad range of measurement tools is converging to yield a rich picture of emotion and its regulation. Calls for translational studies that facilitate communication between basic and applied scientists who study emotion and its regulation have been increasing over the past decade, driven in part by NIMH initiatives aimed at supporting research that transforms our understanding of mental illness and its neurodevelopmental origins (see Austin, 2013; DelCarmen-Wiggins, 2008). Increasingly, researchers are responding to these calls by designing studies of emotion regulation that transcend a single-level-of-analysis approach and that target ways biological processes, viewed through varied lenses, both influence and are shaped by behavior and context (e.g., Oberle, Schonert-Reichl, Lawlor, & Thomson, 2012). In addition, the importance of translating basic-science-informed clinical knowledge into both effective and efficacious practices in the community is informing scholarship on emotion regulation (e.g., Ferrell, 2009).

Anxiety represents a domain of normal and abnormal behavior and psychology that is particularly ripe for such a translational perspective. This is because there is particularly marked cross-species conservation in research on anxiety, relative to other areas. Thus, the increasingly widespread implementation of translational and multilevel approaches to research on anxiety regulation holds numerous implications for both our understanding of anxiety and our efforts to intervene with and prevent its maladaptive manifestations. One key implication is that scientists and clinicians will need to engage with each other in creative ways to bridge the terminological and methodological divides that commonly impede their collaboration (Cicchetti & Toth, 2006). Multidisciplinary teams, as well as cross-site collaborations, are of growing importance in the study of anxiety and its regulation, as is research that looks for underlying biological commonalities among superficially distinct psychopathologies (e.g., Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011).

As a function of broader interactions among scientists and clinicians who bring multiple perspectives to the table, it is likely that diagnostic boundaries for the anxiety disorders will continue to shift and evolve. As this process unfolds, it will be essential for scholars to hold assumptions lightly and loosely, and to be prepared to revise or jettison long-favored conceptions of anxiety and its management in the face of new evidence about its biological correlates and the ways they interact with environmental contingencies to yield varied patterns of response. However, such research on nosology is likely to unfold relatively slowly, compared with research on novel therapeutics. In fact, translational research in this area already has begun to influence anxiety treatment (Pine et al., 2009; Pine & Fox, 2015).

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE WORK

This chapter reviews the literature on the cognitive and neural mechanisms that allow humans to regulate anxiety

over the course of the life span. We provide an integrative perspective on research from clinical psychopathology, developmental psychology, and cognitive neuroscience, with the goal of illustrating the ways these related, but distinct, fields inform each other. Such translational engagement among researchers is critical if we are to identify optimal, personalized approaches to enhancing anxiety regulation repertoires, especially among those who are vulnerable to internalizing psychopathology broadly, and to anxiety disorders specifically. Clearly, this need has been widely recognized among anxiety researchers, who have devised a range of creative approaches to bridging relevant literatures that historically have operated in parallel. In reviewing their work, we find that several themes emerge, each of which suggests directions for future study.

First, although anxiety and its regulation across development have historically been understudied, the past decade has seen an explosion of research focused on this topic. The historical neglect of these topics reflects, in part, a clearly outdated belief that anxiety disorders constitute mild psychopathology. It is now widely acknowledged that anxiety, particularly if it emerges early in life, predicts a variety of negative outcomes, including major depressive disorder and suicide, as well as marked functional impairment across the life span. Further, researchers and clinicians typically recognize that enhancement and expansion of anxious individuals' emotion regulation repertoires has strikingly positive effects on their internal experience and their ability to perform effectively in social, academic, and occupational domains. This new clinical vision resonates with the availability of novel translational neuroscience methods and findings from basic neuroscience to raise particular interest in clinical applications of research on anxiety regulation.

To maintain the momentum of research on anxiety and its regulation, it will be critical that we produce studies that integrate a developmental psychopathology perspective with some of the elegant theoretical models of emotion and anxiety regulation that have been put forth in the past few decades. In particular, attention to developmental variation in patterns of affective chronometry (Davidson, 1998) as they manifest across different anxiety regulation strategies might help identify salient points for targeted intervention. Such work should, ideally, also gather data at multiple levels of analysis (e.g., genetic, neural, and cognitive), to facilitate generation of a more integrative and comprehensive picture of the anxiety regulation process.

In addition, continued effort to move beyond subjective reports of experience as the core markers of anxiety disorders and of the processes that become dysregulated in the context of these disorders is key to advancing the field. Consistent with the RDoC project (Insel & Wang, 2010), which aims to move the diagnostic process away from its reliance on difficult to quantify self-reports and toward the use of readily observable and measurable behavioral and biological data, researchers have begun to identify neural and psychophysiological correlates of both typical and atypical anxiety regulation processes. Extending this work to very young children is an important, if difficult, next step—notably, functional imaging studies have been completed that demonstrate atypical activation in emotion regulation circuitry in depressed preschoolers as young as 3 years of age (e.g., Gaffrey et al., 2011), but no published work has yet emerged to describe neural correlates of anxiety regulation in children this young.

Further, continuing a process that figured prominently in the most recent revision of the *DSM*, it is critical that we draw on novel clinical, genetic, and neuroscientific data to identify alternative classification schemes for anxiety. Given increasingly clear evidence that anxiety disorders represent the end result of complex interplay among many risk factors, it will be important to precisely describe the dynamic processes that can, under some circumstances, lead to a pathological outcome. If we can elucidate both the potential cascading effects of, for instance, genetic perturbations, that may interact with other genes or environmental factors to increase risk at neural and cognitive levels, we will be better poised to identify effective, precisely targeted interventions that can be implemented before an individual crosses the threshold into a full-blown clinical syndrome. Notably, such knowledge may also upend our current nosology for anxiety disorders and diagnostic boundaries may blur or disappear, possibly in different ways at different points in development. Already, research findings have led to the reclassification of OCD and PTSD; as the research base expands, further changes are likely.

Additionally, as Aldao (2013) clearly articulated with regard to emotion regulation research in general, there has not yet been enough research on anxiety regulation that fully considers the contexts in which strategies are learned and implemented. Integrative research that better characterizes the complex interplay among genetics, neurobiology, family environment, peer relations, and other influences is needed and is beginning to emerge in the literature. Research that combines genetic approaches with neuroimaging techniques, for example, has become increasingly common, and fMRI studies that are designed to maximize ecological validity are also appearing frequently in the literature.

Finally, further characterizing the elemental processes that constitute various explicit and implicit anxiety regulation processes in terms that are amenable to research in experimental psychology and neuroscience is likely to advance the field notably. To achieve this goal, it will be useful to move beyond broad constructs such as reappraisal by breaking them down into more fundamental cognitive and neural processes, each of which may have a distinct developmental trajectory. By defining salient constructs in language that bridges neuroscience, clinical, and developmental domains, we will be better poised to capitalize on the important findings emerging in each area and, ultimately, to develop novel, highly personalized, and rapidly effective treatments for anxiety and the regulatory impairments that maintain and perpetuate it.

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CHAPTER 15

Typical and Atypical Brain Development Across the Life Span in a Neural Network Model of Psychopathology

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INTRODUCTION

In this chapter, we present a new diathesis–stress model of the onset of psychopathology across the life span. We highlight the role of the brain in the diathesis–stress processes through the integration of two paradigm shifts in the fields of stress research and psychopathology, respectively: (1) the role of allostasis in stress research (Sterling & Eyer, 1988) and (2) new thinking about the role of the neural connections and networks in psychopathology (Menon, 2011). The brain is central to the concept of diathesis (e.g., Zuckerman, 1999) and, under allostasis, the brain is also central to the stress process (Ganzel, Morris, & Wethington, 2010; McEwen, 2007; Sterling, 2004; Sterling & Eyer, 1988). With the brain as a core feature of both sides of any diathesis–stress interaction, integration of these concepts is facilitated. This has two main benefits. First, bringing research on allostasis and large scale neural networks (connectomics[2]) together in the context of a diathesis–stress

We would like to thank Dr. Nathan Spreng of the Department of Human Development and the Human Neuroscience Institute at Cornell University for his expert advice on the dynamics of large-scale brain networks.

[1]Color versions of Figures 15.2, 15.8, 15.9, 15.12–15.14, 15.17, 15.21–15.24 are available at http://onlinelibrary.wiley.com/book/10.1002/9781119125556

[2]Connectomics is the study of the connectome, the functional and structural connections in the brain (e.g., Johansen-Berg, 2013). In this chapter, we focus on the large-scale connectomics of the human brain.

model enables us to identify stress-vulnerable brain processes that are likely to be implicated in the onset of psychopathology. We note that this effectively reframes the debate about whether the root cause of psychopathology is internal or external to the individual. Second, the central role of the brain in the diathesis–stress process mandates a consideration of the role of brain development; given evidence of a continually changing brain, we posit a developmental model of the onset of psychopathology. In this way, we advance understanding of the neural processes involved in the onset of mental illness and, in so doing, squarely embrace the core principles of developmental psychopathology.

We begin our discussion with a history of the diathesis–stress model in the study of psychopathology. Fifty years ago, clinicians regularly eschewed the role of physiological processes in the onset of psychopathology. More recently, though, the field of psychopathology has slowly come to embrace the joint roles of the internal (diathesis) and external (stress) in the onset of psychopathology. Questions now focus on the form of the diathesis–stress interaction and the processes by which they together produce psychopathology. Even so, it has been only recently that the tools of neuroimaging have allowed the neural processes underlying psychopathology to be explored in depth.

A key turning point in the history of stress research for this discussion is the introduction of the concept of allostasis. The value of the allostatic model is that it explicitly brings that which was considered external (stress) into the brain itself. Our discussion of allostasis builds on our prior work (Ganzel et al., 2010), which used an integrative human neuroscience approach (Cacioppo, Berntson, Sheridan, & McClintock, 2000) to develop theoretical models about the relationship between stress and both physical and mental health. Our own work has highlighted the brain's survival/salience circuitry and associated modulatory systems[3] as the neural front lines of allostasis, making this the specific neural circuitry that is likely to be most vulnerable to the accumulated wear and tear of allostatic load (the physiological cost of stress; Ganzel et al., 2010). This has allowed us to develop an allostatic model of the onset of psychopathology in response to current and prior stressors. Thus, under the concept of allostasis, stress and diathesis are intersecting processes that both take place in the brain.

[3]The neural systems underlying the central motivational "states of the brain" (Rosen & Schulkin, 1998, p. 326) formerly termed the core emotion systems of the brain in our work (Ganzel & Morris, 2011; Ganzel et al., 2010).

Because the brain is the central mediator of allostasis, and allostasis is key in our diathesis–stress model of psychopathology, we have also argued that brain *development* across the life span must play an essential role in the diathesis/stress process. To inform this discussion, we review the evidence for brain maturation and senescence across this life span. Doing so allows us to extend our model of diathesis–stress to include an explicit developmental component (Ganzel et al., 2010). As such, we explicitly examine how life span brain development intersects with developmental psychopathology (Cicchetti, 1993; Cicchetti & Posner, 2005) to inform diathesis–stress models of psychopathology across development.

To a diathesis–stress process taking place in the developing brain, we add a final level of complexity: the role of large-scale brain networks in psychopathology (Menon, 2011; Uhlhaas & Singer, 2012). Much of the prior work linking stress, psychopathology, and the brain has focused on individual regions of the brain thought to underlie the deficits in cognitive and affective functioning that characterize mental conditions, such as schizophrenia and depression. However, given the complexity of psychopathological disorders in their affective, cognitive, and behavioral presentations, it is perhaps not surprising that mapping of disorders onto local differences in brain regions has proved insufficient. Instead, current thinking suggests that neural *circuitry* might be critical here, i.e., it is *networks* of brain regions (and not just individual regions) that matter. Thus, building from a model in which stress can drive long-term structural and functional change in survival/salience-related brain regions (via allostasis; Ganzel et al., 2010), we highlight the role of stress sensitivity in large-scale neural networks in our development of a new diathesis–stress model of psychopathology.

In this work, we strongly espouse a number of key principles of the developmental psychopathology perspective (Cicchetti & Toth, 2009). First, we recognize that the study of normality and pathology are mutually informative, with normal development providing an understanding of the baseline processes on which there is deviation in the context of psychopathology. As such, our discussion of allostasis builds from a discussion of typical (nonpathological) neurophysiological responses to stress and our discussion of brain plasticity draws from what we know about typical (nonpathological) brain development. Second, as discussed previously, we develop a life span model of the diathesis/stress process, arguing for a model that maps brain development across age and stage of development with the development of psychopathology across this same period. Third, in keeping with the field's

focus on the interplay between the internal and the external, and the goal of reducing biological/environmental dualism, we highlight how external processes such as stressor exposure come to be instantiated in the brains of typical (nonpathological) individuals as neural processes and long-term changes in brain structure and function. This approach moves the entire diathesis/stress interaction into the brain. Finally, we draw on information from developmental neurobiology, from stress research in the social sciences and in neuroscience, and from new work on large-scale neural networks in psychopathology to bring cross-disciplinary perspectives to bear on the development of our diathesis–stress model.

DIATHESIS–STRESS MODELS OF THE ORIGINS OF PSYCHOPATHOLOGY

Diathesis Meets Stress

The classic diathesis–stress model was not born whole. Instead, it grew incrementally over time during the *sturm und drang* in psychiatry and clinical psychology that accompanied the decline of psychodynamics in the mid-twentieth century and the emergence of modern, more integrative perspectives on mental health. The 1972 inaugural volume of the *International Journal of Mental Health* provides a case in point. This was a special issue on the topic of genetics and mental disorders, which was a highly divisive topic at the time. A number of the authors in this volume describe the resistance of their clinical colleagues to a consideration of genetics in the origins of psychopathology. For example, the journal's editor, Martin Gittelman, wrote:

> . . . Bear in mind that one of the major theories of the etiology of mental illness is "parentogenesis," i.e., that family characteristics, interaction, milieu, etc., are largely responsible for mental illness, and that long-term hospitalization is therefore considered therapeutic since it removes the patient from the noxious influences of the family. However, if we can entertain the possibility that endogenous factors play an important role in severe mental illness, then one of the principal justifications for long-term hospitalization is made less tenable. . . . The implications for the organization of mental health services are obvious. (Gittleman, 1972, p. 4).

Other authors in this volume expressed parallel sentiments:

> Clinicians typically react negatively to genetic formulations on the ground that a genetic emphasis contradicts what we know about psychodynamics; that, as a corollary, it makes psychological intervention (e.g., psychotherapy, behavior modification, milieu therapy, vigorous combating of the hospitalization syndrome) theoretically incomprehensible or pragmatically useless; and, finally, that the overall result would be the development among professionals of a malignant therapeutic nihilism. (Meehl, 1972, P. 10)

This latter author, Meehl (1962, 1972, 1989), is credited with one of the one of the earliest diathesis[4]–stress models of the development of a mental disorder—in this case, a gene–environment model predicting the origins of schizophrenia (also see Gottesman & Shields, 1967; although they emphasized the polygenic nature of the diathesis more so than its interaction with environmental influence). Meehl's model included a dichotomous diathesis (Zuckerman, 1999), in that schizophrenia was portrayed as the result of a patient's dominant schizogene interacting with an inconsistent and aversive home environment generated by the unfortunate patient's battle-ax mother. This rearing condition was hypothesized to drive the cognitive slippage and soft neurological and psychometric signs that, over time, resulted in the symptoms and inappropriate behaviors associated with schizophrenia. The model broke new ground in that it explicitly embraced the role of biology in mental illness (a contentious point with many mental health professionals of the day) and the role of social and environmental factors in mental health (which was an equally sore point with much of the rest of medicine at that time: Engel, 1977). In an article in the journal *Science*, George Engel articulated the impasse at which the field of psychiatry found itself (Engel, 1977). Psychoanalysis and psychodynamics were still the dominant paradigms in psychiatry, but these approaches were increasingly criticized on a number of grounds (e.g., Delprato & McGlynn, 1985; Grunbaum, 1979, 1982). Psychiatry, as a field, was struggling with the claim that mental illness was a myth (i.e., that many mental disorders did not achieve the medical standard of being identifiable disease states because they had no basis in biological brain dysfunctions; see, e.g., Szasz, 1960). The psychosocial elements of human malfunction were deemed by some in the medical establishment to be the province of the theologian and the philosopher and needed to be disentangled from the organic elements of disease

[4]The concept of a diathesis has a lengthy history in medicine. The term is used in the present day to refer to a biological vulnerability to disorder that is either hereditary or acquired (Monroe & Simons, 1991), although in the more distant past it was also used to refer to the character of a disorder (e.g., hemorrhagic [yellow] fever versus pneumonia; Brown, 1813; LeConte, 1810).

(Engel, 1977; Szasz, 1960). In short, mental illness did not fit the medical model of the time, which emphasized the biological components of disease and eschewed the underbrush of psychosocial variables. But Engel cautioned psychiatrists against embracing the medical model of the 1970's, which he believed to be reductionistic, dogmatic, and irrationally supportive of mind-body dualism (1977). Other clinicians of the time shared this frustration, stating that "reductionism is particularly harmful when it neglects the impact of nonbiological circumstances upon biological processes" (Holman, 1976, p. 134).

In response to this debate, Engel (1977) proposed an inclusive *biopsychosocial medical model* of psychopathology that defied Western medicine's traditional separation of the mental from the somatic, which he argued had a practical basis in medieval Christian church politics and had thereafter devolved into unexamined sociocultural dogma (also see Rasmussen, 1975). Engel's biopsychosocial model included the patient as a biological individual in a social context with a history of early, past, and present life experiences (Engel, 1977). Engel's work was strongly informed by Ludwig von Bertalanffy's (1952) influential work on *general systems theory,* which stood in opposition to the reductionism that had become embedded in the dominant models of biology. Von Bertalanffy argued that the organism is better explained as a functionally interdependent whole rather than the sum of its independent biological parts. Under systems theory, the linkages among all levels of organization are revealed by holistic approaches to scientific inquiry. Following this lead, Engel included consideration of the doctor–patient relationship and the social context of the health care system into his ideas for a biopsychosocial model, thus articulating the interdependent levels of analysis within a patient–doctor system that ranged from biology to society.

The breadth of Engel's vision may have defeated the usefulness of his model, which failed to find practical application in research designs of the day (McCutcheon, 2006). Detractors argue that Engel can be credited with proposing the biopsychosocial model, but he failed to adequately specify its form (McLaren, 1998). Others have pointed out that science has only recently progressed to the point where the form of such a model could be specified, since explicit testing of the associations across a multilevel and interactive biopsychosocial system has been possible only with the recent development of new technologies supporting neuroimaging, genetics, and psychosocial measurement (McCutcheon, 2006) and the statistical modeling of multilevel and dynamic data in complex systems (e.g., Sporns & Chialvo, 2004).

Following Meehl's lead, Zuckerman (1999) is often credited with providing one of the first comprehensive discussions of the onset of psychopathological conditions deriving from two (not one) primary determinants—diathesis and stress. Zuckerman's models draw extensively on work by Meehl (1962), Gottesman and Shields (1967), and Monroe and Simons (1991), who made the case for an interactive diathesis–stress relationship in the onset of schizophrenia and depression, respectively. As with his predecessors, Zuckerman's framework makes it clear that a diathesis is a predisposition, and as such creates a vulnerability to stress, but that vulnerability alone is insufficient to result in expression of the disorder. Rather, psychopathology results from the combination of that predisposition (which he argued is an enduring trait of the individual) and the experience of an environmental stressor (which he argues are objective and external to the individual; Figure 15.1). Notably, for Zuckerman, the term diathesis refers to "genetic and biological factors in the nervous system" (Zuckerman, 1999, p. 7), a point that we will return to later.

Zuckerman's contributions to the diathesis–stress concept are extensive. His contributions expand the relevance of the diathesis–stress model to a broader set of psychopathological outcomes, and make explicit what constitutes stress, diathesis, and their relationship. In doing so, he highlights two aspects of Monroe and Simons's (1991) work that enlarged upon the conceptualization of the diathesis–stress relationship relative to prior formulations (e.g., by Meehl and others). First, he defines a fan-shaped interactive relationship between stress and diathesis in predicting the onset of disorder. While it might seem like only a small step forward from Meehl's (1962) dichotomous-diathesis–stress interactive model, Monroe and Simons (1991) and Zuckerman (1999) present a quasi-continuous model, in which a *diathesis-threshold*

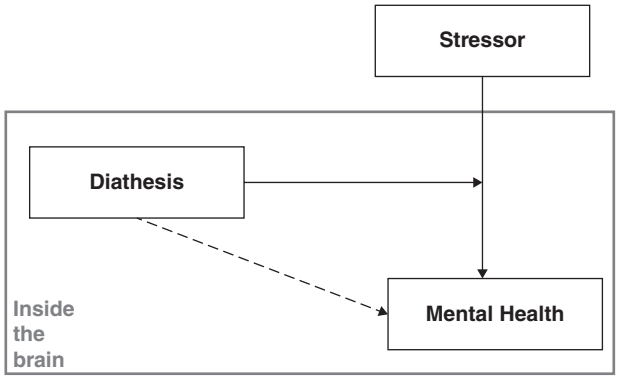


Figure 15.1 Traditional diathesis–stress model.

still exists (the level of the diathesis above which there is a positive relation between stress and disorder) but the strength of the positive relation now varies as a function of the level of the diathesis above this threshold. This is important because it allows for the conceptualization of a continuous diathesis, which was heretofore unacknowledged. Second, these models suggest that diathesis may predict the onset of stress. In this way, the experience of stress is not randomly distributed across persons, such that some (but indeed not all) stressors may be the result of the diathesis. For example, certain personality characteristics may elicit negative behavior from others, and these resulting negative interactions may be the daily stressors that, in interaction with the diathesis, cause the onset of disorder. In this way, the internal becomes external. As we discuss later, the newest models suggest the reverse may be true as well.

Importantly, Zuckerman (1999) also presents diathesis as having two components—the role of personality and the timing of stressor exposure (early in development versus at the onset of the disorder). In so doing, he argues for a dual-diathesis model—one aspect of which is mediated by personality and is the result of the effect of genes on the CNS, and a second aspect that has a biological basis in the nervous system that can originate from the environment. In other words, this second aspect of diathesis derives from the ongoing impact of the environment on the central nervous system (CNS). Such a conceptualization—in which environmental stressor exposure can become the basis of later vulnerability—is highly consistent with the model of stress and allostasis that we discuss later.

The mid- to late twentieth century saw a sweeping upsurge in interest in multilevel approaches that opposed one-sided accounts of biological versus psychosocial functioning (Belsky, 1997; Bronfenbrenner & Morris, 1998; Chrousos & Gold, 1992; Goldstein, 1995a, 1995b; Levine & Ursin, 1991; McEwen & Stellar, 1993; Sterling & Eyer, 1988; Walker & Diforio, 1997; Zuckerman, 1999). Indeed, the entire theory volume of the 2006 *Handbook of Developmental Psychology* is devoted to the implications of von Bertalanffy's (1952) general systems theory as applied to developmental science, which argues for mutually influencing and interactive processes across a multileveled system (Damon, Lerner, & Eisenberg, 2006). This increased consideration of multilevel and interactive perspectives has spanned biology, medicine, psychology, and sociology to foster diverse and comprehensive accounts of an organism's health and development.

Biological Sensitivity to Context

As the previous discussion makes clear, consideration of the multilevel and interactive perspectives inherent in diathesis–stress models of psychopathology is in fact quite young—having emerged over the last few decades from relatively one-sided views of the sources of psychopathology (environment-only versus biology-only). Yet these earliest accounts represent a relatively straightforward formulation of the interaction between diathesis and stress (Figure 15.2a.). As we discuss later, the last 5 years or so have seen a reconsideration of the *form* of that interaction. Gone are discussions of whether it is biology or environment that is the source of psychopathology. However, there is continued debate about precisely *how* stress and diathesis interact to jointly produce psychopathology, as well as about the mediating processes of that relationship.

In Belsky's *differential susceptibility theory* (Belsky, Bakermans-Kranenberg, & van IJzendoorn, 2007), genetic factors do not make children vulnerable; instead, such children are susceptible or *plastic* to environmental influences.

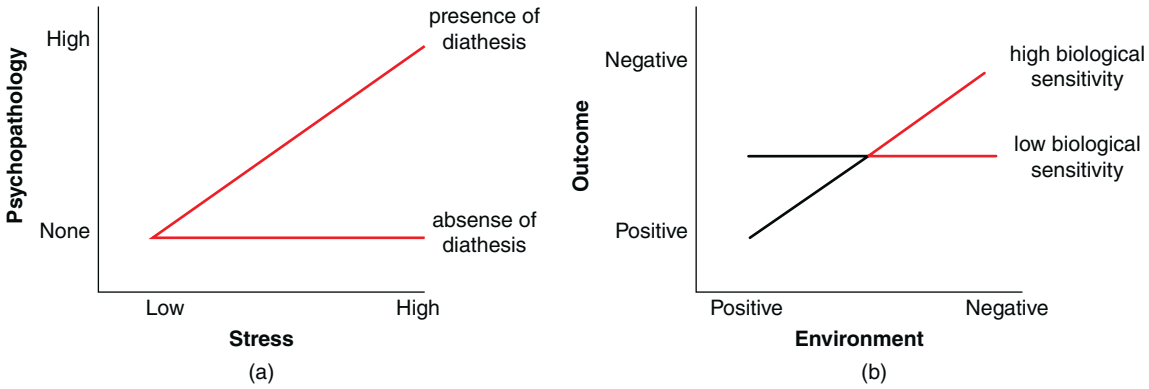


Figure 15.2 Diathesis–stress models. Traditional diathesis–stress model (a). Diathesis–stress model based on differential susceptibility theory/biological sensitivity to context (b). See footnote 1. *Source:* Adapted from Belsky et al. (2007).

As such, the same vulnerability factor that conferred risk in the context of poor environments confers intellectual or social-emotional benefits in positive environments. Statistically, this requires a crossover interaction (rather than a fan-shaped interaction), in which the slope for the susceptible group is different from zero and steeper than that for the nonsusceptible group (which is ideally zero; Figure 15.2b.). In this way, susceptible children are more strongly influenced by environmental influences, but how those children fare depends strongly on the valence of that environment's influences. Thus, the diathesis is less of a precondition or threat to psychopathology and more of a measure of plasticity. Belsky draws heavily on evolutionary theory to suggest that having children varying in susceptibility to different environmental contexts is advantageous because it creates heterogeneity within the population. He cites both experimental and nonexperimental evidence to suggest that some children previously considered vulnerable may actually be the most plastic and benefit the most from positive rearing conditions (Belsky et al., 2007).

Boyce and Ellis's (2005) *biological sensitivity to context* theory provides a rendition of the diathesis–stress interaction that seems empirically similar to Belsky's, but has critical conceptual distinctions. In Boyce and Ellis' formulation, stress reactivity has the potential for negative effects under conditions of adversity and positive effects under conditions of supportive environments. But unlike Belsky's formulation, these highly reactive phenotypes are *not* highly malleable, in that they are inflexible in the face of a variety of ecological conditions. Rather, they are highly responsive to both the threats and dangers in high stress environments, as well as to the social supports in highly supportive environments. It is this increased vigilance or awareness to environmental influence that results in their highly divergent outcomes across contexts.

If we are proposing to model the etiology of psychopathology (the dark side of adaptation), one might think there is little difference between diathesis–stress theories and their more optimistic cousins, differential susceptibility theory (e.g., Belsky et al., 2007) and biological sensitivity to context theory (Boyce & Ellis, 2005). For negative outcomes, all of these theories make precisely the same *statistical* prediction, that is, that an interaction between a preexisting vulnerability and a stressor will drive maladaptation (Roisman et al., 2012). However, these theories do differ with regard to the underlying process by which the interaction between diathesis and stress occurs, and the nature of what happens in high-quality environments.

The interactive nature of stress and diathesis is not the only contribution that Boyce and Ellis (2005) bring to this discussion. As they describe, these biological predispositions are partly the *result* of adaptations of stress-response systems to the environment (although genes and gene–environment interactions are also sources of such predispositions). In the context of low-stress environments, the high reactivity phenotype serves to support children in eking out the good in the environment, allowing them to benefit especially well. But, in the context of highly stressful environments, high reactivity serves to ready the individual to respond to stress, even if it has physiological costs. But to fully understand those physiological costs, we turn to a discussion of how the brain plays a role in this diathesis–stress model of psychopathology.

DIATHESIS AND STRESS IN THE BRAIN

In diathesis–stress models of psychopathology, the brain has consistently been portrayed in the literature as a key mediator of diatheses (e.g., Meehl, 1962; Zuckerman, 1999). Not so the stress process. Stressors are modeled as external (e.g., Zuckerman, 1999) and the stress process itself has largely been conceived as having bottom-up effects on the brain through homeostatic processes and hypothalamic-adrenal-pituitary (HPA) axis effects. We argue here that placement of the brain as the primary mediator of the stress process is potentially transformative for thinking on diathesis–stress models of psychopathology. To fully understand this work, we begin with a brief history of the stress process with attention to the inclusion over time of the role of the brain.

The Stress Concept

Cannon and Selye

Stress research shares common origins in the work of Walter Cannon (e.g., Cannon, 1932) and Hans Selye (e.g., Selye, 1956). In Cannon's conceptualization, the sympathetic-adrenal medullary system mobilizes the body's energy resources by increasing epinephrine (adrenaline), which in turn increases blood pressure, heart rate, and blood sugar, as well as hastening blood coagulation, clearing fatigue products from muscles, and decreasing digestion (Cannon, 1920). In Cannon's view, these processes occurred locally in the body, independent of central nervous system (CNS) control (and hence did not involve the brain). He used the term *homeostasis* to refer to the way this array of independent physiological systems works together to reestablish initial conditions when the system is perturbed (Cannon, 1932).

By the mid-twentieth century, Hans Selye demonstrated that an organism has an adaptive response to adversity that includes both Cannon's sympathetic (adrenaline-driven) responses plus the actions of hormones from the pituitary gland, which globally affect the major organs of the body in indirect but important ways (e.g., Selye, 1956). Selye proposed the existence of a generalized physiological syndrome that occurs in response to a great diversity of threats to the integrity of the organism (e.g., Selye, 1956). The syndrome included three stages of physiological response to stressor exposure, which he called the General Adaptation Syndrome or GAS (Selye, 1956). The first stage is the sequential actions of the hypothalamic-pituitary-adrenal (HPA) axis, including production of corticotropin releasing hormone (CRH), the resulting release of adrenocorticotropin releasing hormone (ACTH), and the production of glucocorticoids (cortisol, in humans) (*alarm stage*). In the second stage, overt symptoms of stress are often reduced or disappear. In the final (*exhaustion*) stage, physiological defenses are depleted and the organism will die if the stressor is not released. For Selye, stress was "that which stimulated the GAS response" (1956, p. 54).

Selye's claims for the scope of the application of the GAS were very broad and his work prompted thousands of articles across medicine, psychology, sociology, and biology (Goldstein, 1995b; Mason, 1975). However, while expanding the concept of homeostasis (Bernard, 1878; Cannon, 1932), his work retained many of the omissions inherent in Cannon's original conceptualization, including inattention to the significance of psychological state, anticipation, coping, life history, and environmental context beyond the specific stressor (Burchfield, Woods, & Elich, 1980; Mason, 1975; Toates, 1995). Moreover, Selye wrote of a hypothetical neural or endocrine common mediator that lies between application of the noxious stressor and the GAS response (1950, p. 105). This unknown common mediator would serve to receive and integrate local inputs and then transmit generalized messages to all parts of the body to activate the GAS response, including facilitating changes in regulatory (i.e., homeostatic) set points during the stage of resistance (e.g., Selye, 1950, 1956). Selye never identified this critical common mediator.

Work following Selye balked at these gaps with increasing intensity. For example, in psychosocial research, it was noted the measurement of the *valence* or the level of *threat* posed by a given stressor often improved the amount of variance explained in the outcomes (Brown & Harris, 1978; Dohrenwend, Ashkenasy, Krasnoff, & Dohrenwend, 1978; Holmes & Rahe, 1967; Pearlin & Schooler, 1978; Wheaton, 1999). Changes in stressor *context* over time also made significant independent contributions to the outcomes of stress models (e.g., Baltes & Baltes, 1990; Furstenberg, Brooks-Gunn, & Morgan, 1987**;** Hobfoll, Johnson, Ennis, & Jackson, 2003; Holahan, Moos, Holahan, & Cronkite, 1999; Lazarus, 1993; 1999; Masten et al., 1988; Rutter, 1979; Sameroff, Seifer, Barocas, Zax, & Greenspan, 1987), as did individual differences in cognitive and emotional response (e.g., anticipation, appraisal, coping, learning, and other types of information processing: Foa & Kozak, 1986; Holahan, Moos, Holahan, & Cronkite, 1999; Ironson et al., 2000; Lazarus, 1991; Siegal & Allan, 1998; Sterling & Eyer, 1988; Stone, 1995; Toates, 1995; Tolin & Foa, 2002; Wheaton, 1985). Taken together, this body of work has stretched the psychosocial requirements for models of the stress process well beyond the classical homeostatic perspective or the GAS.

Similarly, within biomedical research, evidence of the influence of cognitive and affective processing on the stress process was also prompting reconsideration of classical homeostasis and Selye's GAS (Mason, 1971, 1975; Pacák & Palkovits, 2001; Schulkin, 2004). For example, Mason (1971, 1975) documented substantial variation in elements of the GAS response as a function of the stressor context, the individual's history, and the individual's perception of the noxiousness of the stressor, thus raising questions about the specificity of the "nonspecific" GAS response (also see Pacák & Palkovits, 2001). "The knowledge that the psyche is superimposed upon the humoral machinery for endocrine regulation drastically complicates our whole view . . . " (Mason, 1975, p. 177). Thus, the biomedical stream of stress research also found itself in need of a model that included appraisal, cognition, and affective (or emotional) state as primary elements of the stress process (Frankenhaeuser, 1980; Moore-Ede, 1986; Weinberg & Levine, 1979).

The Brain Enters the Stress Process

This work set the stage for Sterling and Eyer (1988) to propose the concept of *allostasis*, which holds that the central nervous system (CNS) exerts executive control over all physiological regulatory responses to environmental demand in the alert, intact organism (see Figure 15.3). CNS control of the stress response, in turn, allows the regulatory set points of the organism to vary in response to environmental demand (McEwen & Wingfield, 2003; Sterling & Eyer, 1988). This placed the CNS in general, and the brain in particular, squarely in the role of Selye's common mediator between environmental demand and physiological response (1950).

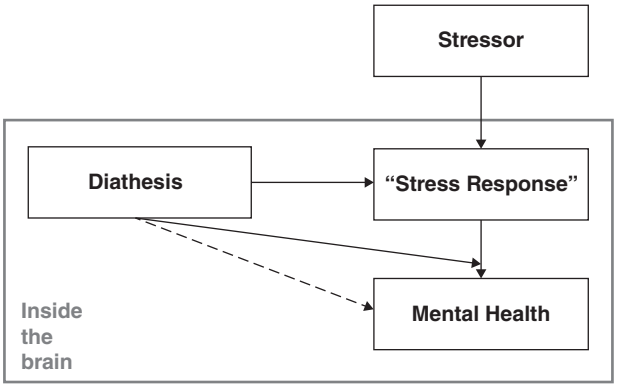


Figure 15.3 Bringing stress into the brain. The most basic diathesis–stress model of response to a current stressor is presented as a traditional psychosocial *stressor → stress response → distress* model of the stress process; with the exception that the processes are represented as occurring within the brain (the solid gray line represents operations that occur within the brain, within which all processes are biological).

This work went largely unnoticed at the time of its publication. Three years later, Levine and Ursin (1991) proposed that the sensory input from all types of stressors is gated through the brain before affecting any other physiological regulatory response, and that this input is modified by expectation and evaluation. They argued that this is true even for stressors that do not appear overtly psychological, such as cold exposure and tissue damage, because novelty, expectation, and efforts to avoid noxious stimuli will all activate brain responses (Levine & Ursin, 1991). Soon after, Chrousos and Gold (1992) and Goldstein (1995a, 1995b) independently proposed a model in which homeostasis resets itself in response to stress exposure, and Goldstein (1995b) argued that "distress invariably resets homeostasis." P. 41. Thus, by the end of the twentieth century, it was clear that homeostasis required revision to account for the influences of environment and the CNS on physiological regulation.

None of these proposed modifications of homeostatic theory addressed the accumulating consequences of physiological accommodation to environmental challenge over the life span. This prompted McEwen and Stellar (1993) to introduce the concept of *allostatic load*, which they defined as the physiological cost of making long-term adaptive shifts across a broad range of systems to match internal functioning to environmental demand. With the inclusion of allostatic load as a key element of the theory, allostasis became the most comprehensive account of regulatory accommodation to environmental demands and accumulated physiological cost over time. The adaptation and dissemination of allostatic theory by McEwen and an expanding cohort of colleagues is lending allostasis the status of "a new conceptual framework" (Schulkin, Gold, & McEwen, 1998, p. 220) for the study of stress (e.g., McEwen, 1998, 2000, 2001, 2003; McEwen & Seeman, 2003; McEwen & Stellar, 1993; McEwen & Wingfield, 2003; Schulkin, 2004; Schulkin, McEwen, & Gold, 1994; Singer, Ryff, & Seeman, 2004).

The concept of allostasis provides us with a new approach to specifying the mechanisms of the diathesis–stress model of mental disorder. In particular, it suggests a need to update the classic diathesis–stress model to include the role of the brain in the stress process. In the following sections, we will argue that the process by which diathesis and stress result in psychopathology occur through the central mechanisms of allostasis. A key consequence of model is that diathesis is no longer static, but is dynamically changing over time. Articulating this process requires that we briefly specify these mechanisms.

Allostasis Situates the Brain in Diathesis–Stress Models

Allostasis and Response to a Current Stressor

In prior work, we used the theory of allostasis as the foundation for a model of the ongoing stress process (Ganzel et al., 2010). The most basic model of allostatic accommodation to a current stressor (Figure 15.4) is presented as a classic psychosocial *stressor → stress response → distress* model of the stress process. In this model, the stress response allows the resetting of homeostatic set points during the process of reestablishing physiological equilibrium during and after stressor exposure (i.e., allostasis). From the previous discussion (Figure 15.3), recall that the brain is the central mediator of allostasis (e.g., McEwen, 2007; Sterling, 2004; Sterling & Eyer, 1988).

Allostatic response and adaptation to a current stressor can be viewed as a two-stage process, wherein a brain-based *central allostasis* has executive control over *peripheral allostasis* in stress-responsive physiological systems external to the central nervous system (which in turn have critical feedback on the brain: for a full discussion, see Ganzel et al., 2010). These effects include, but are not limited to, production of stress hormones and catecholamines, inhibition of the reproductive system; and alterations of metabolism, cardiovascular activity, and gastrointestinal and immune system function (Davis, Walker, & Lee, 1997; Heinrichs, Menzaghi, Pich, Britton, & Koob, 1995; Maier & Watkins, 1998; Stratakis & Chrousos, 1995). These processes feed back on the brain via interoceptive, hormonal, catecholamine, and immune signals (Damasio, 2003; Davidson, Maxwell, & Shackman, 2004; Sapolsky,

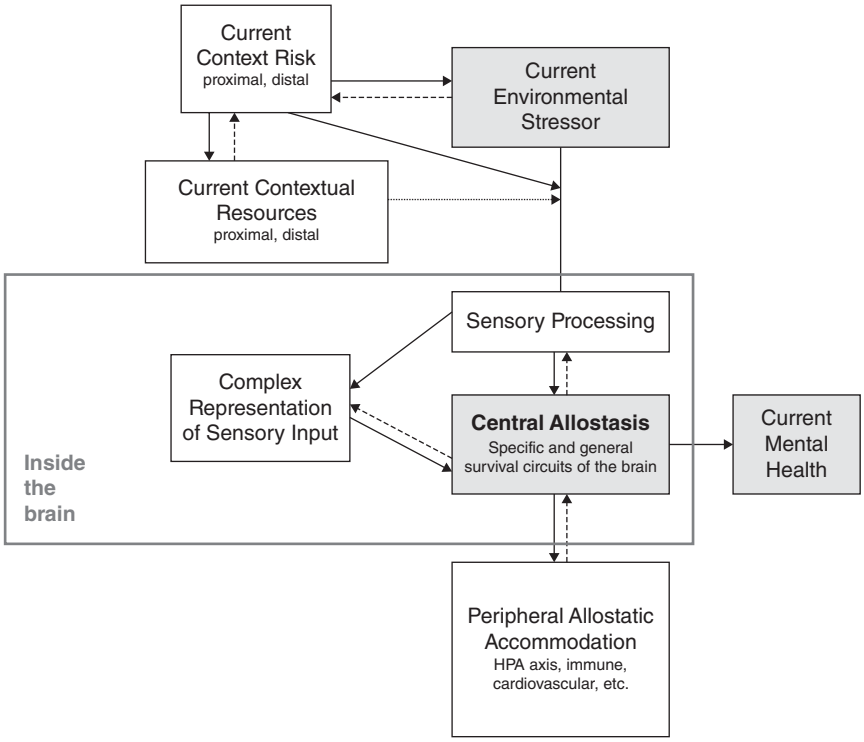


Figure 15.4 An allostatic model of response to a current stressor. Here, the brain is shown as a dynamically adapting interface between ecological challenge (in context) and the biological self. This model shows the role of central and peripheral allostasis in predicting mental health. Dotted lines indicate active feedback. Interaction would be expected between allostatic load and major pathways of allostatic accommodation (not shown). The role of genes is not shown here. *Source:* Adapted from B. L. Ganzel, P. A. Morris, & E. Wethington, Allostasis and the human brain: Integrating models of stress from the social and life sciences, *Psychological Review, 117*(1), 134, 2010.

1998) and create iterative sequelae of physiological and psychological effects over time in response to the trigger stimulus, as discussed later. This central-peripheral distinction allows us to specify the neural mechanisms underlying the moment-to-moment physiological response to a current stressor.

Genes serve as an additional source of input to these processes (Figure 15.5). As with a classical diathesis–stress model, there is a role for both biological and social/environmental processes. But stress gets under the skin and into the brain/body system, so our model posits that diathesis is not biological and stress is not external—but rather both are deeply embedded within convergent neural processes.

Previously, we highlighted the brain's *survival circuitry* (LeDoux, 2012) and its closely linked domain-general modulatory processes[5] as the neural front lines of allostasis, and we reviewed the evidence that these brain regions are particularly vulnerable to the accumulated wear and tear of allostatic load (Ganzel et al., 2010). There are multiple, overlapping survival circuits in the brain, each of which detects a particular class of trigger stimulus (e.g., defense–avoidance, reward, energy and nutritional maintenance, fluid balance, thermoregulation) and then integrates relevant sensory and motor information to drive adaptive response behavior (LeDoux, 2012). The triggers for each survival circuit are *salient*, either because they have intrinsic biological value (stimulating stereotypical approach or avoidance behaviors) or because they have learned, personal value (for discussions, see LeDoux, 2012). These specific survival circuits, together with a general-purpose modulatory system, form an interconnected network that serves to represent salient stimuli and produce and regulate behavioral response. This extended (specific + general) survival network constitutes the central motivational states of the brain (Rosen & Schulkin, 1998) that underlie human behavioral adaptation to the environment (also see core affect: Barrett, Mesquita, Ochsner, & Gross, 2007; Bechara, Damasio, Damasio, & Anderson, 1994; Damasio, 1999; LeDoux, 2012). We have argued that

[5]Termed the core emotion systems of the brain in our prior work (Ganzel & Morris, 2011; Ganzel et al., 2010). Also see discussion on this topic by LeDoux (2012) and Barrett and Satpute (2013).

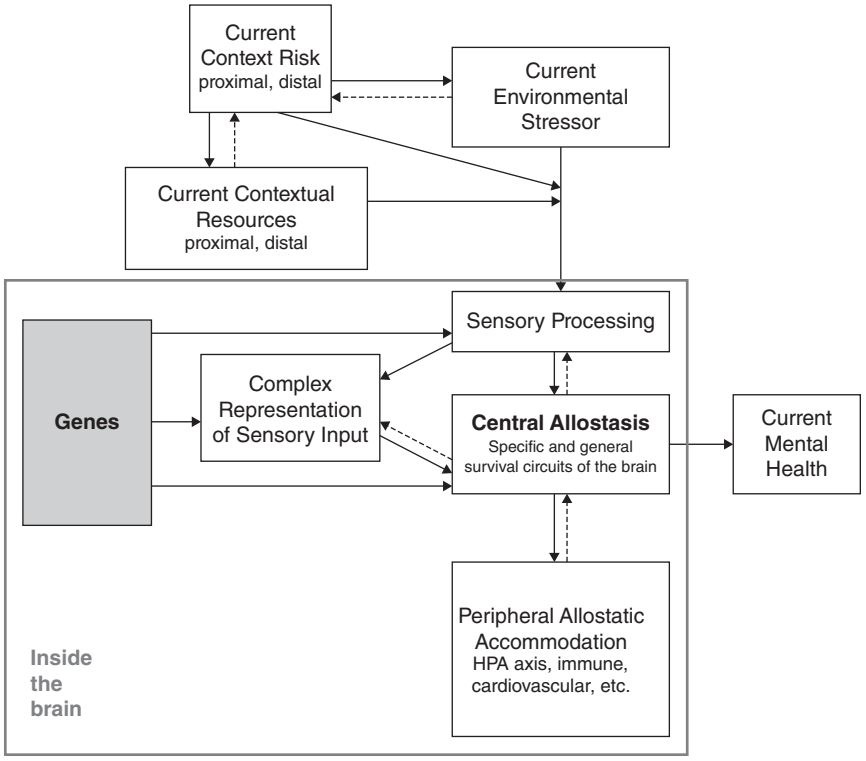


Figure 15.5 The direct effect of genes on central allostasis. Here, we emphasize the main effect of original genetic compliment on central allostasis, but we note that genes are also likely to serve as a moderator of associations within central and peripheral allostasis. We also anticipate an effect of genes on input to the model—that is, on current contextual risk, current contextual resources, and the current stressor itself.

this extended survival circuitry is also the main organizing factor in allostasis (i.e., in the translation of stressor exposure into a behavioral or physiological stress response) and thereafter into stress-related changes in mental health (Ganzel et al., 2010). Variously called the limbic system (but see LeDoux, 1996, pp. 98–102) or the emotional brain (but see Barrett & Satpute, 2013), this extended survival system is at the heart of the diathesis–stress model.

We will focus on the *defense circuit* (LeDoux, 2012) as our exemplar of a specific survival circuit. The defense circuit detects and responds to threat; it includes the amygdala and periamygdaloid regions, hippocampus, thalamus, hypothalamus, midbrain periaqueductal gray, and the basal forebrain/brainstem nuclei that underlie stress-related neurotransmitter production, all which work together to process threatening stimuli and facilitate behavioral response (e.g., Armony & LeDoux, 1997; Davis et al., 1997; LeDoux, 1996; Phan, Wager, Taylor, & Liberzon, 2002; Phelps, 2004, 2006). Other key survival circuits exist. Notable among these is the reward circuitry of the brain, within which the ventral striatum plays a key role. The amygdala and ventral striatum are highly connected with one another and with the anterior insula, with which they share many functional similarities.

The more domain-general modulatory regions (e.g., insula, anterior cingulate cortex, orbitofrontal cortex) integrate information from multiple survival circuits with interoceptive information and prior experience to provide threat evaluation or response modulation (e.g., Bremner & Vermetten, 2001; Kaufman & Charney, 2001; Sanchez, Ladd, & Plotsky, 2001) (also see supporting human neuroimaging data : e.g., Dolcos, LaBar, & Cabeza, 2004; H. Kim et al., 2004; Urry et al., 2006; Wager, Phan, Liberzon, & Taylor, 2003). The high level of structural and functional connectivity between these brain regions and the rest of the cortex allows this extended defense circuitry to recruit and integrate a wide range of the brain's computational resources to process threatening or stressful stimuli (Pessoa, 2008; Stephan et al., 2000). Such stimuli effectively engage attention, inhibit other activities (Choi & Brown, 2003; Gray, 1987; Petrovich, Setlow, Holland, & Gallagher, 2002), and are prioritized in the competition for processing resources in the brain (e.g., Anderson, 2005; Ohman, Flykt, & Esteves, 2001; Vuilleumier, Armony, Driver, & Dolan,

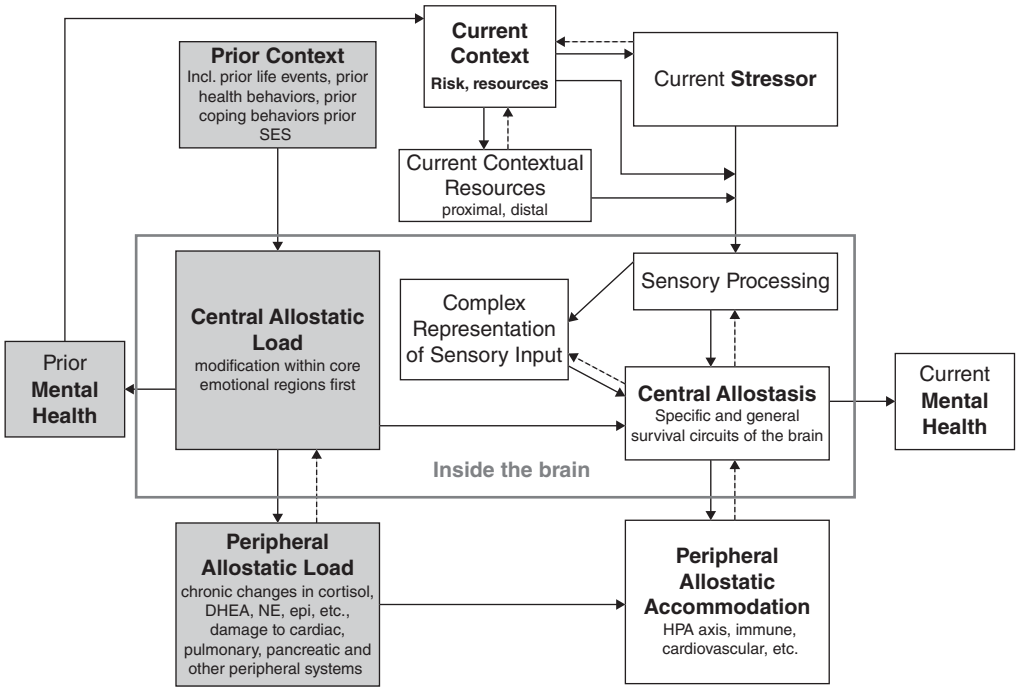


Figure 15.6 Including allostatic load in the model. The allostatic model, including the role of central and peripheral allostatic load in the response to a current stressor. Interaction would be expected between allostatic load and major pathways in central allostatic accommodation (not shown). The role of genes is not shown here. *Source:* Adapted from B. L. Ganzel, P. A. Morris, & E. Wethington, Allostasis and the human brain: Integrating models of stress from the social and life sciences, *Psychological Review, 117*(1), 134, 2010.

2001). This provides salient (in our exemplar, threatening) stimuli with a privileged status[6] in the brain (Davidson et al., 2004; LeDoux, 2012) and underscores the critical role that the survival circuits play in allostasis.

Allostasis Across Time: Allostatic Load

The expanded version of this model (Figure 15.6) shows the accumulation of physiological wear and tear in the form of allostatic load (McEwen & Stellar, 1993). Under chronic and repeated exposure to stressors, the short-term gains of allostatic accommodation are reduced and associated physiological adaptations may become entrenched and automatic (e.g., chronic high blood pressure: Sterling & Eyer, 1988). In this figure, previous stressors have also contributed to the need for allostatic accommodation, which, over time, has accumulated in the form of allostatic load. Acquisition of load, in turn, affects the individual's ability to respond to a current stressor. In this way, the body carries with it the long-term results of prior experiences into its current responses to a stressful event (Geronimus, Hicken, Keene, & Bound, 2006).

The relationship between stressor exposure and adaptive physiological outcomes takes the form of an inverted U-shaped curve (e.g., McEwen & Lasley, 2002). With mild stressors, the accumulation of load that results from ongoing allostatic accommodation is likely to be negligible—well within the elastic limit of human resilience described by Cannon (1932) in his engineering model of stress. In the adaptive portion of the U-shaped curve, the benefits of allostatic accommodation outweigh the costs. Moderate amounts of stress (good stress or eustress: Lazarus, 1966; Selye, 1974) may be associated, for example, with enhanced neurogenesis (e.g., Kirby et al., 2013; Rhodes et al., 2003), improved brain metabolism and enhancements of neuronal architecture (e.g., Kempermann, Kuhn, & Gage, 1998; Sirevaag & Greenough, 1988), improved executive function (Colcombe et al., 2003), and improved immune system function (Sapolsky, Romero, & Munck, 2000). For example, moderate amounts of exercise are associated with increased cortical plasticity and improved executive function, even in adults (Colcombe et al., 2003). However, allostatic load will increase over time when allostatic accommodation to a

[6]We note that this privileged status is vulnerable to high attentional load and strongly competing sensory input (e.g., Pessoa, Japee, Sturman, & Ungerleider, 2006; Pessoa, McKenna, Gutierrez, & Ungerleider, 2002).

stressor is sustained, when it is repeated, or when it is large (McEwen, 1998, 2000; McEwen & Stellar, 1993). Studies of peripheral allostatic load using a composite index of biological risk factors (e.g., cortisol, norepinepherine, epinephrine, glycosated hemoglobin, systolic and diastolic blood pressure, cholesterol, waist-to-hip ratio) suggest that load is accumulated according to stress dosage, such that increased stressor exposure is associated with increased load (e.g., Brody et al., 2013; Evans, Kim, Ting, Tesher, & Shannis, 2007; Glover, Stuber, & Poland, 2006). In addition, different types of stressors are likely to accumulate allostatic load somewhat differently, and accommodation to some types of stressors may be more costly than others (Alleva & Santucci, 2001; Pacák & Palkovits, 2001).

The tipping-point in the inverted U-shaped curve is the point at which a healthy challenge becomes a progressively unhealthy stressor. Healthy exercise, for example, can segue to being worked to death. Within the body, there is a point at which stressor exposure begins to compromise immunity, neurogenesis, dendritic growth in the hippocampus, and the host of other negative physiological consequences of increasing stressor exposure (for a review of these, see Ganzel et al., 2010). In terms of the present model, this is the point at which the process of allostatic accommodation begins to generate deleterious amounts of allostatic load. Under chronic, repeated, or severe stress, the short-term gains of allostatic accommodation dwindle, while its physiological adaptations become entrenched and automatic (fixed automatisms, see: Sterling & Eyer, 1988) and the long-term physiological costs of that sustained accommodation continue to accumulate. Under extreme stress, this process may happen very quickly.

Fast or slow, continuing accrual of load-related symptoms will be physiologically overwhelming and ultimately lethal, as described in Selye's general adaptation syndrome (GAS; Selye, 1950, 1956). On the way to the deadly end of stage three of the GAS, it is increasingly likely that the individual will experience physiological and/or psychological failure to compensate for intolerable levels of stressor exposure (e.g., Seeman et al., 2004; Seeman, McEwen, Rowe, & Singer, 2001; Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). That individual's diathesis will determine when decompensation is reached, and how, but no one is exempt. Vulnerable individuals simply reach decompensation earlier and perhaps in a nonstandard way.

Allostasis Across the Life Span and Generations: Epigenetics

Finally, recent work suggests that continuity in load and its associated physiological consequences may reflect intergenerational contributions of environmental experience through *epigenesis,* or environmental effects on gene expression (Moffitt, Caspi, & Rutter, 2006). What is important for this discussion is that stress in the environment may result in changes in DNA expression that can have implications for an individual's physiology and mental health throughout that individual's own life span and for subsequent generations (Harper, 2005). As such, environmental conditions present in one generation are remembered in the behavioral and physical responses of the subsequent generation even after the precipitating environmental conditions have ended (see Harper, 2005, for a discussion). Some of the most compelling empirical evidence driving this theory comes from studies of rodents in Meaney's lab (Champagne, 2010; for reviews, see Diorio & Meaney, 2007; e.g., Francis, Diorio, Liu, & Meaney, 1999; Weaver et al., 2004). This work demonstrates that rat pups who experienced low levels of maternal care during the first week of lactation go on to show more fear of novelty as adults and increased HPA-axis reactivity to stressors, relative to pups who experienced higher levels of care from their mothers.

In this example, DNA methylation patterns appear to be the key mediating mechanism (Weaver et al., 2004). That is, alterations in the methylation of a glucocorticoid receptor gene affect the hippocampus' ability to regulate glucocorticoid negative feedback on the HPA axis, producing a lasting increase in HPA-axis response in offspring who received lower levels of maternal care (Weaver et al., 2004). This is an example of epigenetics serving as the mechanism through which environmental conditions produce central allostatic accommodation to environmental challenge (for a discussion, see Ganzel & Morris, 2011). This environmentally-mediated epigenetic alteration in hippocampal function carries forward in the life of the rat pup as allostatic load. These changes appear to have long-lasting implications to future generations (Champagne, 2010). Notably, parallel processes may take place among humans, as demonstrated by evidence that severe food shortages during pregnancy have similar lasting effects on later health of the child (physical growth; Susser & Stein, 1994). In this way, epigenetics serves as a key process by which early experiences may carry forward to bring lasting modifications in the individuals' response to stressors at later points in development and in future generations. These discoveries require diathesis–stress models of psychopathology to reflect past history of adversity. Future models might benefit from including past history of the parent generation, as well (for a first foray, see Ganzel et al., 2010).

THE CASE FOR A CONSTANTLY CHANGING BRAIN

In a prior theory paper (Ganzel & Morris, 2011), we presented a set of models that were a first step toward a more developmentally informed understanding of allostasis and stress-related health outcomes. In that work, we touched on how stress-sensitive periods may manifest as windows of plasticity, on one hand, and as windows of vulnerability on the other. Our aim in the present chapter is to expand on this previous work by applying it to diathesis–stress models of the origins of psychopathology.

To best do so, we will first provide an overview of early brain development. As with other complex systems, brain development is observable across multiple levels of analysis. So to lay the groundwork for our allostatic diathesis–stress model, we weave together information from multiple levels of analysis, from molecules to genes to large-scale neural networks. Activity across these levels of analysis can be observed across a wide range of time spans (milliseconds to years) using multiple methods of measurement. Electroencephalography (EEG) measures millisecond changes in voltage from the scalp that directly indicate electrical current flow in neurons. Magnetic resonance imaging (MRI) gives a static measure of tissue densities in the brain, thus providing a spatially detailed map of brain structure that we discuss here as gray matter and white matter. Diffusion tensor imaging (DTI) allows the mapping of white matter fiber tracts and their integrity. Functional MRI provides a dynamic (although indirect and somewhat slowed) measure of brain activity—usually in response to a stimulus or task (fMRI) but also in the resting state (RSFC). These are all techniques that can be used to study the brains of living people; we will also refer to findings from studies of dead brains (e.g., immunohistochemistry of autopsy tissue), which provide very detailed information about brain structure that cannot be obtained from living humans. Our goal here is to provide relevant snapshots of brain development at these several levels of analysis to illustrate our point that the brain undergoes constant nonlinear change across the life span. We then develop our allostatic diathesis–stress model within this framework.

We will begin with a focus on the relatively early-maturing processes that underlie increasing *functional specificity* within local (several cubic millimeters) ensembles of neurons or *nodes*. We follow with a discussion of the slower-growing white matter tracts that link these nodes into mature *functionally integrative* large-scale *neural networks* that span the entire brain (Hagmann et al., 2010; Honey et al., 2009; Stevens, 2009; van den Heuvel, Mandl, Kahn, Pol, & Hilleke, 2009). The vastly enlarged capabilities of the mature human brain are thought to be supported by synchronous neural activity within these complex large-scale networks (e.g., Fair et al., 2007; Fries, 2005) and there is increasing evidence that dysfunction within these networks plays a prominent role in psychopathology (Menon, 2011; Uhlhaas & Singer, 2012). The emergence and senescence of these nodes and networks across the life span creates a constantly changing neural landscape within which diathesis and stress intersect to predict mental health. This sets the stage for the subsequent section, in which we integrate this information into new diathesis–stress models.

Early Human Neurodevelopment

The central nervous system (CNS) begins to form during the first few months of fetal development in humans (the first few weeks of gestation in rodents; Rice & Barone, 2000). The neural plate is formed first via neural induction, then a further series of inductive processes leads to the expression of different developmental programs within distinct subregions of the new neural plate. These dictate the formation of the major subdivisions of the CNS and the early progenitors of its major structures (e.g., Rakic, 1995; Rubenstein, 2009). Subsequently, region-specific early precursor cells proliferate outward following radial glial processes. In the process, they undergo differentiation, axogenesis, synaptogenesis, pruning, and myelination as they form the mature neural circuits that underlie normal physiological function and complex behavior (Caviness & Takahashi, 1995; Oda & Huttenlocher, 1974; for a comprehensive review, see Rubenstein & Rakic, 2013).

The wiring of the human nervous system is accomplished through the construction and sculpting of connections that foster information exchange among multiple cell types (e.g., Courchesne, Chisum, & Townsend, 1994). The two primary cell types within the brain are neurons and neuroglia (glia). In neuroimaging terms, neurons make up the gray matter of the brain, which is composed of neuronal cell bodies, dendrites, and short axons, while neuroglia (oligodendrocytes in particular) make up the white matter of the brain, the most visible element of which is the pale-colored myelination on long neural axons that connect regions of gray matter (e.g., Wonders & Anderson, 2006). In the period between the third prenatal trimester and the third year of life in humans, a period of heightened apoptosis (programmed cell death) eliminates about half of previously generated neurons (e.g., Davies, 2013; Lossi & Merighi, 2003). In the mature brain, the ratio of

neurons to glia varies by brain region. For example, the adult human cerebral cortex has approximately four times more glia than neurons, while the cerebellum has four times more neurons than glia (Pelvig, Pakkenberg, Stark, & Pakkenberg, 2008).

Neurons have long been considered the core components of the nervous system, and the mechanisms that guide neuronal maturation and senescence are well studied (e.g., Rubenstein & Rakic, 2013). Until relatively recently, however, neuroglia have been thought to play passive structural or housekeeping roles in the brain (e.g., myelination, ionic homeostasis, metabolic support of neighboring neurons and glia: Kurth & Huber, 2012; Parpura & Verkhratsky, 2012; Wang & Bordey, 2008). It has become clear, however, that different classes of neuroglia variously (1) interact with neurons to allow signal transfer at synapses, (2) play a critical role in brain development (for a review, see Wang & Bordey, 2008), (3) function as neural stem cells (e.g., Cameron, Woolley, McEwen, & Gould, 1993; Doetsch, Caillé, Lim, García-Verdugo, & Alvarez-Buylla, 1999) and as precursor cells for other types of glia (e.g., Alvarez-Buylla & Kriegstein, 2013). There is also preliminary evidence that glia (e.g., oligodendrocyte precursor cells) may use neurotransmitters to signal to other glia to allow ongoing plasticity in white matter structure and thus promote ongoing plasticity in the functional capabilities of neural networks (Alvarez-Buylla & Kriegstein, 2013). The fact that both neurons and glia play unique and critical functions in the brain argues for the consideration of both in a developmentally informed diathesis–stress process.

Early Functional Specialization of Local Neural Networks: Focus on Gray Matter

Early Cortical Development via Proliferation and Pruning

In humans, much of the basic adult form of the brain (overall size, weight, cortical folding, and rudimentary functional specialization) is in place by early to middle childhood (Armstrong, Schleicher, Omran, Curtis, & Zilles, 1995; Giedd et al., 1999). During this time, local brain areas begin to develop varying levels of specialization, i.e., they learn to process specific types of information in specific ways. Refinement of functional specificity in local information processing involves the formation and experience-dependent remodeling of synapses. This process is largely complete by young adulthood. This early phase of adaptive organization/re-organization is instantiated in developmental changes in gray matter thickness, which are measurable using magnetic resonance imaging (MRI: e.g., Good et al., 2001). Cortical (gray matter) thickness rises and falls across the life span; it is greatest around 10 years of age in girls and around 12 years of age in boys (e.g., Giedd, 2004; Sowell et al., 2003; Westlye et al., 2010b). Different brain regions vary as to when they reach maximum thickness. In general, the human brain develops from posterior to anterior and from the medial regions out to the lateral portions of the brain. For example, the occipital pole (the primary visual processing area at the very back of the brain) is one of the first brain regions to reach its maximum gray matter thickness (at about age 7.5 years; e.g., Shaw & Gross, 2008), while the superior and lateral prefrontal regions are among the last to reach their maximum thickness at ages 10–12 (between 10 and 12 years of age: Giedd, 2004; Shaw & Gross, 2008). Maximum thickness does not, however, define the maximum *adult* cognitive capacity that is yet to come.

In humans, neural synaptogenesis and the expression of synaptic genes in the prefrontal cortex begin to rise steeply before birth; this continues until the fifth postnatal year, after which rates increase more slowly until about age 10 (Liu et al., 2012). Increased synaptogenesis is associated with enhanced cortical plasticity and roughly coincides with increasing gray matter thickness and increases in cognitive capacity (McArdle, Ferrer-Caja, Hamagami, & Woodcock, 2002). This early proliferation of synapses is countered by bouts of accelerated synaptic pruning, the first of which occurs in early childhood and the second of which occurs during later adolescence (Gogtay et al., 2004; Rakic, Bourgeois, & Goldman-Rakic, 1994). During pruning, the neurons themselves are preserved but any neural connections (synapses and dendrites) that have not undergone experience-dependent strengthening are eliminated, leaving a more efficient circuit, as well as room in the skull for continuing myelination (for a discussion, see Paus, Keshavan, & Geidd, 2008). Pruning is argued to streamline the neural circuitry of the brain to *do best what it has been doing,* and it thus defines a period when experience may profoundly shape brain structure and function (i.e., the spontaneous or evoked activity of a neural system specifies its long-term connectivity: e.g., Changeaux & Danchin, 1976; Huttenlocher & Dabholkar, 1997).

The effects of synaptic pruning during adolescence are profound (see Figure 15.7). Postmortem studies allow direct count of synapse density. Such studies of humans and macaques have found a 50 to 55% decrease in the number of synapses across the entire cortex between late childhood and early adulthood (Good et al., 2001; Huttenlocher & Dabholkar, 1997; Rakic, Ayoub, Breunig, & Dominguez, 2009). These findings are reflected in MRI research, which has identified a 40% thinning in cortical

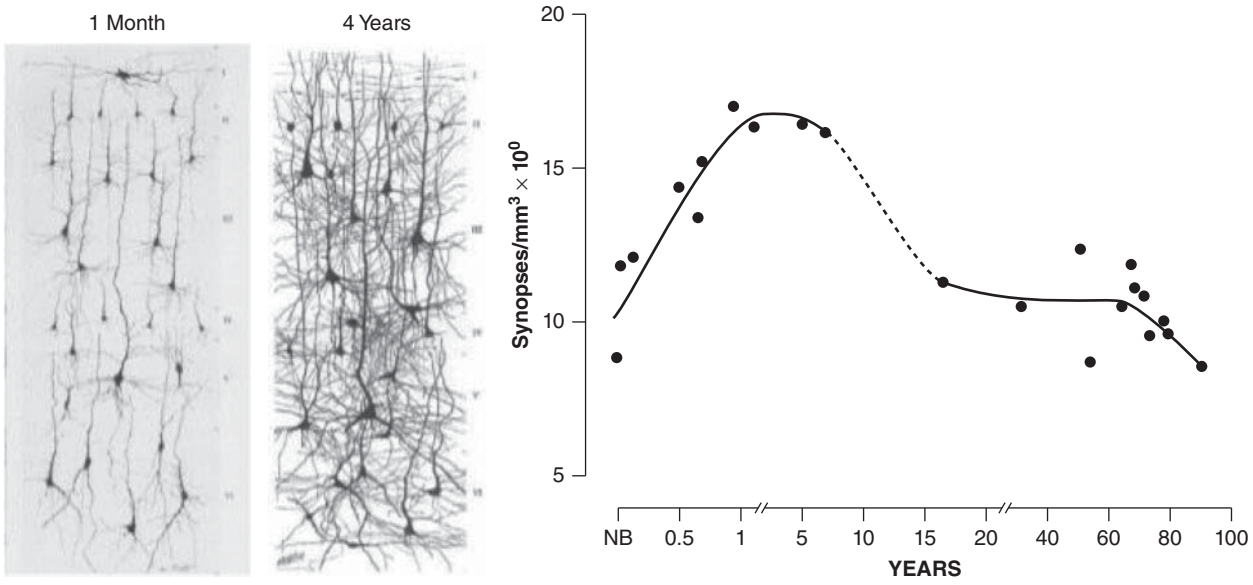


Figure 15.7 Pruning in multiple waves. These figures illustrate the acceleration of neuronal synaptogenesis and dendritic arborization in early childhood, followed by a rapid decline (via pruning) during adolescence (note expansion of time scale in early years). This These waves of synaptic pruning are associated with brain maturation and improved cognition. Another decline in synapse number and cortical thickness occurs late in life and is associated with brain senescence and impaired cognition. *Source:* Adapted from I. Feinberg & I. G. Campbell, Sleep EEG changes during adolescence: An index of fundamental brain reorganization, *Brain and Cognition, 72*(1), 59, 2009.

gray matter during adolescence (Shaw & Gross, 2008; Sowell et al., 2003). This cortical thinning is a marker of brain maturation and is associated with enhanced cognitive ability. It is considered to be a distinctly different process from the cortical thinning in the latter half of the life span, which is associated with the atrophy of large neurons, loss of neuropil (mostly dendritic arbors and synapses), and white matter degeneration (Bertoni-Freddari et al., 2002; Terry, DeTeresa, & Hansen, 1987; Westlye et al., 2010b).

As with cortical thickening and synaptic proliferation, synaptic pruning and cortical thinning/maturation proceed from posterior to anterior and from medial regions out to the lateral portions of the brain. Thus, the occipital pole (shown in black in Figure 15.8) is one of the first brain regions to mature, while the prefrontal and lateral temporal regions are among the last (shown in lighter shades in Figure 15.8; Giedd, 2004; Westlye et al., 2010b). Regional differences in the development of brain structure can be mapped onto maturational differences in brain function, leading to the progressive maturation of cognitive and perceptual capabilities. For example, the early maturation of the primary visual cortex (occipital pole) can be demonstrated through the early emergence of visual acuity (Teller, 1981). Complex motor skills mature later, during adolescence, and executive skills (associated with anterior and lateral PFC function) are not fully developed

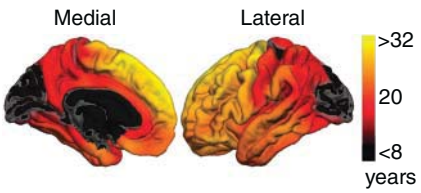


Figure 15.8 The developmental timing of gray matter maturity varies by brain region. Posterior regions develop earlier than prefrontal regions. Superior and lateral prefrontal regions develop last. Areas in black reach maturity prior to 8 years of age. See footnote 1. *Source:* Adapted from L. T. Westlye, K. B. Walhovd, A. M. Dale, A. Bjørnerud, P. D. Due-Tønnessen, A. Engvig, . . . A. M. Fjell, Differentiating maturational and aging-related changes of the cerebral cortex by use of thickness and signal intensity, *NeuroImage, 52*(1), 175, 2010.

until well into early adulthood (e.g., Kurth et al., 2012), along with dramatic increases in information processing capacity and speed (Demetriou, Christou, & Spanoudis, 2002; Luna & Sweeney, 2004).

Each brain region has a different developmental trajectory, so that the aggregate of these trajectories at any given age will demonstrate different patterns of local maturation. During adolescence, for example, the striatal regions (heavily implicated in reward-related behavior) mature earlier than the superior and lateral prefrontal regions that underlie complex cognition and planning (e.g., Galvan et al., 2006). The maximum imbalance in the maturity

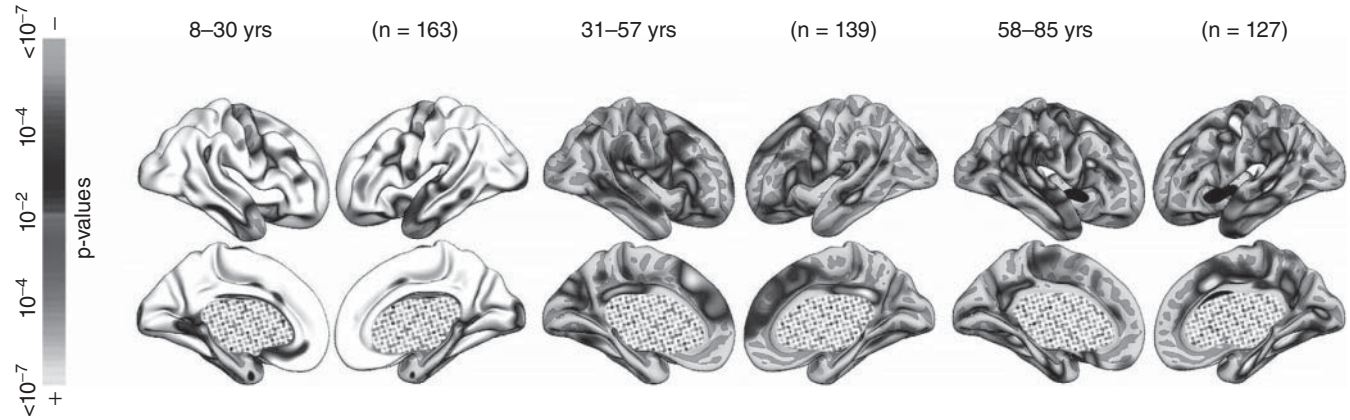


Figure 15.9 Change in cortical thickness with increasing age. See text for a discussion of the global cortical thinning associated with brain maturation in childhood and youth and the distinctly different pattern of cortical atrophy in aging. Also note the small regions of cortical thickening in anterior insula and dorsal cingulate in the aging brain, which will be relevant to our discussion of large-scale neural networks in subsequent sections of this chapter. See footnote 1. *Source:* Adapted from L. T. Westlye, K. B. Walhovd, A. M. Dale, A. Bjørnerud, P. D. Due-Tønnessen, A. Engvig, . . . A. M. Fjell, Differentiating maturational and aging-related changes of the cerebral cortex by use of thickness and signal intensity, *NeuroImage, 52*(1), Figure 4, 2010.

of these systems occurs during adolescence, and evidence suggests that this underlies at least some of the increase in risk-taking behavior observed during this developmental period (Casey, Jones, & Hare, 2008; Steinberg, 2008).

Cortical Development in Maturity

The post-adolescent brain continues to experience widespread reductions in gray matter volume that accelerate during old age. MRI data from cross sections of the total span of adulthood from early to very late in life (18 to 90 years) indicate that this involves a monotonic decrease in gray matter volume across most of the brain (Figure 15.9; Alexander et al., 2006; Giorgio et al., 2010; Good et al., 2001; Grieve, Clark, Williams, Peduto, & Gordon, 2005; Taki et al., 2004). Neuroimaging findings regarding declines in total gray matter volume (in vivo) are paralleled by stereological findings (postmortem) of significant decreases across the life span in neuronal size and total number of neurons (approximately 10% decrease between the ages of 20 and 90 years: (Pelvig et al., 2008).

Compared to the profound maturation-related decreases in cortical thickness observed in earlier development, gray matter thinning associated with cortical senescence may be considered moderate (Westlye et al., 2010a). As previously noted, however, cortical thinning in maturity and old age is considered to be atrophy and it is associated with accelerating declines in cognitive function and increasing frequency of aging-related mental disorders. Recent research supports the view that this version of cortical thinning starts during middle age in both the posterior portions of the brain (cuneus and lateral occipital cortex) simultaneous with thinning in the anterior regions (superior PFC, dorsal anterior cingulate, and lateral OFC; Michielse et al., 2010; Westlye et al., 2010b). With increasing age, thinning extends down from the cuneus to the inferior parietal lobes and the posterior cingulate and fusiform gyri and from the superior PFC to the lateral PFC, temporal gyri, and entorhinal cortices (Figure 15.9; e.g., Westlye et al., 2010b). Thus, the overall picture of gray matter change in middle and old age is one of ongoing atrophy.

There has, however, also been mixed evidence that the midline brain structures, including amygdala, hippocampus, thalamus, entorhinal cortex, insula, and (sometimes) the cingulate gyrus, are exceptions to this rule of ongoing atrophy, at least during midlife (Giorgio et al., 2010; Good et al., 2001; Grieve et al., 2005; Kennedy et al., 2009; Westlye et al., 2010b). When researchers took a closer look at regional variation in gray matter volume between the ages of 20 and 50 years, they were presented with a much more varied picture of gray matter change (Figure 15.10; Terribilli et al., 2011). This group found robust support for the preservation, and even expansion, of medial temporal structures in middle age, including amygdala, extended amygdala, hippocampus, entorhinal cortex, and nearby structures (Terribilli et al., 2011). This is notable, as these areas are particularly vulnerable to tissue loss associated with a wide range of common biological and environmental insults, including depression, anxiety, cardiovascular disease, diabetes, stress, and hardship (Anan et al., 2010; Butterworth, Cherbuin, Sachdev, & Anstey, 2012; Frodl et al., 2002; Ganzel, Kim, Glover, & Temple, 2008; Gianaros et al., 2008; Gianaros, Jennings, et al., 2007; McEwen, 2007; Rauramaa et al., 2011). Nevertheless, there appears to be a significant increase

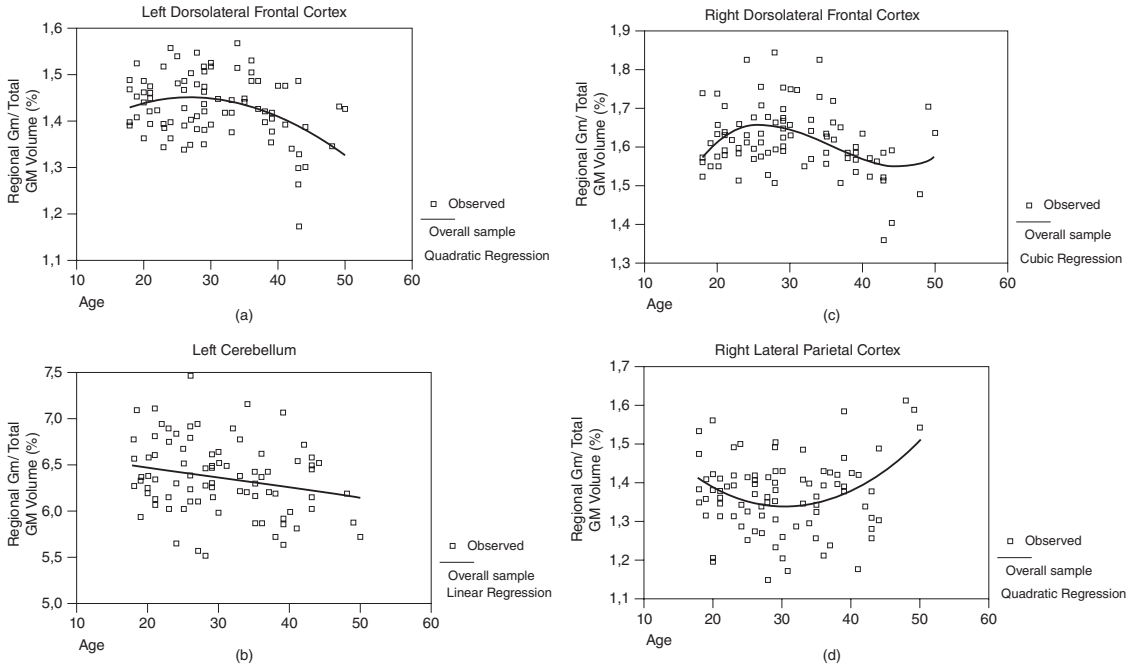


Figure 15.10 There is significant regional variation in gray matter volume across mature adulthood. *Source:* Adapted from D. Terribilli, M. S. Schaufelberger, F. L. S. Duran, M. V. Zanetti, P. K. Curiati, P. R. Menezes, . . . G. F. Busatto, Age-related gray matter volume changes in the brain during non-elderly adulthood, *Neurobiology of Aging, 32*(2), 2011.

in gray matter volume in medial temporal regions over the decades of midlife. This is consistent with findings of preserved structural integrity of amygdala in healthy aging (Good et al., 2001; Grieve et al., 2005; Rubinow & Juraska, 2009; Soininen et al., 1994), although preserved *functional* integrity of amygdala in old age is still debated (e.g., Mather et al., 2004; St Jacques, Dolcos, & Cabeza, 2010). Overall, this work suggests that there is significant decade by decade regional variation in gray matter development and senescence throughout midlife and into old age.

Glial Contributions to Local Connectivity

Neuroglia (especially myelinating oligodendrocytes) are best known for their support of long-range connectivity in the brain, as we discuss in detail later. However, glia also play a role in optimizing *local* synaptic connectivity and signaling between neurons. Astrocytes, in particular, figure prominently in this function by promoting neuron survival, synaptogenesis, and synaptic activity. Astrocytes line nearly all the capillary walls in the brain, which gives them a central role in the blood–brain barrier, as well as enabling them to couple local blood flow to neuronal activity (note that this provides the signal detected in functional magnetic resonance imaging, e.g., Raichle, 2001; Rossi, 2006). This placement allows astrocytes to absorb glucose, the primary energy source for both neurons and glia, and redistribute it to feed the cells of the brain (Rajkowska & Miguel-Hidalgo, 2007; Wang & Bordey, 2008). Astrocytes also regulate the availability of extracellular glutamate in the brain, thus providing critical protection to both neurons and glia, which are otherwise vulnerable to excitotoxic damage (e.g., Barres, 2008; Nedergaard & Verkhratsky, 2012; Rajkowska & Miguel-Hidalgo, 2007). In addition, astrocytes produce growth factors, such as ciliary neurotrophic factor (CNTF), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), which serve a wide range of functions in the brain, including neuronal protection and support of neuronal maturation (Vaca & Wendt, 1992; Wang & Bordey, 2008). Glial growth factors also facilitate local connectivity in the brain by robustly promoting synaptogenesis and synaptic activity (Rudge et al., 1992; Seil, Eckenstein, & Reier, 1992).

Although they are electrically silent, astrocytes have been observed to play an active role in modulating neuronal synaptic transmission during development and across the life span (e.g., Araque, Parpura, Sanzgiri, & Haydon, 1999; Sun et al., 2013). Astrocytes partner with presynaptic and postsynaptic neurons to create a tripartite synapse (Araque et al., 1999) that acts in concert to regulate local availability of neurotransmitters (thus giving astrocytes a role in the therapeutic effects of antidepressants; e.g., Bal, Figueras, Vilaro, Sunol, & Artigas, 1997; Rajkowska & Miguel-Hidalgo, 2007). Early in development, astrocytes are also excitable in the sense that they can integrate multiple incoming signals into a single calcium (Ca^{2+}) signal/wave that modulates the activity of surrounding neurons, glia, and blood vessels (e.g., Hoogland et al., 2009; Schummers, Yu, & Sur, 2008). New research suggests that this form of gliotransmission shuts down quite early in brain development, after which there is a shift to more synapse-specific signaling (Sun et al., 2013). Thus, neuron-glia crosstalk via calcium waves is thought to support the enhanced synchronous neuronal activity observed in very early development, which in turn is hypothesized to support the establishment of large-scale neural circuits (e.g., Grotsch & Reichenbach, 2013). Subsequent developmental suppression of calcium wave gliotransmission is argued to increase functional specificity in local neural networks and thus supports mature information processing (Grotsch & Reichenbach, 2013). Notably, calcium wave gliotransmission can be reinstated by brain injury or in response to certain brain pathologies, even later in development (Grotsch & Reichenbach, 2013; Nedergaard & Verkhratsky, 2012). It is an open question whether psychological trauma also reinstates calcium wave gliotransmission and we suggest this as a topic for future research.

Global Changes in Local Connectivity: Evidence from Deep Sleep

Astrocytes also regulate slow wave activity during non-rapid eye movement (NREM) sleep (Frank, 2012; Postkanzer & Yuste, 2011), which is measured using EEG. Neurons are bi-stable in that they oscillate between "up" and "down" states[7] (Beltramo et al., 2013; Kurth & Huber, 2012; Steriade, 2006). During NREM sleep (deep sleep), this synchronized slow wave activity propagates smoothly through the cortex and is thought to play a critical role in memory consolidation and brain homeostasis. By resetting learning-related increases in synaptic weight (the strength of the connection between nodes of a synapse) to a constant baseline, long-term potentiation (LTP) function is optimized upon waking, while memory remains preserved (Tononi & Cirelli, 2003, 2006, 2012). Since neuronal LTP

[7]The "up" state of a neuron is characterized by a sustained elevation of the resting membrane potential, at the peak of which occur action potentials (neuronal firing). The "down" state is characterized by neuronal silence and cessation of signal input into the network (Beltramo et al., 2013).

is one of the fundamental cellular mechanisms of memory and learning, this synaptic resetting is a crucial for cognition and ongoing neural plasticity across the life span (Frank, 2010, 2013; Kurth & Huber, 2012). A previously noted, glia (especially astrocytes) release molecules that regulate synaptic transmission and neuronal excitability, and these in turn mediate sleep and also brain function during sleep (Fellin et al., 2009; Frank, 2012; Halassa et al., 2009). We will return to the importance of glia in local connectivity and neuronal function when we discuss theories about the role of astrocytes in stress-related changes in brain function and psychopathology across the life span.

EEG measurement of slow wave activity during NREM sleep is also valuable as a noninvasive biomarker of brain development. Slow wave activity during NREM sleep is characterized by low frequency (1.0–4.5 Hz), high amplitude (>75 μV) EEG waves that represent oscillating membrane potentials of cortical neurons that are synchronized in local networks. During NREM sleep, there is a marked loss of effective connectivity across the brain's large-scale neural networks that does not occur during waking or in other sleep stages (Tononi & Cirelli, 2009). Thus, EEG slow wave activity during NREM sleep is related in a systematic manner to moment-to-moment changes in *local* synaptic strength among cortical neurons (Huber et al., 2013; Vyazovskiy, Cirelli, Pfister-Genskow, Faraguna, & Tononi, 2008).[8] In other words, regional variation in slow wave activity provides a direct measure of the synaptic strength within local cortical networks (e.g., Steriade, Timofeev, & Grenier, 2001; Timofeev, Grenier, & Steriade, 2001; Vyazovskiy et al., 2009). Looking across the entire brain, NREM EEG slow wave activity serves as a biomarker of *global* changes in *local* synaptic maturity in the developing brain (Kurth & Huber, 2012).

Use of this biomarker in cross sectional and longitudinal studies has shown that there is a profound reorganization of the architecture of sleep during adolescence (Feinberg & Campbell, 2009; Kurth & Huber, 2012). Between the ages of 12 and 16, there is a steep (65%) and permanent drop in the amplitude of EEG recordings of slow wave activity (Campbell & Feinberg, 2009; Puligheddu et al., 2005). This drop in slow wave amplitude coincides with a strong developmental decline in overall energy metabolism in the brain (glucose utilization) as measured via positron emission tomography (Chugani, 1998). Slow wave activity and synapse number/strength are linked, per the earlier discussion, as are metabolism and synapse density (Attwell & Laughlin, 2001), so these changes are thought to be driven by that second wave of synaptic pruning that occurs in adolescence (Feinberg & Campbell, 2009). Taken together (see Figure 15.11), these observations demonstrate the scope of the fundamental reorganization of the structure, metabolism, and electrophysiology of the brain during childhood and adolescence, which in turn is linked with robust long-term increases in cognitive capability (McArdle et al., 2002).

Notably, there is some evidence that the steep adolescent decline in slow wave activity is specifically linked to puberty, rather than age (Campbell & Feinberg, 2009; Ringli & Huber, 2011). The magnitude of slow wave activity during NREM sleep is highest immediately before the onset of puberty, then drops across adolescence and stabilizes during middle adulthood (Campbell & Feinberg, 2009). These data are correlational and cannot speak to the question of whether changes in slow wave activity are caused by the neuroendocrine events of puberty and further research will be needed to determine whether these phenomena are physiologically linked. Nevertheless, these associations do raise the question of whether related maturational changes in the developing brain (e.g., changes in local synaptic connectivity or the second wave of synaptic pruning) are linked to pubertal timing rather than increasing age.

Local Connectivity Across the Life Span

As discussed previously, slow wave EEG activity during NREM sleep is a biomarker for local synaptic network maturity. Thus, the posterior-to-anterior pattern of gray matter maturation shown in Figure 15.8 is reflected in the topography of slow wave activity. This point was demonstrated in a cross sectional study of children and youth that found a steady shift in the location of maximum slow wave activity from the occipital lobe to the prefrontal cortex between the ages of two and 19 years (Kurth et al., 2010). In this study, regional slow wave maturation during childhood and adolescence preceded regional gray matter maturation, which in turn preceded region-specific increases in cognitive capacity (Figure 15.12b) (Kurth et al., 2010). EEG slow wave activity and the BOLD signal (the signal measured using fMRI) are coupled, so that the robust developmental decrease in the amplitude of spontaneous EEG slow wave signals is paralleled by a steep decrease in the absolute amplitude of the fMRI signal (Lüchinger, Michels, Martin, & Brandeis, 2012; Uhlhaas

[8] Regional variation in NREM EEG slow wave (delta-band) activity reflects regional variation in spontaneous neural activity, as measured by single cell recordings of rate and synchronicity of firing, and the slope of the local field potentials evoked by electrical stimuli (Huber et al., 2013; Vyazovskiy et al., 2008).

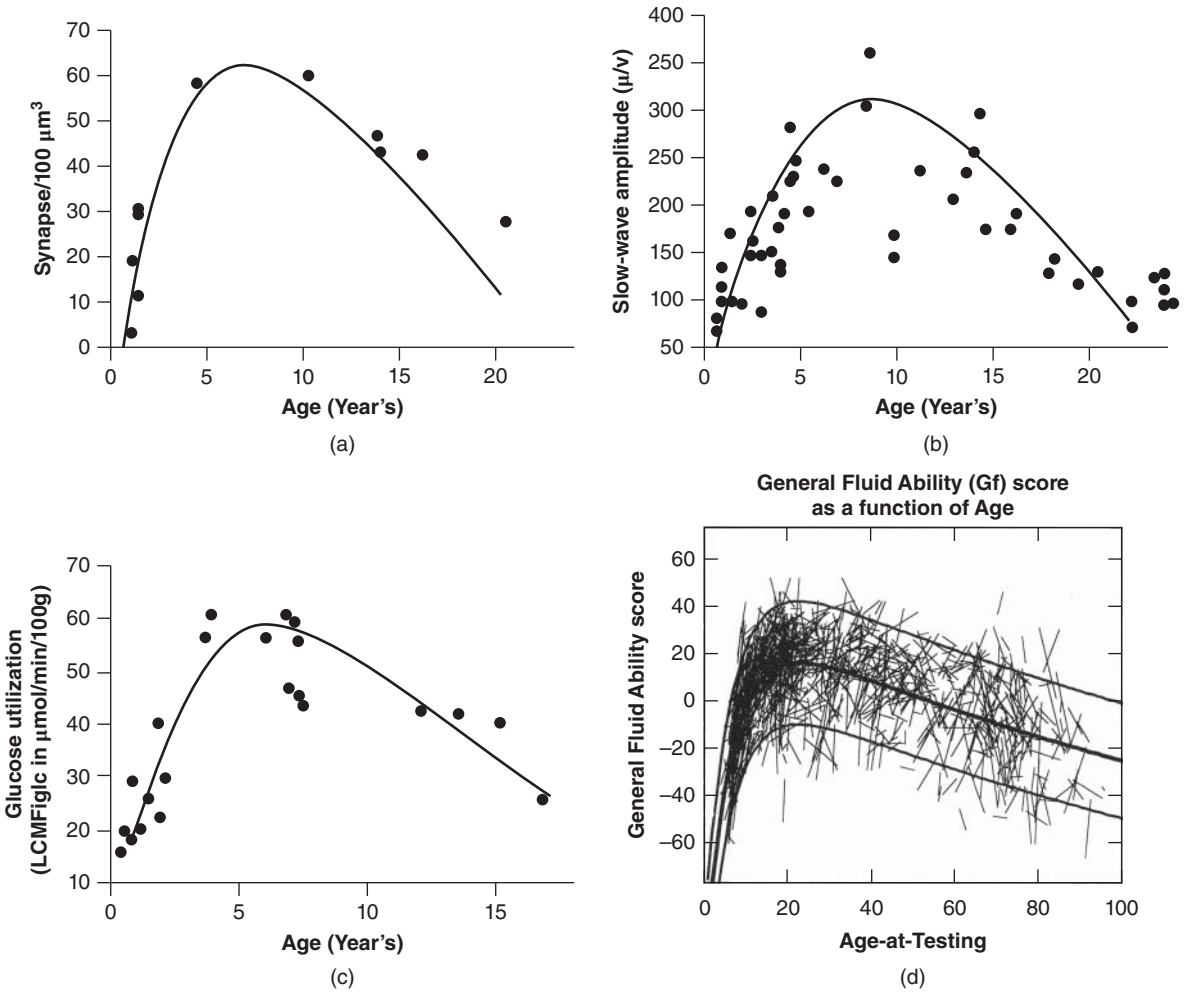


Figure 15.11 Parallel developmental trajectories of (a) synapse density (postmortem tissue), (b) slow wave amplitude (EEG), (c) energy consumption in terms of glucose utilization (adapted from Kurth & Huber, 2012), and (d) the trajectory of human intellectual abilities over development. *Source:* Adapted from J. J. McArdle, E. Ferrer-Caja, F. Hamagami, & R. W. Woodcock, Comparative longitudinal structural analyses of the growth and decline of multiple intellectual abilities over the life span, *Developmental Psychology, 38*(1), 133, 2002.

et al., 2009). Note that the maximum amplitude of the EEG slow wave is reduced by a factor of six between the ages of 8 and 17 years, reflecting the overall decrease in total number of synapses and mean brain metabolism over this time (the peak signal is shown in red numbers, upper right, in Figure 15.12a; see also Figure 15.11).

During adulthood, the peak amplitude of slow wave activity during NREM sleep stays focused in the medial prefrontal cortex (mPFC), which remains a major generator of EEG slow waves until this process is disrupted by tissue degeneration in mPFC in late aging (Murphy et al., 2009). As discussed already, the mPFC is one of the first brain regions to show gray matter atrophy with aging (Raz, 2000; Westlye et al., 2010b). This atrophy is inversely correlated with age-related impairment in memory (i.e., more atrophy predicts less memory), and recent research has demonstrated that age-related decreases in slow wave sleep statistically mediate this association (Mander et al., 2013). It is relevant here that the transfer of hippocampal memory to long-term storage in the neocortex is thought to occur during slow wave NREM sleep (e.g., Fogel et al., 2012; Mander et al., 2013). Together, these data support a model in which progressive age-related atrophy of the mPFC damages the EEG slow wave generator in the adult mPFC and thus disrupts healthy slow wave activity (Mander et al., 2013). This, in turn, interferes with memory consolidation to the neorcortex, resulting in impaired long-term memory (Mander et al., 2013).

In Sum

We have described early-maturing processes that underlie increasing segregation of the cortex into functionally

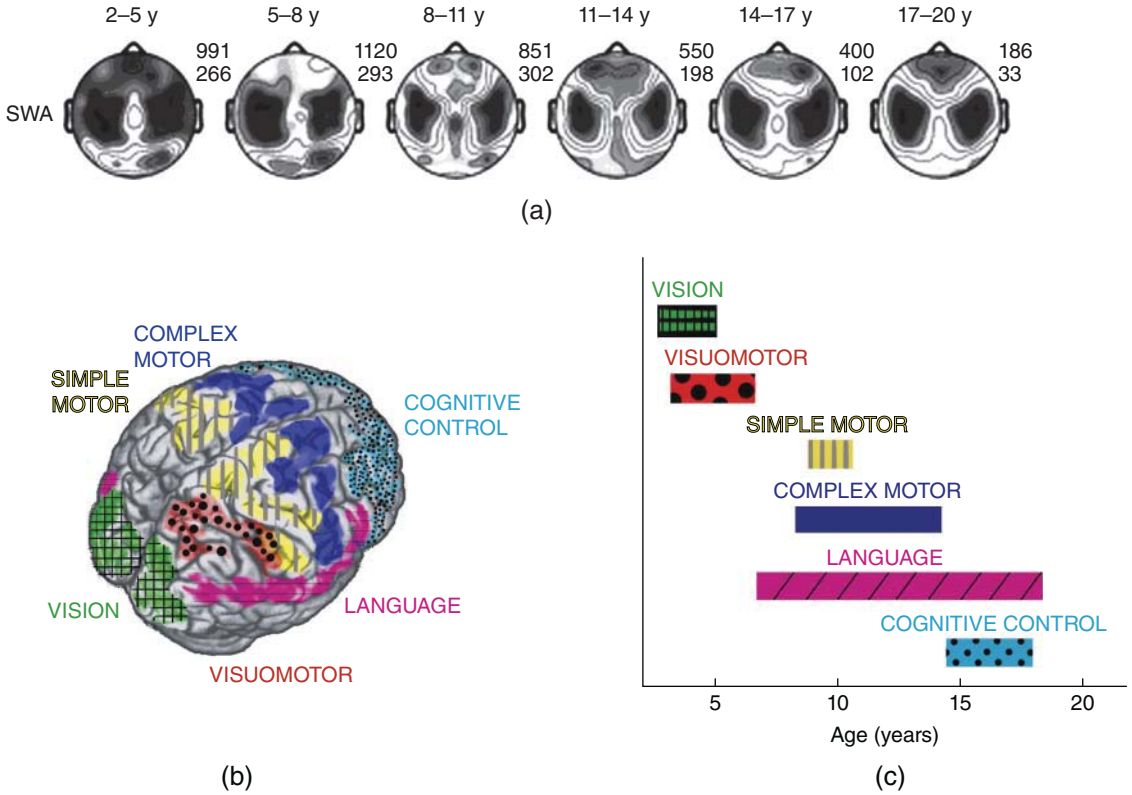


Figure 15.12 Linking local and global brain maturation with cognitive development. (a) The maximum amplitude of the EEG slow wave during NREM sleep moves from posterior to anterior brain regions, reflecting regional change in synaptic maturation (see text). Global gray matter maturation (b) and cognitive development (c) follow these maturational changes in slow wave activity. See footnote 1. Sources: Adapted from (a) S. Kurth, M. Ringli, A. Geiger, M. LeBourgeois, O. G. Jenni, & R. Huber, Mapping of cortical activity in the first two decades of life: A high-density sleep electroencephalogram study, *Journal of Neuroscience, 30*(40), -13214, 2010; and (b,c) S. Kurth, M. Ringli, M. LeBourgeouis, A. Geiger, A. Buchmann, O. G. Jenni, & R. Huber, Mapping the electrophysiological marker of sleep depth reveals skill maturation in children and adolescents, *NeuroImage, 63*(2), 962, 2012.

specialized subregions, i.e., functional specificity in local networks of neurons and glia. Maturation within these local networks peaks and then undergoes age-related deterioration, with strong evidence for significant regional variation in these processes. These data are consistent with a model of coherent and continuous regional variation in cortical structure and function across the life span. We next turn to evidence for changes in functional integration in the human brain across the life span.

Late-Maturing Structural and Functional Integration: Focus on White Matter

Over the course of brain development, functionally specialized local networks (nodes) of neurons and glia become anatomically connected by later-developing subcortical white matter tracts (e.g., Dosenbach et al., 2010; Engel, 1977). This allows synchronous co-activation of nodes that are linked together into functionally integrative large-scale assemblies of neurons (Hagmann et al., 2010; Honey et al., 2009; M. C. Stevens, 2009; van den Heuvel et al., 2009).

Age-related change in the volume and integrity of white matter tracts reflects the maturation and (in old age) the breakdown of myelin, a fatty insulation around axonal processes that is produced by oligodendrocytes (Giedd, 2004; Westlye et al., 2010b). Myelination speeds up the transmission of information between neurons up to 100 times relative to an unmyelinated state (Giedd, 2004; Westlye et al., 2010b). Developmental expansion of white matter volume may also include increases in the cross sectional diameters of neuronal axons that traverse long distances in the brain, but verification of this point will rely on the development of new imaging technology. Specific white matter tracts continue to show developmental increases in volume and integrity through age 30 (e.g., Sowell et al., 2003; Westlye et al., 2010a). Maturation of these tracts is associated with increased ability for complex cognition, which is likely to be a consequence of increased efficiency

in large-scale neural networks (e.g., Sridharan, Levitin, & Menon, 2008; Uddin, Supekar, Ryali, & Menon, 2011). For example, the latest-maturing of these tracts include the uncinate fasciculus and the dorsal and hippocampal cingulum bundles, which connect the survival circuitry of the brain to regions of the prefrontal cortex that underlie planning, executive function, and behavioral inhibition (Hasan et al., 2009; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Westlye et al., 2010a). Increasing myelination in these tracts is thought to underlie emotion regulation and mature decision-making, and possibly mature episodic memory (Levine et al., 1998; E. A. Olson et al., 2009; Schmahmann, Smith, Eichler, & Filley, 2008). Reduced integrity in these tracts is associated with trait anxiety, harm avoidance, and memory problems (M. J. Kim & Whalen, 2009; Levine et al., 1998; Westlye, Bjornebekk, Grydeland, Fjell, & Walhovd, 2011), as well as a wide range of mental disorders, including generalized anxiety disorder (Tromp et al., 2012), social anxiety disorder (e.g., Phan et al., 2009), bipolar disorder (e.g., Wang et al., 2009), and schizophrenia (e.g., Mandl et al., 2013). Focal damage to the right uncinate fasciculus results in failure of retrieval of episodic autobiographical memory (retrograde amnesia) and impacts autonoetic awareness (the awareness or *feeling* of oneself as an individual existing continuously through time; Levine et al., 1998; Tulving, 1985). Damage to similar pathways on the left side of the brain affects episodic encoding and semantic retrieval, thus impacting noetic awareness/generalized knowledge of the world (Levine et al., 1998; Tulving, 1985).

Although specific white matter tracts mature around age 30, overall white matter volume does not peak until around 50 years of age, after which there is a decline in white matter integrity that accelerates toward the end of life (>70 years: Giedd et al., 2006; Westlye et al., 2010b; see Figure 15.13). For example, the average total length of myelinated fibers (axons) in the brain of a 20-year-old male has been estimated to be approximately 176,000 km or 109,361 miles, and the total length of myelinated fiber in the brain of a 20-year-old female has been estimated to be 149,000 km or 92,584 miles (Marner, Nyengaard, Tang, & Pakkenberg, 2003). By 80 years of age, males have only about 97,200 km (60,397 miles) of myelinated fiber in their brains and females have approximately 82,000 km (50,952 miles). Age-related loss of oligodendrocytes underlies this observed 45% decrease in the length of myelinated fibers, which represent a significant loss in the efficiency of intercellular information transfer in the aging human brain (Marner et al., 2003). As with gray matter, the rate of white matter loss varies by brain region (Hasan et al., 2009; Lebel et al., 2008; Westlye et al., 2010a), which supports the concept of regional variation in brain development and senescence across the life span (a constantly changing brain).

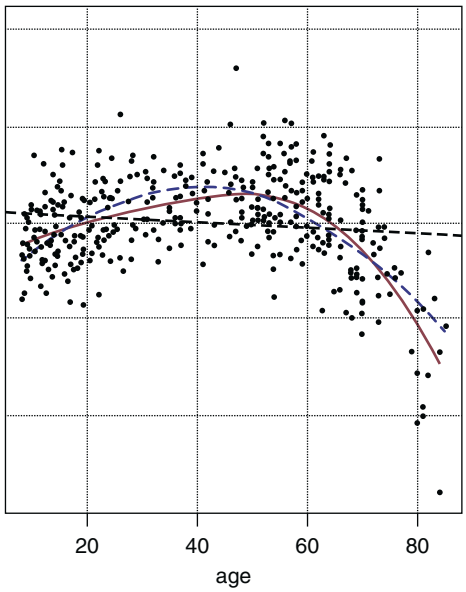


Figure 15.13 The longitudinal trajectory of human white matter development peaks at approximately 50 years of age. See footnote 1. *Source:* Adapted from Westlye, L. T., K. B. Walhovd, A. M. Dale, A. Bjørnerud, P. D. Due-Tønnessen, A. Engvig, . . . A. M. Fjell, Life-span changes of the human brain white matter: Diffusion tensor imaging (DTI) and volumetry, *Cerebral Cortex, 20*(9), 2060, 2010.

Developing Long-Range Connectivity in the Human Brain

Evidence suggests that brain maturation involves a shift from bottom-up neural processing in posterior regions to top-down controlled cognition (e.g., Fair et al., 2007; also see Figure 15.12). Mature cognition involves not only the local development of frontotemporal regions, but also increasingly robust interregional communications in broad neural networks that can extend from the prefrontal cortex to the parietal lobes and the cerebellum (e.g., Dosenbach et al., 2010; Fair et al., 2008; Fair et al., 2007; Rubia, 2012). Once mature electrical and chemical communications are established across each large-scale neural network, then coordinated activity is made possible through the oscillatory properties of neurons (e.g., Bechara, Damasio, Damasio, & Lee, 1999; Convit, Wolf, Tarshish, & de Leon, 2002). As the brain matures, populations of neurons are increasingly able to fire rhythmically and in synchrony, creating oscillating networks that link neural activity across multiple spatial and temporal levels of analysis (Barrett et al., 2007; Dosenbach et al., 2010; Engel, 1977). In this way, the firing of a single neuron in a local network may

be linked to oscillatory activity in vast neural assemblies that span the brain (Convit et al., 2002; Uhlhaas & Singer, 2012). Moreover, oscillatory activity may show partial coherence at high and low frequencies in different cortical layers of the same brain region, thus allowing the generation of complex, flexible, and swiftly changing patterns of neural activity (Uhlhaas & Singer, 2012). Synchronous neural rhythms shape brain states and underlie healthy brain functioning (e.g., Fries, 2005), and disrupted patterns of synchronization have been increasingly associated with a very wide range of psychopathologies (e.g., Kempermann et al., 1998; Uhlhaas & Singer, 2012).

In humans, these functional connections between spatially remote regions of the brain are inferred from correlations in the timing of neurophysiological signals from those areas (e.g., Friston, Frith, & Frackowiak, 1993; Friston, Frith, Liddle, & Frackowiak, 1993). Early human functional connectivity studies examined regional coupling in glucose metabolism using positron emission tomography (e.g., Clark, Kessler, Buchsbaum, Margolin, & Holcomb, 1984; Raichle, 2001). Today, connectivity in large-scale neural networks is more often studied as temporal correlations in the amplitude of blood oxygen level-dependent (BOLD) signal acquired while a study participant completes tasks in the MRI scanner (functional connectivity or fc-MRI) or as the amplitude of low-frequency (< .08 Hz) fluctuations in fMRI studies that do not involve tasks (resting state functional connectivity or RSFC; e.g., Whitfield-Gabrieli & Ford, 2012). Notably, there is accumulating evidence that functional connectivity in the human brain reflects anatomical connectivity (especially white matter connectivity; e.g., Greicius, Supekar, Menon, & Dougherty, 2009; Honey et al., 2009; Koch, Norris, & Hund-Georgiadis, 2002), so that an understanding of anatomical brain development and senescence can inform an understanding of functional neural connectivity across the life span.

The Canonical Large-Scale Neural Networks. In the present discussion, we will focus on three core neurocognitive networks—the default mode network (DMN), the salience network (SN), and the central executive network (CEN), described herein (Figure 15.14). Neural activity in these networks is, with a few exceptions, non-overlapping (e.g., Fox et al., 2005; Yeo et al., 2011). By flexibly coupling or competing with each other, these three networks frame the brain's intrinsic functional architecture and are thought to play a critical role in the emergence of complex cognition during development (e.g., Sridharan et al., 2008; Uddin et al., 2011). Likewise, decreases in the efficiency of long-distance interneuronal communication in old age signify decline in the integrity of these networks (e.g., Mander et al., 2013; Rajkowska & Miguel-Hidalgo, 2007; Ringli & Huber, 2011). Moreover, there is a growing body of evidence suggesting that dysfunction within these canonical networks plays a prominent role in the onset and continuation of psychopathology, which is of high interest to us as we build our allostatic diathesis–stress model.

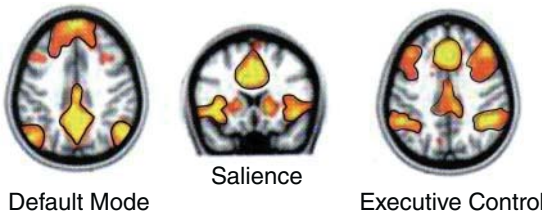


Figure 15.14 Functional MRI shows fluctuating patterns of intrinsic activity in the canonical resting state networks of the brain: the default mode network, the salience network, and the executive control network, also called the central executive network (CEN). See footnote 1. *Source:* Adapted from Whitfield-Gabrieli, S., & Ford, J. M. (2012). Default Mode Network Activity and Connectivity in Psychopathology. *Annual Review of Clinical Psychology, 8*(1), 62. doi: doi:10.1146/annurev-clinpsy-032511-143049

The Default Mode Network (DMN). In the resting state (i.e., when there is no experimental stimulus and the mind is free to do nothing), synchronous regional activity is observed within a distributed neural network that includes the medial prefrontal cortex, the posterior cingulate cortex and adjacent regions, with additional nodes in the posterior inferior parietal lobules (Binder et al., 1999; Fox et al., 2005; Greicius, Srivastava, Reiss, & Menon, 2004; Greicius, Krasnow, Reiss, & Menon, 2003; McKiernan, D'Angelo, Kaufman, & Binder, 2006; Raichle, 2001) and in the superior and inferior frontal gyri, and the medial and lateral temporal lobes (Buckner, Andrews-Hanna, & Schacter, 2008; Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013). This network is referred to as the *DMN* (Raichle, 2001). It was initially characterized as having more activity in the aforementioned regions while the brain was at rest rather than when the brain is engaged in generating task-specific behavior (for reviews, see Mazoyer et al., 2001; Whitfield-Gabrieli & Ford, 2012). In this view, DMN activation was thought to reflect the internal, intrinsic consideration of one's own experience (thoughts, feelings, memories, goals, and mental time traveling, as opposed to a focus on extrinsic stimuli or goal-oriented activity; Gusnard & Raichle, 2001; Kelley et al., 2002; Northoff & Bermpohl, 2004; Whitfield-Gabrieli et al., 2010). More recent thinking places the DMN in a more dynamic role

in which it actively interacts with elements of the CEN to direct or inhibit self-generated thought (Andrews-Hannah, Smallwood, & Spreng, in press; Spreng, 2012). Activity and connectivity in this network have been associated with tasks that involve planning for or thinking about the future, memory retrieval, reasoning about moral dilemmas, theory of mind, self-reflection (reviewed in Andrews-Hannah et al., in press), as well as social cognition (Spunt & Lieberman, 2013), monitoring of the surrounding environment (Gusnard & Raichle, 2001), and the integration of cognition and emotion (Greicius et al., 2003).

The default mode network was among the first large-scale neural networks to be discovered (Greicius et al., 2003). Further functional connectivity studies have isolated multiple stable neural networks that appear to be fundamental to the organization of information processing in the human brain. These networks consist of local brain regions (nodes) in which fMRI responses are coupled in time, such that they activate in synchrony. These networks are said to demonstrate *intrinsic connectivity*, in that they show strong spontaneous temporal and spatial coupling during tasks (Smith et al., 2009) and at rest (typically detected using independent components analysis [ICA]; e.g., Seeley et al., 2007). At least a dozen highly structured functional networks have been identified in the human brain and each appears to serve a more-or-less distinct function (e.g., vision, language, spatial attention; Menon, 2011; Yeo et al., 2011) and demonstrate network activity in response to a more or less distinct set of tasks. Some of these networks consist of only a few nodes, while others span the entire brain and include multiple subnetworks (e.g., Buckner et al., 2008; Corbetta & Schulman, 2002; Dosenbach et al., 2010; Fox & Raichle, 2007; Fox et al., 2005; Mander et al., 2013; Niendam et al., 2012; Raichle, 2001; Seeley et al., 2007; Sporns, Chialvo, Kaiser, & Hilgetag, 2004; Spreng & Schacter, 2012; van den Heuval & Hulshoff-Pol, 2010; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). In general, these networks are nonhierarchical (no one node dominates activity in the system), however the large-scale networks tend to converge on association areas in prefrontal and parietal cortex that are likely to be the most recently evolved and also the latest to mature (Yeo et al., 2011).

The intrinsic neural networks of the human brain are observed to have efficient small-world properties, a term describing a complex network that has (1) a high degree of local connectedness, so that the nodes form tight clusters or cliques and (2) short path lengths between nodes and clusters (Sporns & Zwi, 2004; van den Heuval & Hulshoff-Pol, 2010; Watts & Strogatz, 1998). A growing body of evidence suggests that network properties (e.g., the strength of the correlation between nodes; the average path length between nodes) predicts individual differences in cognitive function (e.g., Kelly, Uddin, Biswal, Castellanos, & Milham, 2008; Seeley et al., 2007; van den Heuvel et al., 2009) and that learning and experience can shape spontaneous activity within these networks (Berkes, Orba'n, Lengyel, & Fiser, 2011; Kurikawa & Kaneko, 2013; Lewis, Baldassarre, Committeri, Romani, & Corbetta, 2009; W. D. Stevens, Buckner, & Schacter, 2010; Tambini, Ketz, & Davachi, 2010). Together, these findings suggest that intrinsic functional connectivity within large-scale neural networks encodes information relevant to behavior, as well as enjoying some level of experience-dependent plasticity (also see Stevens & Spreng, 2014). However, the strong link between functional and structural connectivity in the brain, noted previously, also suggests that activity within these networks is strongly canalized by anatomy (e.g., Greicius et al., 2009; Honey et al., 2009; Koch et al., 2002) and thus by anatomical development and senescence.

The Central Executive Network (CEN). The intrinsic CEN is active in situations requiring information maintenance and manipulation in the service of goal-directed behavior (e.g., J. R. Anderson, Fincham, Qin, & Stocco, 2008; Koechlin & Summerfield, 2007; Miller & Cohen, 2001; Seeley et al., 2007; Spreng et al., 2013). The anchoring nodes in this network are the dorsolateral PFC (DLPFC) and lateral posterior parietal cortex (PPC), with multiple additional nodes making up this large neural network (e.g., Habas et al., 2009; Seeley et al., 2007; Tomasi & Volkow, 2011). Some researchers divide this system into two functionally distinct subnetworks, a *dorsal attention network* (including dorsolateral PFC, dorsal anterior cingulate cortex [dACC], superior parietal lobule, and superior occipital gyrus with additional nodes in the inferior precentral sulcus, frontal eye fields, and middle temporal motion complex; Corbetta & Schulman, 2002; Fox et al., 2005; Seeley et al., 2007; Spreng et al., 2013) and a *frontoparietal control network* (bilateral anterior insula, dACC, lateral PFC, medial superior PFC, anterior inferior parietal lobule, and [sometimes] precuneus, dorsal striatum, and ventrolateral thalamus; Spreng & Schacter, 2012; Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010; Tomasi & Volkow, 2011; Vincent et al., 2008). Although the default network and the dorsal attention network share very few connections, the frontoparietal control network is highly connected with both, which puts it in position to mediate information flow between the default network and the dorsal attention network

(Spreng et al., 2013). For this reason, the frontoparietal control network has been characterized as the gatekeeper of goal-directed cognition (Spreng et al., 2013). A subset of this network (anterior insula [AI]/dorsal ACC) plays a critical role in maintaining goal-directed cognition across time (set maintenance activity; e.g., Dosenbach, Fair, Cohen, Schlagger, & Petersen, 2008; Dosenbach et al., 2007; Dosenbach et al., 2006; Touroutoglou, Hollenbeck, Dickerson, & Barrett, 2012). The right side of the anterior insula/dorsal ACC subnetwork is also argued to play a critical and causal role in switching between the default mode network and the central executive network (Sridharan et al., 2008). Together, these data suggest that executive control of network switching lies within a frontoparietal control network, within which the right anterior insula and dorsal ACC appear to play a pivotal role in linking networks, as discussed later.

The Salience Network. The anterior insula and dorsal ACC are also core elements in a third intrinsic neural network, the salience network. Evidence from animal and human models suggests that the anterior insula plays a prominent role in monitoring and subjective evaluation of salient (survival-related) information from outside and inside the body, regardless of whether the precipitating stimulus is cognitive, affective, or homeostatic (e.g., Borsook, Edwards, Elman, Becerra, & Levine, 2013; Downar, Mikulis, & Davis, 2003; Seeley et al., 2007; Uddin et al., 2011). The dorsal ACC has been implicated in response modulation in sensory cortex, motor cortex (e.g., motor planning), and association cortex (e.g., executive function), as well as in both physical and social pain detection (Bush, Luu, & Posner, 2000; Eisenberger, Lieberman, & Williams, 2003; Kempermann et al., 1998). The anterior insula/dorsal ACC subnetwork shows heightened activity in situations of uncertainty, pain, empathy for pain, social pain/rejection, metabolic stress, temperature variation, and hunger (Buchel, Morris, Dolan, & Friston, 1998; Craig, 2003, 2008; Critchley, 2004; Critchley et al., 2003; Critchley, Weins, Rotshtein, Ohman, & Dolan, 2004; Downar, Crawley, Mikulis, & Davis, 2002; Downar et al., 2003; Eisenberger et al., 2003; Rainville, Duncan, Price, Carrier, & Bushnell, 1997; Seeley et al., 2007; Singer et al., 2004; Taylor, Seminowicz, & Davis, 2009; Touroutoglou et al., 2012). This subnetwork is also responsive to positive stimuli, such as pleasant touch and seeing the faces of loved ones or friends (Bartels & Zeki, 2004; Craig, 2003). Critically, the anterior insula/dorsal ACC subnetwork (particularly on the right side of the brain) is argued to mediate between *all three* canonical large-scale neural networks (Kempermann et al., 1998), thus serving as a critical hub for internetwork neural switching. In this model, the anterior insula/dorsal ACC hub detects salient events and then switches attention and processing resources among the salience network, the central executive control network, and the default mode to access memory resources at all levels, plan goal-directed action, and modulate autonomic response (Kempermann et al., 1998).

Membership of additional nodes in the salience network varies somewhat across studies but typically include rostral medial PFC (Brodmann area [BA] 10) and the presupplementary motor area (preSMA), and sometimes include dorsolateral PFC, dorsal or ventral basal ganglia, hippocampus, dorsomedial thalamus, and the temporal poles (e.g., Hill, Patel, et al., 2010; Seeley et al., 2007; Sridharan et al., 2008; Thomason, Hamilton, & Gotlib, 2011; Tomasi & Volkow, 2011). As with the CEN, the salience network can be divided into two somewhat expanded co-networks (Touroutoglou et al., 2012). Meta-analytic studies show that *dorsal* anterior insula is more engaged in tasks including attention and goal-related behavior, whereas the *ventral* anterior insula is more likely to be engaged in tasks involving affect and emotion (Kurth et al., 2010; Wager & Barrett, 2004). Consistent with this, dorsal anterior insula coactivates with more dorsal brain regions (e.g., dmPFC, dACC, superior parietal lobule, inferior parietal lobule, and superior temporal cortex, lateral occipital cortex, and dorsal striatum), whereas ventral anterior insula coactivates with more ventral regions (e.g., subgenual and perigenual ACC and associated mPFC, lateral OFC, PCC, ventral striatum, and basal forebrain; Taylor et al., 2009; Touroutoglou et al., 2012). This subdivision is compatible with earlier evidence that there are separable ventral and dorsal streams for attentional and affective processing that are integrated in the anterior cingulate (Dolcos & McCarthy, 2006; Yamasaki, LaBar, & McCarthy, 2002).

A Life Span View of Neural Networks

Establishing Neural Networks in Human Development

Coherent patterns of electrical activity are detectable in the human neocortex very early in development (Kilb, Kirischuk, & Luhmann, 2011; Rakic et al., 2009 for a discussion of these phenomena in animal models). These reflect spontaneous activity in emerging large-scale and local neural networks that, in turn, shape normal brain development across multiple systems (Kilb et al., 2011). Disturbances in these early patterns of activity can disrupt cortical development across a broad cross section of

neurophysiology, from neurogenesis (Bonetti & Surace, 2010) and apoptosis (Golbs, Nimmervoll, Sun, Sava, & Luhmann, 2011), to neuronal migration (De Lima, Gieseler, & Voigt, 2009; Heck et al., 2007; Komuro & Rakic, 1996) and the formation of large-scale neural networks (e.g., early vision and somatosensory networks; Catalano & Shatz, 1998; Galli & Maffei, 1988; Iwasato et al., 2000; Weliky, 2000; Weliky & Katz, 1999). Although accurate neural network formation is understood to be crucial to adaptive functioning of the central nervous system, study of the developing architecture of functional connectivity in very young humans has faced serious technological challenges.

Despite these challenges, resting state fMRI investigation of the development of neural networks in healthy fetuses has recently been conducted in the second and third trimester of pregnancy (Geronimus et al., 2006). These are, to date, the earliest data on the development of spontaneous synchronized neural activity in the human brain. In this study, fetal resting state fMRI data showed relatively constrained (anatomically proximal) neural networks with limited unilateral and cross-hemispheric connectivity that increased in strength with increasing fetal age (also see Power, Fair, Schlaggar, & Petersen, 2010, for a discussion of anatomically proximal neural networks in early brain development; Thomason et al., 2013). Increasing cross-hemispheric functional connectivity with increasing gestational age had been previously observed in very premature infants (Glover, 2006). However, prematurity itself is an insult, rendering these results more difficult to interpret. Relative to full-term controls, term-equivalent premature infants show reduced thalamocortical connectivity and no connectivity between medial PFC and posterior cingulate, which is suggestive of disruption in the precursors of mature large-scale neural network activity (Brody et al., 2013; Glover, 2006; Glover et al., 2006). Nevertheless, resting state fMRI studies of premature infants support the premise that anatomically limited neural networks emerge during the third trimester of pregnancy (Brody et al., 2013; Glover, 2006; Glover et al., 2006; Seeman et al., 2004) and this position is strengthened by the parallel findings in neurotypical fetal samples, discussed earlier (Geronimus et al., 2006). A number of forms of psychopathology include abnormalities in functional connectivity that are thought to have prenatal origins (e.g., autism, schizophrenia; Beltramo et al., 2013; Bluhm et al., 2007; Seeman et al., 2001; Seeman et al., 1997), so that better understanding of neural network development in utero may provide early biomarkers of these disorders.

Human functional neural networks show efficient small world properties, as previously discussed. These properties are established by at least middle childhood (Fair et al., 2008) and are maintained across the life span, despite dynamic development and senescence of the functional architecture of the brain through childhood and maturity, and into old age (Dosenbach et al., 2010; Engel, 1977; Markham et al., 2005; Tononi & Cirelli, 2012). There are systematic properties of developmental change in these functional neural networks.[9] In children, nodes appear more likely to cluster as a function of anatomical proximity[10], whereas in adults, nodes are more likely to cluster by their functional roles (e.g., Carstensen, Gross, & Fung, 1997; Dosenbach et al., 2010; Engel, 1977; Markham et al., 2005). This results in a profound reorganization of the overall network structure between the prenatal period and adolescence, but the efficiency and modularity of these complex networks has been assessed to remain remarkably similar across development (Engel, 1977; Markham et al., 2005; Tononi & Cirelli, 2003).

Across infancy and childhood, local circuit development is accompanied by dramatic increases in synapse density, EEG slow wave amplitude, and energy consumption in the brain, as discussed before. Across adolescence, there is a drop in synapse density, EEG/MEG slow wave amplitude, BOLD signal amplitude, and energy consumption that is nearly as profound. Gray matter is pruned. White matter expands. There is a parallel increase in variability and complexity in brain activity, accompanied by improved neural network efficiency, cognitive ability and task performance (see Garrett, McIntosh, & Grady, 2011 for the distinction between variability and complexity in moment-to-moment change in fMRI or EEG signals; McIntosh, Kovacevic, & Itier, 2008; Nakagawa, Jirsa, Spiegler, McIntosh, & Deco,

[9]There is a recent report of movement-related imaging artifacts that reduce the likelihood of detecting long-distance functional connections relative to short-distance connections during resting state fMRI (Tononi & Cirelli, 2003). Clinical samples, children, and older adults are more likely to move during neuroimaging, relative to young adults (Tononi & Cirelli, 2003). The impact of these artifacts on age-related and clinical RSFC MRI findings is still being assessed (e.g., Buckner, Krienen & Yeo, 2013).

[10]There is ongoing debate whether the constrained, anatomically proximal neural networks observed in early development should be studied as immature, fragmentary versions of adult cognitive networks or whether they should be viewed as intact, adaptive functional networks that are qualitatively different from mature networks (Engel, 1977; Markham et al., 2005). The latter would require a more global sampling approach during assessment of functional network properties (Markham et al., 2005).

2013; Uhlhaas & Singer, 2011). Increased whole-brain functional integration of neuronal processing is associated with decreases in the amount of information processing in anatomically local neuronal assemblies (as discussed previously, also see M. C. Stevens, 2009; Vakorin, Lippé, & McIntosh, 2011; Vogel, Power, Petersen, & Schlaggar, 2010). Interestingly, the hub architecture of the brain remains relatively stable across development, but connectivity between these hubs increases (Hwang, Hallquist, & Luna, 2012). In particular, the right anterior insula/dorsal ACC subsystem assumes increasing centrality as an integrative multinetwork hub (e.g., Carstensen et al., 1997; Fair et al., 2007; Markham et al., 2005), which is demonstrated in the late development of the right uncinate fasciculus, the white matter tract that links the dACC with the anterior insula (Uddin et al., 2011).

Large-Scale Neural Networks in an Aging Brain

Maturity brings a putative peak in neural signal variability/complexity and cognitive performance, which then decline with increasing rapidity with advancing age (Fellin et al., 2009; Frank, 2010, 2013; Halassa et al., 2009; Uchino, Birmingham, & Berg, 2010). There is emerging evidence that this is accompanied by decreases in functional neural network connectivity and cognitive function, particularly in the default network at rest (Mander et al., 2013; Rajkowska & Miguel-Hidalgo, 2007; Ringli & Huber, 2011) and during task performance (affected nodes vary; e.g., Ringli & Huber, 2011; Sambataro et al., 2010). These data are supported by evidence for a corresponding aging-related reorganization of large-scale network patterns within brain *structure*, as represented by cortical thickness measurements (assessed via MRI; Chen, He, Rosa-Neto, Gong, & Evans, 2011; He, Chen, & Evans, 2007; Niendam et al., 2012; Tononi & Cirelli, 2012; Zhu et al., 2012).[11] In these studies, both young and old cohorts showed a modular network-like organization of brain structure that corresponded topographically with the standard functional networks previously discussed (e.g., default, executive control, sensorimotor). In normal aging, however, structural networks showed lower efficiency (Zhu et al., 2012) and reduced connectivity within and across structural modules that overlapped with the default network and the executive control network (Chen et al., 2011). These aging-related differences in structural networks were accompanied by the escalating breakdown white matter structural integrity and gray matter atrophy previously discussed in normal aging. As with children and younger adults, small-world network organization was observed to be maintained in the aging brain, despite the evident reorganization of neural networks (Niendam et al., 2012; Tononi & Cirelli, 2012).

[11]The mechanisms through which neuronal activity is systematically translated into regional differences in cortical thickness or volume are not yet clear, but this question will arise in other contexts in the next section, and we will discuss it there.

In Sum

Healthy brain development involves a shift from early functional segregation of activity (local node development) to integration of mature nodes into large-scale functional neural networks that have efficient small-world properties (distributed processing in a complex system). Mature local circuits (nodes) make the most efficient contribution to large-scale neural networks, so that local maturation precedes establishment of mature large-scale neural networks. These processes are linked because the maturation of local PFC circuitry dramatically increases the territory into which large-scale neural networks can expand. During the period in which these extensive neural networks are being established, there is likely to be considerable instability in the global system.

In prior work (Ganzel & Morris, 2011), we provided evidence that each brain region has a unique developmental trajectory. Given the data presented already, we argue that this point is valid across the life span, so that close examination of the brain at any age will reveal different local patterns of maturation and senescence. We conclude here that human brain is constantly changing. In the next section, we apply this concept to our allostatic diathesis–stress model. In doing so, we discuss how both development and strong experience (good or bad) may open windows of instability in allostasis over time, which may create vulnerability to insult—but also opportunity for intervention.

ALLOSTASIS IN A CONSTANTLY CHANGING BRAIN

In this section, we will present models of stress, diathesis, and mental health that explicitly include the concept of a constantly changing brain that we presented in the previous section. There, we argued that brain undergoes continuous age-related change in structure and function across the life span—and that the trajectories of this change vary systematically by brain region. This regional variation occurs in the context of global changes in white matter development and functional network connectivity. In this section, we apply this concept to the diathesis–stress

model. If the brain is the central mediator of allostasis, then we argue that there is ongoing age-related change within the neural circuitry that underlies central allostasis, i.e., within the neural mechanisms of the stress process itself. Allostasis, allostatic load, and stress outcomes—including psychopathology—would thus be expected to vary with the developmental/life span timing of the target stressor. We review evidence in support of this hypothesis and then expand our allostatic diathesis–stress models to incorporate this information.

The focus of this discussion is the occurrence *of sensitive periods,* a term that describes a restricted time span when the effects of experience or insult are particularly strong (e.g., early childhood, adolescence, transitions in developmental stage; Knudsen, 2004). The centrality of the brain in allostasis makes it necessary to consider stress-sensitive periods in neurodevelopment and neurosenescence. However, it is not yet clear how a concept of stress-sensitive periods applies to the allostatic model. Strong implicit models in current developmental stress research include the view that only early-life stressors have long term effects, particularly in the absence of psychopathology (for a discussion, see Ganzel & Morris, 2011). But the ongoing processes of allostasis necessarily generate central and peripheral allostatic load—so what does this mean for a life span allostatic model? Is allostasis then restricted to sensitive periods in youth? We have written about the need for explicit attention to developmental stage in thinking about the allostatic process and the physiological cost of stress (Ganzel & Morris, 2011). We expand on that discussion here.

The processes of development and senescence uniquely constrain physiological response, creating periods or windows of varying sensitivity to experience. The source of these windows is multiply determined (e.g., Levine, 2000; Mead, Beauchaine, & Shannon, 2010). It has been argued that such windows arise because of system instabilities that are either inherent in development or that come about in response to experience (Knudsen, 2004). These have been likened to a temporary broadening of the stability landscape within a neural system that would otherwise be more heavily constrained and protected by innate programming, and thus less subject to change (Knudsen, 2004). Our focus is on those system instabilities that result in changes in the stress response itself, i.e., within the mechanisms of central allostasis. These, in turn, will drive changes in all downstream elements of the allostatic model, including alterations in allostatic load and current mental health. *These* will alter future contexts, future stressors, and future ability to engage allostasis, and—ultimately—future mental health.

In discussing long-term effects of stress on central allostasis, we will focus on the canonical large-scale neural networks discussed earlier. We will take a moment to make a clarification here about the salience network and related survival circuitry, which we have discussed as separate entities up until now. In the next sections, we will typically refer to survival and salience circuitry as a single coherent network. This is for parsimony, and also because these networks are rarely distinguished in discussions of neuroimaging findings for practical reasons. We have seen that activity in the salience network can be studied during rest—a stimulus is not required. In contrast, study of activity in a given survival circuit requires exposing the study subject to the appropriate circuit-specific trigger stimulus (e.g., Bachis, Cruz, Nosheny, & Mocchetti, 2008; Ganzel et al., 2008; Kang et al., 2012; LeDoux, 2012; Phan et al., 2004; Phan et al., 2002). Critically, however, survival circuitry and the salience network unite during the detection and evaluation of salient/survival-related information, and in the planning and execution of adaptive response.[12] Thus, for brevity, we will refer to the survival/salience network when we discuss co-activation of the salience network and LeDoux's (2012) defense circuit in imaging studies incorporating threat-related stressors.

Windows of Vulnerability; Windows of Opportunity

Stress Sensitivity in the Developing Brain

Here we examine some of the processes of development and senescence that create periods/windows of differences in sensitivity to stress or insult. For example, the typically developing brain is vulnerable to perturbation during neural and glial cell development (Knudsen, 2004). Stress-related disturbance or outright insults that occur during periods of rapid developmental are more likely

[12]Barrett (2013) argued that the salience network serves to orient and mobilize the brain's resources in response to generic (domain-general) innate or learned stimuli that have metabolic or homeostatic relevance. This domain-general salience network could be hypothesized to serve as the critical interface between LeDoux's (2012) survival circuits and the rest of the brain's neuronal architecture. As previously noted, however, there continues to be a lack of clarity as to whether the amygdala, ventral striatum, and closely related regions belong in the salience network proper or as inputs to the salience network. We propose that the salience network (both ventral and dorsal components) serves as a general-purpose neural modulator of the survival circuits described in an earlier section.

to disrupt brain structure and function than are system challenges that occur at any other time (Rice & Barone Jr., 2000). There are multiple points during brain development where these system instabilities may arise. At birth, the human brain has approximately 100 billion neurons. These neurons develop from early precursor cells and proliferate outward following radial glial processes, undergoing differentiation, axogenesis, synaptogenesis, pruning, and mylenation in the process of forming the mature neural circuits that underlie normal physiological function and complex behavior (Caviness & Takahashi, 1995; Oda & Huttenlocher, 1974). A window of stressor-sensitivity arises because perturbations or insults to the brain are exacerbated during rapid cell development, compared to perturbations/insults that occur before or after a developmental spurt (Rice & Barone Jr., 2000).

The increased plasticity that occurs during a period of sensitivity is likely to produce adaptive accommodation under typical conditions (e.g., normal maternal care; Diorio & Meaney, 2007). Conversely, accommodations made under atypical conditions are more likely to be adaptive in the short term, but maladaptive in the long term (for discussions, see Ganzel et al., 2010; McEwen & Lasley, 2002). Extreme, negative experiences constitute "failure of the average expectable environment" (Cicchetti & Valentino, 2006, p. 129). The additional plasticity inherent in development can heighten stress-related vulnerability, resulting in atypical physiological development and negative long-term health outcomes in stressed children and youth. Examples include the documented long-term physiological responses to neglect or prolonged early separation (Levine, 2000; Spinelli et al., 2009; Tottenham et al., 2010; Vazquez et al., 2006), early maltreatment (Andersen et al., 2008; De Bellis, Baum, Birmaher, Keshavan, & Ryan, 1999), or high levels of chaos in early rearing environments (Coplan et al., 2001; Evans et al., 2007; Taylor, Eisenberger, Saxbe, Lehman, & Leiberman, 2006).

We begin our discussion of stress-sensitive periods in early childhood. We focus on early childhood because it provides a case in point, allowing us to demonstrate by example the presence of stress-sensitive periods in development. In fact, the primacy of early experience is perhaps the defining concept of developmental stress research; most developmental models of stress in the social and life sciences include heightened stress-sensitivity to early experience with varying levels of exclusivity (e.g., Diorio & Meaney, 2007; Loman & Gunnar, 2010; Lupien, McEwen, Gunnar, & Heim, 2009; McEwen, 1987). Following the discussion of early life stress, we expand to include a life span perspective.

Animal Models of Early Stress-Sensitive Periods

Perinatal Sensitivity to Environment

There is clear evidence in rodent models for sensitive periods in the stress response during the perinatal period (for reviews, see Chapillion, Patin, Roy, Vincent, & Caston, 2002; Cottrell & Seckl, 2009; Matthews, 2002). The best-studied of these is a window of sensitivity in the first 8 days of a rat pup's postnatal life, in which the maturing stress response of the rat pup is hyporeactive, with low basal levels of glucocorticoids[13] and low levels of glucocorticoid response to stimulation (termed the *stress hyporeactive period*; De Kloet, Rosenfeld, Van Eekelen, Sutanto, & Levine, 1988). During this period, gradients in level of maternal care (e.g., licking, grooming, and arched-back nursing [LGABN] of pups) are observed to cause changes in offspring stress physiology and behavior that extend into adulthood (for reviews, see Diorio & Meaney, 2007; Levine, 2000). For example, rat pups that receive high levels of LGABN from their mothers during the first postnatal week grow up to show lower hypothalamic-pituitary-adrenal (HPA) axis response and less fear of novelty as adults, relative to adult pups of low LGABN mothers (Admon et al., 2009; D. Liu et al., 1997). If the mother is separated from her pups for too long (12 to 24 hours), her caregiving becomes disrupted and LGABN decreases. Notably, these effects can be eliminated by direct pharmacological downregulation of hippocampal glucocorticoid receptor levels in the offspring (Meaney, Aitken, Viau, Sharma, & Sarrieau, 1989), indicating a mediating role for glucocorticoid receptor activity in the association between maternal care and offspring stress response. Although low-LGABN mothers are more fearful and have more reactive HPA axis responses (and the converse is true for high- LGABN mothers), the distinct biobehavioral traits of their pups are not a function of genomic inheritance. When the offspring of low-LGABN

[13]Glucocorticoids are one of the primary products of the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis starts in the brain, where an area of the hypothalamus (the paraventricular nucleus) responds to perceived adversity and produces corticotropin releasing hormone (CRH). This, in turn, activates the anterior pituitary to produce adrenocorticotropin releasing hormone (ACTH), which stimulates the adrenal cortex to produce corticosteroids, including glucocorticoids (in humans, the primary glucocorticoid is cortisol). Corticosteroids, in turn, act broadly and relatively slowly to mobilize the body's energy resources (for a discussion, see Loman & Gunnar, 2010).

mothers are fostered by high-LGABN mothers, they are less fearful as adults and show lower HPA response—the opposite is true when pups of high-LGABN mothers are fostered by low-LGABN dams (Francis et al., 1999). Together, these data provide compelling evidence that, in rodents, early maternal care within a narrow developmental window is responsible for organizing lasting differences in the offspring's stress response.

In this system, epigenetics underlies the long-term effects of maternal care on the stress response. For these rat pups, the DNA methylation patterns of the exon 1_7 glucocorticoid receptor promotor are affected by maternal care. These stable alterations in the methylation of this glucocorticoid receptor gene affect the hippocampus' ability to regulate glucocorticoid negative feedback on the HPA axis. This produces the aforementioned increases in HPA-axis response in pups who experience low-LGABN maternal care (Weaver et al., 2004). Notably, severe food shortages during pregnancy (only) have been shown to have similar lasting effects on later health (physical growth; Susser & Stein, 1994), suggesting that parallel processes may take place among humans. In this way, epigenetics is one process by which early experiences carry forward to bring lasting modifications in the individuals' response to stressors at later points in development.

Early Stress Sensitivity in Humans

Research has repeatedly demonstrated that the neural correlates of prior stress and trauma look qualitatively different in human children, relative to those observed in adults. In adults with or without PTSD, exposure to psychological trauma is associated with characteristic dysregulation in the survival/salience network, including increased amygdala response to threat-related stimuli, relative to non-trauma-exposed adults (Ganzel, Casey, Glover, Voss, & Temple, 2007; Ganzel et al., 2008; Rauch et al., 2000; Sharot, Martorella, Delgado, & Phelps, 2007; Williams et al., 2006). Stress-related amygdala hyperactivity is frequently accompanied by either decreased (e.g., PTSD) or increased (e.g., resilience) signal in dorsal anterior cingulate cortex, medial PFC, or inferior frontal areas, along with regional decreases in gray matter volume in amygdala, anterior insula, anterior hippocampus, and medial PFC (Blair et al., 2013; Ganzel et al., 2008; Rauch, Shin, & Wright, 2003; Rauch et al., 2000; Shin et al., 2001, 2004; Williams et al., 2006; Yamasue et al., 2003).

In contrast, stress and trauma exposure in children appear to have qualitatively different sequelae; they are more likely to be associated with global differences in brain structure and function, including smaller intracranial volumes and larger ventricles, relative to nontrauma-exposed children (De Bellis et al., 1999; De Bellis et al., 2002). Other sequelae of stress and trauma in children include variable amygdala reactivity (Taylor et al., 2006; Tottenham et al., 2011) and regional volumetric decreases in ventral PFC, right temporal lobe, corpus callosum and cerebellum—but not in amygdala or insula (Carrion, Weems, Richert, Hoffman, & Reiss, 2010; De Bellis & Kuchibhatla, 2006; De Bellis et al., 1999, 2002; Seckfort et al., 2008). Very early social stress (maternal separation in institutionalized infants) is associated with increased amygdala volume, even in the absence of pediatric anxiety (Tottenham et al., 2010). Together, these data suggest that developmental timing influences the acquisition of allostatic load (a.k.a. the neural embedding of stress and trauma).

Early-Only Allostasis

An early-only allostatic model effectively captures these critical elements of developmental timing in stress process (Figure 15.15). Indeed, early-only models are implicit in much of stress research in the social and life sciences. While few stress researchers explicitly adhere to exclusive critical-period models, we note that much of developmental stress research focuses on early-life stressor exposure to the exclusion of studying age-related modulation of the stress-response at other points in the life span (although see Andersen & Teicher, 2008; Lupien et al., 2009).

There is robust evidence for developmental modulation of stress processing early in life. As previously discussed, adverse care (e.g., abuse or neglect) occurring in early childhood is likely to be damaging because this early period is a time of rapid development in the neural systems underlying the processing of salient stimuli (e.g., Tottenham & Sheridan, 2009). A compounding factor is the heightened social dependency of the younger child, which may make such experiences more overwhelming (Cicchetti, Rogosch, Gunnar, & Toth, 2010). For example, maternal stress and child cortisol levels during early childhood—but not later childhood—have been observed to predict externalizing symptoms in adolescent girls (Burghy et al., 2012). This association was mediated by disrupted amygdala-ventromedial PFC connectivity during adolescence, which suggests that connectivity between these brain regions is a potential key player in the mechanisms associating early cortisol levels with later symptoms (Baron & Kenny, 1986). Similarly, human infants who spend more time in orphanage care (an unfortunate natural experiment in maternal separation) are more likely to show neural differences and behavioral problems as older

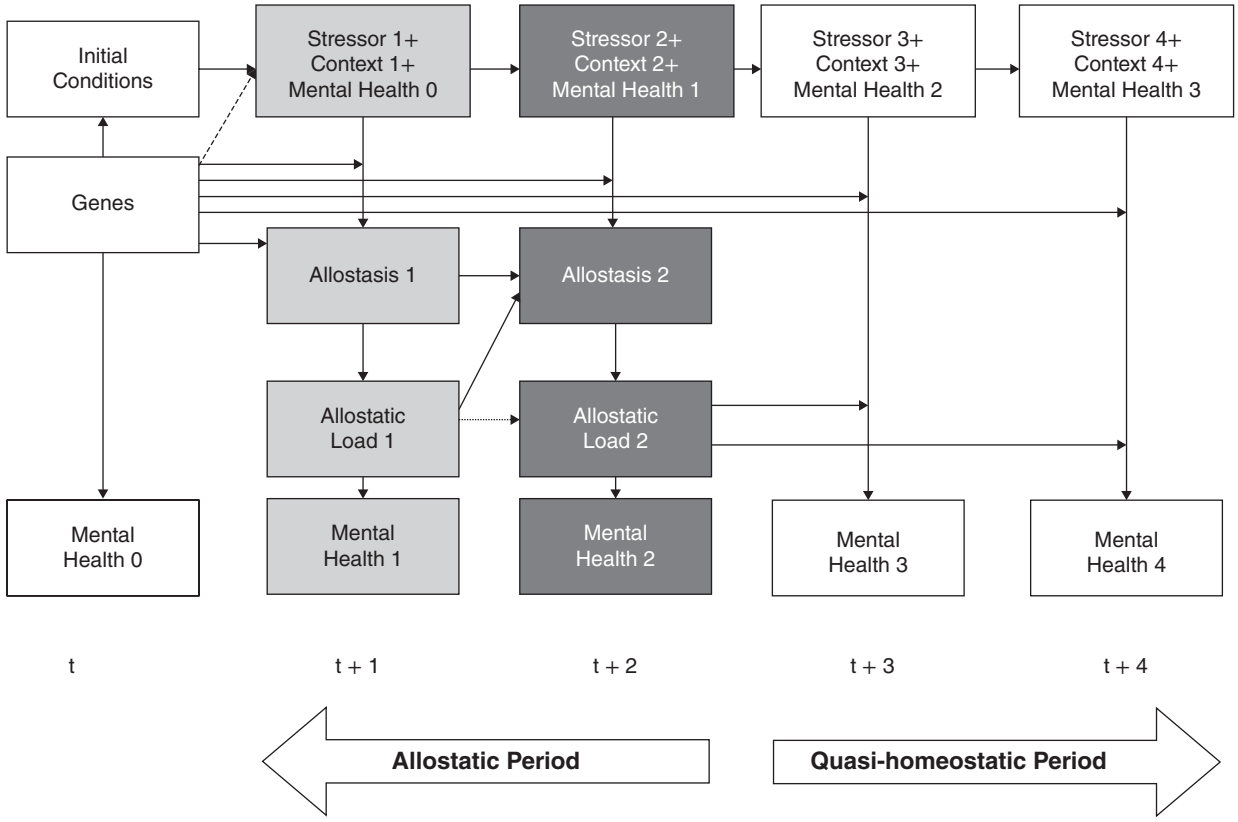


Figure 15.15 An early-only allostatic diathesis–stress model. This model illustrates strong tacit assumptions about early stress-sensitivity that are currently held in the field. In this conceptualization, allostasis is an early-life phenomenon that is active during a circumscribed allostatic period and not thereafter. The different shades of gray indicate developmental differences in central allostasis during this allostatic period (e.g., early childhood versus adolescence). Homeostasis or quasi-homeostasis best describes physiological response to a current stressor after this early period of allostatic flexibility. In this model, early diathesis is a dynamic construct that includes initial genetic loading plus early accumulation of allostatic load, which influence the biological stress response throughout the life span. *Source:* Modified from B. L. Ganzel & P. A. Morris, Allostasis and the developing human brain: Explicit consideration of implicit models, *Development and Psychopathology, 23*(4), 955, 2011.

children, relative to children who were adopted earlier in life (Gunnar et al., 2007; Rutter, 1998; Tottenham et al., 2010). For example, children between the ages of 5 and 12 years who were adopted after 15 months of age were observed to have larger amygdala volume, increased anxiety, and impaired emotion regulation, relative to children who were adopted earlier in life (Tottenham et al., 2010). This said, our intent here is not to argue for or against early stress-sensitive periods in development (as we have discussed, such periods clearly exist). Rather, we wish to expand the concept of developmental variation in stress sensitivity to include the life span.

Stress Sensitivity in Adolescence

Stress and trauma during sensitive periods can drive neural circuits into alternate patterns of connectivity and these new patterns can become entrenched if adverse conditions continue (Knudsen, 2004). Moreover, pruning during later developmental periods may uncover vulnerabilities that were acquired due to atypical earlier development (Williamson & Allman, 2011) and this may result in the later emergence of psychopathology. Happily, there is also evidence that strong, genetically preferred circuit configurations can be reestablished as a stable alternative to the atypical pattern, even after the end of the sensitive period (e.g., Brainard & Knudsen, 1998). The brain is organized in multiple parallel pathways of information processing, making it less likely that irrevocable change in a given circuit will lead to irrevocable change in complex behavior. In addition, even irrevocable change within one circuit may be compensated by changes in other circuits that may have later windows of sensitivity (Knudsen, 2004).

Differential Sensitivity to Intervention

We return to the example of the first postnatal days of a rat pup's life, and the long-term effects of maternal care on the pup's stress response. There is evidence that many of the deficits associated with poor early care can be reversed by providing the pups of low-LGABN mothers with enriched environments during the adolescent period (postnatal days 22 to 70; Bredy, Grant, Champagne, & Meaney, 2003; Bredy, Zhang, Grant, Diorio, & Meaney, 2004). In these studies, environmental enrichment consisted of increased social interaction with peers in a living environment with interconnected tunnel systems and many novel toys (versus standard solo laboratory caging with no toys). This environmental enrichment reversed the impact of low-LGABN maternal care on learning and memory and on the encoding of glutamate receptor genes that contribute to hippocampal-dependent learning. These effects were observed only for environmental enrichment during adolescence—enrichment applied before or after adolescence appeared to have no effect. Moreover, enrichment was only effective for the pups of low-LGABN mothers; it had no impact on the physiology or behavior of pups of high-LGABN mothers (Bredy et al., 2004).

In animal models, adolescent environmental enrichment also attenuates many of the neural and behavioral consequences of prenatal stress (Koo et al., 2003), postnatal extended maternal separation (Lu et al., 2003), and early lead exposure (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008), all of which have different long-term outcomes relative to the consequences of adverse maternal care. Champagne (2010) emphasizes that ongoing plasticity is possible in later life stages through changes in the epigenome. Her work shows that pharmacological treatments can reverse the effects of both positive and negative maternal care, including methylation of hippocampal GR and the behavioral response to stress (Weaver et al., 2004). These findings have clear relevance to our model, in showing how epigenetic process later in development may overlay earlier epigenetic effects, thus modifying the carry-forward of allostatic load. This is an example of how past experience and current context can create iterative modifications of the stress response itself, with long-term consequences for behavior and mental health.

Stress and Human Adolescence

Figure 15.16 provides examples of the developmental time course of brain areas and processes that are likely to play a role in stress-sensitivity and central allostasis from the prenatal period through to young adulthood. From this, we can see that there are likely to be continuing effects of development on the stress response through to the end of adolescence. For example, development in the frontal cortex is region-specific, such that maturation starts in the motor area (just forward of the central sulcus) and the frontal pole (the front-most part of the prefrontal cortex [PFC]) and ends with maturation of the dorsolateral prefrontal cortex (DLPFC) in late adolescence or early adulthood (Gogtay et al., 2004). Stress processing often recruits these brain areas, as previously discussed. This point provides further evidence that the stress process itself can be expected to vary continuously as these brain regions mature in connectivity and efficiency.

Developmental trajectories also vary across key nodes of the survival/salience network, and the amygdala provides a case in point. Total amygdala volume increases rapidly in early childhood and then maintains a relatively steady volume across adolescence and early adulthood (Papagni et al., 2011). However, *functional connectivity* between the amygdala and the rest of the brain continues to undergo robust change from early childhood into adulthood (Convit et al., 2001; Tottenham et al., 2010; Wright, Dickerson, Feczko, Negeira, & Williams, 2007). For example, children show positive connectivity between amygdala and medial PFC, but adolescents and young adults show *negative* amygdala-mPFC functional connectivity that strengthens with increasing age (Convit et al., 2001). Relative to preadolescent children, adults also show much stronger and more segregated functional connectivity between key nuclei of the amygdala (basolateral and centromedial) and network nodes in the cortex and subcortex (Figure 15.17; Qin, Young, Supekar, Uddin, & Menon, 2012). Amygdala *response* also varies systematically with development (Thomason et al., 2011). For example, the adolescent amygdala is more reactive to standardized emotional stimuli (e.g., negative emotional faces) than are the amygdalae of younger children or adults (Hare et al., 2008).

In early adolescence, the salience network appears relatively mature, with resting-state synchronous activity in anterior insula/dorsal ACC, and also inferior parietal lobe, precuneus, and anterior cerebellum (Thomason et al., 2011). In this developmental period, increased hypothalamic-pituitary-adrenal (HPA) axis reactivity has been associated with greater temporal coupling of the salience network with subgenual ACC and other midline PFC regions during resting state imaging (Thomason et al., 2011). It is not yet clear whether this stress-related coupling is specific to young adolescents or how it may influence

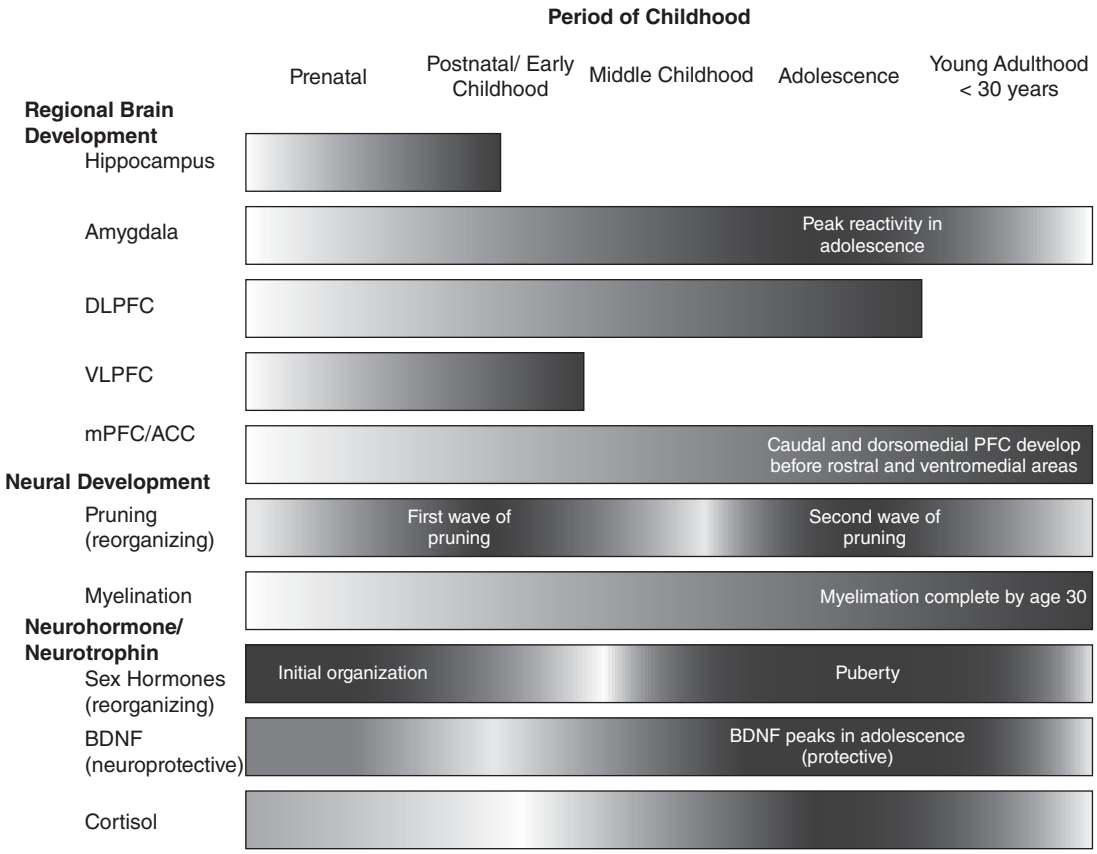


Figure 15.16 Some contributors to early variation in stress sensitivity in the human brain. Darker areas indicate periods in which developmental timing is likely to increase the impact of experience on specific brain regions, processes (pruning or myelination), or neurohormone/neurotrophin systems. In cases where there is limited information from middle childhood (ages 5 to 9 years), we have interpolated smoothly between values from infancy and adolescence. DLPFC—dorsolateral prefrontal cortex, VLPFC—ventrolateral prefrontal cortex, mPFC—medial prefrontal cortex, ACC—anterior cingulate cortex, BDNF—brain-derived neurotrophic factor. *Source:* From B. L. Ganzel & P. A. Morris, Allostasis and the developing human brain: Explicit consideration of implicit models, *Development and Psychopathology, 23*(4), 955, 2011.

the adolescent's future social-emotional adaptation or psychopathology.

Global Changes Within the Adolescent Brain

In addition to the regional variations in brain development that continue through adolescence, discussed earlier, there are also multiple global alterations in brain function that occur during adolescence. We previously discussed the massive and permanent elimination of synapses that occurs during the second wave of pruning, accompanied by an abrupt downward shift in brain energy metabolism. We also reviewed the precipitous drop in the amplitude of slow wave EEG activity during NREM sleep that occurs during adolescence, which is accompanied by the migration of the peak amplitude of the slow wave EEG activity from brain's posterior to the frontmost parts of the prefrontal cortex. We noted that, because of the putative role of NREM slow wave activity in the optimization of learning and memory, this may play an important role in cognitive development.

During adolescent development, there is also a global shift in *neuromodulatory tone*, i.e., in the balance of *excitation and inhibition* (E/I) in neural circuits (Bavelier, Levi, Li, Dan, & Hensch, 2010; Hensch & Bilimoria, 2012). This follows from the fact that a major neurotransmitter, gamma-aminobutyric acid (GABA), switches from being excitatory in early development to being the main inhibitory neurotransmitter in the adult brain (Ben-Ari, Gaiarsa, Tyzio, & Khazipov, 2007; Li & Xu, 2008; Wang & Kriegstein, 2009). During the years of adolescence, this reorganization of inhibitory and excitatory neurotransmission prompts a massive reorganization of neural networks, including a short period of wholesale destabilization of network synchrony in late adolescence (15 to 17 years of age; Uhlhaas et al., 2009). E/I balance also has a regulatory

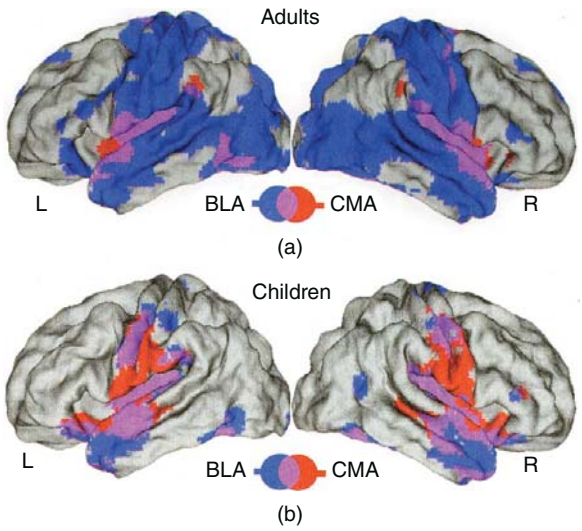


Figure 15.17 Immature integration and segregation of survival/salience network in children versus adults. The basolateral amygdala (BLA) is critical for the perception and evaluation of salient stimuli, whereas the centromedial amygdala (CMA) controls fear-related behavior. Intrinsic connectivity analyses show that (a) adults have strong segregation of the brain areas networked with the BLA and the CMA. Conversely, children (b) show relatively weak and undifferentiated functional connectivity of BLA and CMA. This is proposed to underlie immature evaluation and regulation of response to salient stimuli. See footnote 1. *Source:* Adapted from S. Qin, C. B. Young, K. Supekar, L. Q. Uddin, & V. Menon, Immature integration and segregation of emotion-related brain circuitry in young children, *Proceedings of the National Academy of Sciences of the United States of America, 109*(20), 7943, 2012.

role in the timing of sensitive/critical periods and developmental changes in neuroplasticity (e.g., Bavelier et al., 2010). For example, manipulation of GABA production (and hence the E/I balance) in the brain will alter the timing of onset of developmental critical periods or abolish them entirely (e.g., Di Cristo et al., 2007; Fagiolini & Hensch, 2000; also see Huang et al., 1999; Sugiyama et al., 2008). In short, E/I balance is fundamental to local and global brain development and plasticity, and to the organization of the canonical large-scale neural networks in the mature cortex (Bavelier et al., 2010; Hensch & Bilimoria, 2012; Uhlhaas & Singer, 2012). To our knowledge, the impact of stress- or trauma-related disruptions to this system during adolescence remains unexplored.

Implications for Psychopathology

We have argued here for a constantly changing brain so that a stressor experienced within one developmental time period is likely to have a different effect on long-term physiology and mental health than a stressor experienced later or earlier (Ganzel & Morris, 2011). There is emerging evidence for this type of developmental specificity in the neural embedding of stress. This is illustrated in an MRI study of young women who were similar in age at time of imaging, but who had experienced child sexual abuse (CSA) during different developmental periods (Andersen et al., 2008). Compared with women without a history of CSA, women who were abused between 3 and 5 years of age had the greatest reductions in hippocampal volume, relative to nonabused women and the other women with CSA. Women with CSA between 11 and 13 years of age also had significantly smaller hippocampal volumes, but the effect was not as strong as among the women with preschool CSA. By contrast, CSA between the ages of 9 and 10 was associated with reduced size of the front-most portion of the corpus callosum (the white matter conveying information between the two hemispheres of the brain) and CSA between the ages of 14 and 16 was associated with reduced volume of the prefrontal cortex. If replicated, these data suggest that there are different long-term effects of repeated childhood sexual abuse (CSA) on brain structure depending on when the abuse occurred (Andersen et al., 2008).

The mental health of the young women with CSA also varied as a function of the developmental timing of their abuse. Current symptoms of depression were associated with CSA during early childhood (preschool years) and current symptoms of posttraumatic stress disorder (PTSD) were associated with abuse between the ages of 9 and 10 (for a discussion, see Andersen & Teicher, 2008). There is a substantial body of research that examines the impact of early stress on the brain or mental health, or both. It is becoming clear, however, that there is further need to articulate the role of developmental timing in studies of the long-term effects of stress on brain, behavior, and mental health.

Stress-Related Neural Plasticity and/or Damage in Adults

Despite a general focus on early life stress in the literature, there is accumulating evidence for stress- or trauma-related functional and structural change in local brain regions in mature humans and other animals (Ansell, Rando, Tuit, Guarnaccia, & Sinha, 2012; Cerqueira, Mailliet, Almeida, Jay, & Sousa, 2007; Ganzel, Casey, et al., 2007; Ganzel et al., 2008; Gianaros, Horenstein, et al., 2007; Gianaros, Jennings, et al., 2007; McEwen, 2005; Mitra et al., 2005; Vyas, Mitra, Rao, & Chattarji, 2002). We briefly review this evidence here. In presenting data from humans, we will focus on research involving stress- or trauma-exposed adults who do not have PTSD or another mental disorder

(i.e., nonclinical or resilient adults). Acknowledging the neural embedding of stress in the nonclinical/resilient adult brain is a crucial step in constructing an allostatic diathesis–stress model. As previously discussed (Ganzel et al., 2010), the concept of allostasis fails unless it applies to everyone, regardless of current mental health and developmental stage. We review evidence for long-term effects of stress in the nonclinical/resilient adult brain. With this as a foundation, we will incorporate the intertwining roles of diathesis and life span development into our allostatic diathesis–stress model.

Evidence for Allostatic Load in the Adult Brain: Animal Models

Research with healthy adult animals has provided important evidence for long-term stress-related changes in neuronal architecture and activity in the adult brain. This research has largely focused on regions of interest, with particular focus on amygdala, hippocampus, and prefrontal cortex. For example, adult rodents exposed to a relatively intense single-event stressor will show increases in amygdala spine density (Mitra et al., 2005) and persistent amygdala hyperexcitabilty, which renders the amygdala and related structures more easily activated later (Adamec, Blundell, & Burton, 2005; Maier & Watkins, 1998; Rosen & Schulkin, 1998; Vyas, Pillai, & Chattarji, 2004). This is accompanied by blocked long-term potentiation within the hippocampus and in the pathway between the amygdala and the medial PFC (e.g., Maroun & Richter-Levin, 2003). Subsequent amygdala hyperreactivity does not require the original triggering stimulus (it can be stimulated by mild, ambiguous, or contextual stressors) and is accompanied by heightened anxiety-like behavior (Adamec et al., 2005; Mitra et al., 2005; Olson et al., 2011; Rosen & Schulkin, 1998). Research suggests that this may be driven by plasticity or pathology within the noradrenergic system, which is responsible for norepinepherine (NE) production in the brain (Olson et al., 2011). These stress-related alterations in amygdala, hippocampus, and medial PFC function, structure, and connectivity are arguably biomarkers of allostatic load.

Chronic or repeated stress intensifies the effects of acute stress (Rao, Suvrathan, Miller, McEwen, & Chattarji, 2009). Chronically stressed adult rodents develop long-term increases in dendritic arborization and spine density in pyramidal neurons in amygdala, this neuronal remodeling is associated with persistent increases in amygdala excitability and heightened anxiety-like behavior (Cui, Sakamoto, Higashi, & Kawata, 2008; Hill et al., 2012; Vyas, Jadhav, & Chattarji, 2006; Vyas et al., 2002). Recent work suggests that endocannabinoids play a critical role in these processes (e.g., Finn, 2010; Hill et al., 2012; Hill, McLaughlin, et al., 2010). Endocannabinoids are endogenous lipid-based neuromodulators that are involved in pain, hunger, mood, and memory, although they are probably best known for underlying the psychoactive effects of cannabis. Endocannabinoid receptors are expressed in amygdala, hippocampus, ventral striatum, medial PFC, and hypothalamus (at the head of the HPA axis) (Hill, Patel, et al., 2010). In these regions, endocannabinoids serve to regulate inhibitory (GABA) and excitatory (glutamate) neurotransmitter release to vary synaptic strength (Freund, Katona, & Piomelli, 2003). Chronic stress (but not acute stress) alters the availability of endocannabinoids in amygdala and this has been demonstrated to underlie the stress-related remodeling of amygdalar neuronal architecture, as well as stress-related changes in anxiety-like behavior (Hill et al., 2012; Hill, McLaughlin, et al., 2010) and habituation of the HPA axis under chronic stress (Hill, McLaughlin, et al., 2010). Endocannabinoids also interact with glucocorticoids (e.g., cortisol) to underlie many of the effects of chronic stress on memory, including increasing emotional memory consolidation in amygdala (Campolongo et al., 2009) and interfering with contextual memory retrieval in hippocampus (Atsak et al., 2012). While it is clear that the endocannabinoid system is emerging as a key player in the rodent stress response, it remains an open question whether identical processes occur in humans and how they may vary across the life span.

In parallel with stress-related expansion of dendritic architecture in amygdala, chronic stress has also been linked to gray matter loss in the prefrontal cortex and hippocampus in adult rodents (e.g., Bremner et al., 1995; Cerqueira et al., 2005; Gurvits et al., 1996; Sapolsky, 1985; Sapolsky, Krew, & McEwen, 1986; Uno, Tarara, Else, Suleman, & Sapolsky, 1989), and these are often accompanied by cognitive deficits (Cerqueira et al., 2007; Cerqueira et al., 2005). A similar pattern of effects is observed in humans. Stress-related alterations in gray matter volume have been argued to consist of synapse regression (Bennett, 2011). There is experimental support for this, as recent research has found that chronic stress or depression in humans and rodents increases the transcription factor GATA1 in the PFC, which in turn is responsible for reducing expression of several genes that regulate synaptic integrity (Kang et al., 2012). Increases in GATA1 in the PFC of rodents reduce spine density and dendritic complexity in PFC pyramidal neurons *and* cause depression-like behaviors (Kang et al., 2012). Notably,

stress-related increases in GATA1 expression are reversed by administration of antidepressants in rodents, but the same effect is not achieved in humans.

Stress-related changes are observed in other neural processes that are likely to affect global or regional brain structure or function. For example, chronic stress is observed to kill approximately 5% of the neurons in the rodent cortex (Bachis et al., 2008) and to decrease proliferation of glia by 35% in the rodent anterior cingulate, motor cortex, and hippocampus (Banasr et al., 2007). Chronic stress also decreases hippocampal neurogenesis (Gould, McEwen, Tanapat, Galea, & Fuchs, 1997) and generates chronic alterations in the neurohormones and neurotransmitters that have regulatory roles in the brain (Albeck et al., 1997). Some of these effects are reversible with rest, e.g., decreased neurogenesis (Gould et al., 1997), decreased medial PFC function (Liston, McEwen, & Casey, 2009) and hippocampal atrophy (Vyas et al., 2002). This may reflect a heartening elasticity in at least some components of adult central allostasis and suggests that at least some elements of allostatic load can be undone.

Evidence for Allostatic Load in the Adult Human Brain

Parallel findings arise in human neuroimaging studies of long-term correlates of prior trauma exposure (natural disaster, terrorist attacks, domestic violence) in the nonclinical/resilient adult brain. In these studies, trauma exposure in adulthood predicts persistent increases in amygdala reactivity—not only to trauma reminders (Admon et al., 2009; Sharot et al., 2007) but also to standardized affective stimuli (fearful versus calm faces)—even years after exposure to the target trauma (Ganzel, Casey, et al., 2007; Ganzel et al., 2008). A study by our group examined the effects of a naturally occurring disaster on affective processing of cues of threat (Ganzel, Casey, et al., 2007; see Figure 15.18). Specifically, we used fMRI to assess the impact of trauma exposure (proximity to the World Trade Center disaster on September 11, 2001) on amygdala function in 22 nonclinical adults. More than three years after the terrorist attacks, we found that amygdala activity in response to viewing fearful faces compared to calm ones was higher in people who were within 1.5 miles of the World Trade Center disaster, relative to those who were living more than 200 miles away that day (all were living in the New York metropolitan area at time of imaging). This effect was statistically driven by time since worst trauma in lifetime and intensity of worst trauma, as indicated by reported symptoms at time of trauma. These data are consistent with a model of heightened amygdala reactivity following psychological trauma exposure in nonclinical adults, with slow recovery (potentially on the order of decades).

There is also evidence for trauma-related alterations in emotional cognition in trauma-exposed nonclinical adults, compared with adults with PTSD and also with non-trauma-exposed controls (Blair et al., 2013; New et al., 2009). Relative to both other groups, resilient adults are observed to have unique increases in PFC activity during effortful emotion regulation (New et al., 2009) and in response to an emotional Stroop task (Blair et al., 2013; Qiu et al., 2010). This is argued to be trauma-related neural plasticity that fosters resilience in these adults, allowing them to employ increased top-down control during the processing of emotional stimuli (Blair et al., 2013; New et al., 2009).

Stress and trauma are also implicated in differences in brain *structure* in nonclinical adult humans. In the 9/11-exposed adults discussed previously, we observed broad 9/11-related reductions in gray matter volume that included amygdala, anterior insula, anterior hippocampus, dorsal ACC, and medial PFC, during imaging done approximately three years after 9/11/01 (Ganzel et al., 2008). This finding has been replicated in other samples by other groups (e.g., Ansell et al., 2012, although this study did not include amygdala as a region of interest). Our group has replicated the finding of stress-related reductions in amygdala gray matter volume in another sample, this time of nonclinical young adults with varied histories of trauma exposure (Monohan, McConnell, Salo, Sellers, Wong, & Ganzel, in preparation). In this sample, adults with more traumas in lifetime were observed to have decreased gray matter volume in amygdala. Interestingly, within the same sample, younger age the time of their first trauma was associated with decreases in gray matter volume in the subgenual cingulate (Brodmann area 25), whereas more recent trauma exposure was linked with decreases in gray matter volume in right insula (Monohan et al., in preparation). From prior literature, the association between early trauma exposure and decreased gray matter volume in subgenual cingulate (area 25) is consistent with the intersecting roles of early trauma and Brodmann area 25 in depression (e.g., Heim et al., 2008; Lozano et al., 2012; Mayberg et al., 2005). In addition, a robust association between trauma recency and smaller right insula has been replicated in another study (Ansell et al., 2012), with the additional finding of decreased gray matter volume through the rostral and ventral midline of the PFC (Ansell et al., 2012; Papagni et al., 2011). To our knowledge, this study is the first time that both findings have been identified in the same sample of nonclinical

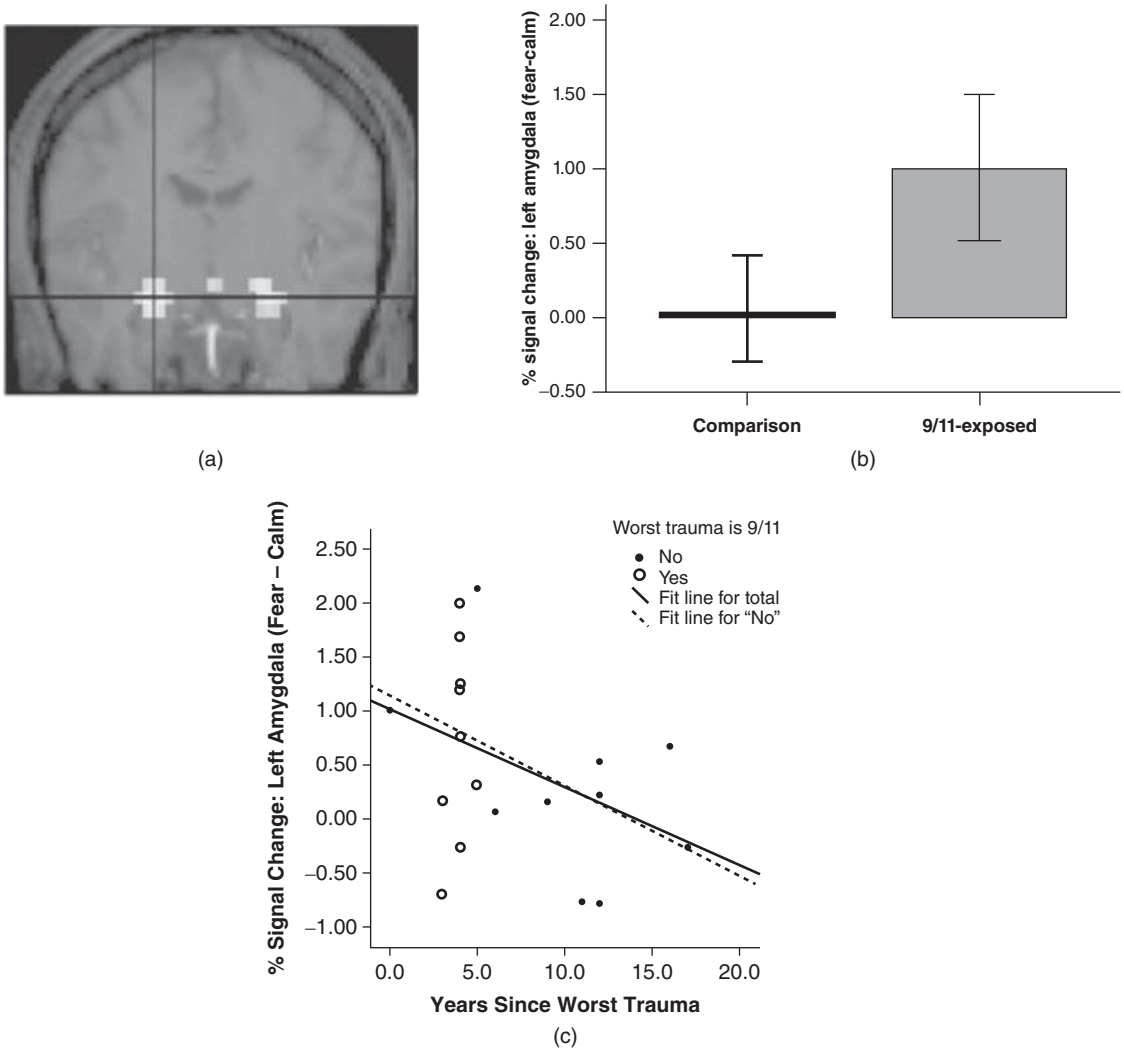


Figure 15.18 Slow amygdala recovery after trauma exposure in nonclinical adults. (a) Fearful versus calm faces elicited greater amygdala activity in the group that was near the World Trade Center disaster relative to the comparison group that was living more than 200 miles away at the time of the attacks. (b) Region of interest analysis showed signal in amygdala in response to fearful versus calm faces was higher in the 9/11-exposed group. (c) Partial plots for the whole group show mean signal change in left amygdala (fearful versus calm faces) versus years since worst trauma in lifetime, controlling for age. Data for those endorsing non-9/11 traumas as worst traumas are shown for comparison. *Source:* From B. L. Ganzel, B. J. Casey, G. Glover, H. U. Voss, & E. Temple, The aftermath of September 11th: Effect of intensity and recency of trauma on outcome, *Emotion, 7*(2), 231, 2007.

adults, thus lending weight to our life span perspective on the neural embedding of stress.

The observations of smaller amygdala volumes in nonclinical trauma-exposed adults appears counter to the animal data on chronic stress or even acute stress, discussed previously. If stress-related gray matter loss is driven primarily by synapse regression (Bennett, 2011), i.e., the retraction of dendritic arborization and synaptic boutons, then stress-related *increases* in amygdalar dendritic arborization and synaptogenesis should logically be associated with increases in amygdala volume. This is indeed observed in children with a history of postnatal stress (maternal separation combined with orphanage care), who show amygdala hyperactivity to standardized emotional stimuli (Tottenham et al., 2011) and larger amygdala volumes (Tottenham et al., 2010), both of which are associated with impairments in emotion regulation. As we discuss later, this effect is also observed in adults who are experiencing their first episode of depression. The mechanisms through which neuronal activity is systematically translated into regional differences in cortical thickness or gray matter volume are not yet clear, but this question will arise in other contexts in the next section and we will address it there.

Evidence for Allostatic Load in the Aging Brain

Age-related variation in neural stress sensitivity does not stop in adulthood, even into old age. Structure and functional response of amygdala, for example, continues to change systematically throughout the life span. In aging rodents, for example, the total number of neurons in the basolateral nucleus of the amygdala remains stable but the number of glia increases, along with increases in dendritic arborization (Rubinow, Drogos, & Juraska, 2009; Rubinow & Juraska, 2009). This is suggestive of ongoing plasticity in the aged amygdala, which is consistent with evidence for spared amygdala function in older humans (Denburg, Buchanan, Tranel, & Adolphs, 2003; Mather et al., 2004; Wright et al., 2007). In contrast, the aged hippocampus and medial PFC show notable shrinkage and loss of dendritic material in rodents and humans (Convit et al., 2001; Markham & Juraska, 2002; Markham et al., 2005; Raz, Rodrigue, & Haacke, 2007) and this is accompanied by significant functional decline (Driscoll & Sutherland, 2005; Resnick, Lamar, & Driscoll, 2007).

Older adults show increased sensitivity to stress relative to young adults, as demonstrated by increased stress-related cardiovascular and immune system dysregulation (e.g., Ong, Rothstein, & Uchino, 2012; Uchino et al., 2010). Along with heightened stress-vulnerability, older adult humans show a strong goal-directed decrease in attention to negative stimuli (a *positivity bias*), which is believed to be motivated by an increased interest in preserving positive emotionality and well-being (e.g., Carstensen et al., 1997; Fischer et al., 2005; Gross et al., 1997; Mather et al., 2004; Mather & Carstensen, 2003; St Jacques et al., 2010; Tessitore et al., 2005; Urry et al., 2006). Despite this positivity bias, increased stress sensitivity in older adults combines with increased exposure to stressors (a normal hazard of aging) to predict age-related declines in health (e.g., Cohen & Williamson, 1991; Kiecolt-Glaser & Glaser, 2001). This synergy of sensitivity and exposure is exacerbated by contextual factors, such as increased loneliness (Cole et al., 2007; Ong et al., 2012). There is also emerging evidence that prior trauma exposure carries unique risks for older adults. Older adults with a history of trauma exposure in adulthood have a higher likelihood of dementia than older adults with no trauma history (Burri, Maercker, Krammer, & Simmen-Janevska, 2013; Tsolaki et al., 2010; Yaffe et al., 2010). Notably, older adults with a history of childhood trauma do not appear to share this increased risk of dementia (e.g., Burri et al., 2013; Ravona-Springer, Beeri, & Goldbourt, 2011), but they are more at risk for geriatric depression (Kuhlman, Maercker, Bachem, Simmen, & Burri, 2013). Thus, the developmental timing of stress and trauma continues to be an important modulating factor in the diathesis–stress process, even into old age.

Incorporating Modulated Allostasis Into Diathesis–Stress Models

The Implications of a Constantly Changing Brain

The brain is the central executor of allostasis. Thus, we expect there to be multiple points across the life span in which the mechanisms of allostasis are uniquely constrained or expanded, or qualitatively changed by the processes of development or senescence. These changes may be temporary (a window) or long-term (a stage). Allostatic accommodation to a stressor that occurs during such a time period will generate a different pattern of physiological wear and tear (allostatic load) compared to a stressor that occurs before this window opened or this stage began. The large and small physiological insults that make up the new allostatic load from this stressor will be unique to this stressor and to this age/developmental period, with distinctive long-term consequences for mental health.

We integrate this concept of modulated allostasis into our diatheses-stress model (Figure 15.19). The tones and shading in each column of the model represent differences in the physiological processes of allostasis at different ages/developmental periods in the life span. These age-related differences in stress-sensitivity are expected to arise out of normal development and then senescence within the survival/salience network, the stress-sensitive peripheral systems, and the processes of plasticity themselves. As previously discussed, allostatic load is accumulating to a greater or lesser degree across the life span.[14] Thus, in this model, diathesis is *dynamic*; it is the sum of an individual's initial genetic compliment and accumulated (central and peripheral) allostatic load at any given point in time.

In Sum

We have argued that brain development is contiguous with brain senescence. Together, they constitute age-related change in the brain that is continuous and

[14]Note regarding *acquired* resilience and cognitive reserve, which may be described as antiload; see McEwen's (2002) argument regarding exercise and dietary interventions. Social interventions, too, must be instantiated in neurophysiology to influence future health and behavior (see Ganzel et al., 2010, for discussion of resilience and antiload).

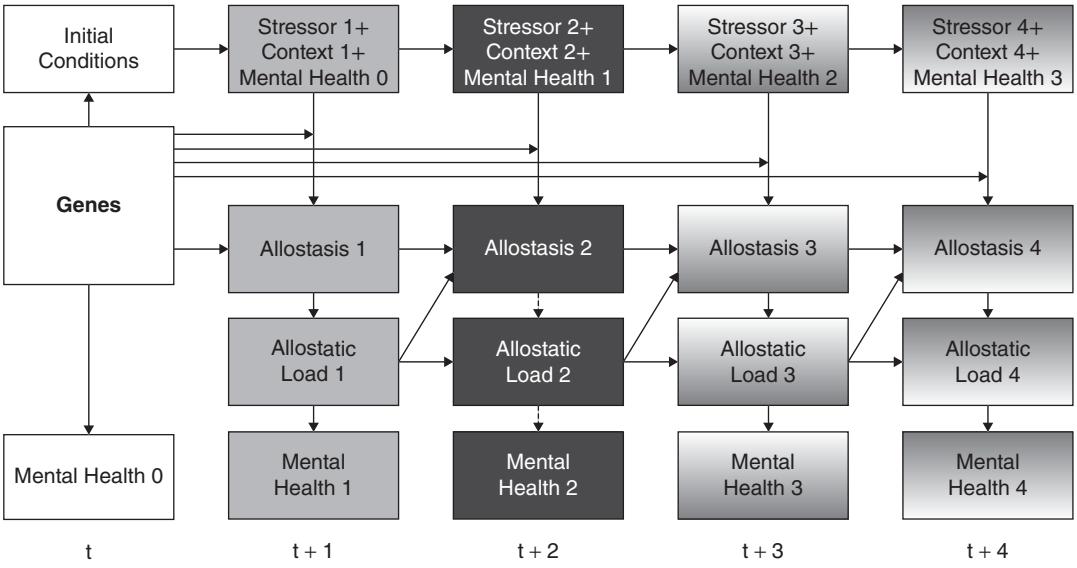


Figure 15.19 Life span diathesis–stress model with modulated allostasis. In this model, diathesis is a dynamic construct that includes initial genetic loading plus lifelong accumulation of allostatic load. Allostasis and allostatic load are shown varying as a function of changing stress sensitivity across the life span. The different shading at each time period in the model represents qualitative or quantitative differences in the physiological processes of allostasis and acquisition of load that arise as the result of these variations. Figure 15.19 shows the relative timing of some of these modulatory physiological processes. Note that mental health at one time period (t) becomes part of the context of any subsequent stressor. This is our most general allostatic diathesis–stress model. *Source:* Adapted from B. L. Ganzel & P. A. Morris, Allostasis and the developing human brain: Explicit consideration of implicit models, *Development and Psychopathology, 23*(4), 955, 2011.

multidimensional, varying across time, (brain) space, and neurobiological level of analysis. Focusing on the central role of the brain in allostasis, we have discussed evidence that the neural mechanisms of the stress process (i.e., of central allostasis) also develop and senesce as part of the phenomenon of the constantly changing brain. If the central mechanisms of allostasis are constantly changing, then the nature of allostatic load (the wear and tear due to ongoing allostasis) is also expected to vary continuously across the life span. We have reviewed the early evidence for this, along with generating unique downstream effects on mental health outcomes. These health outcomes are thus the product of each individual's diathesis (genes + prior allostatic load), stressor exposure, and the developmental timing of that stressor exposure.

Example: A Diathesis–Stress Model of Depression

There have been relatively few attempts to make a multilevel model of the onset and progression of psychopathology from a life course perspective. One illustrative example has been offered by Rajkowska and Miguel-Hidalgo (2007), who addressed the progression of the neurobiology of depression from onset through to old age. In this section, we will discuss this model in the context of our prior argument concerning the constantly changing human brain. To do so, we have adapted Rajkowska and Miguel-Hidalgo's hypothesized scheme of glial cell/neuronal pathology in depression into the format of our life span diathesis–stress model (Figure 15.20). The result is an explicit example of an allostatic diathesis–stress model of psychopathology onset and progression across the life span. To wrap up this subsection, we will then explore some of the ways in which this allostatic diathesis–stress model of depression might be used in hypothesis generation.

In the Rajkowska/Miguel-Hidalgo (R-MH) model, initial diathesis (genetic vulnerability) combines with stressor exposure (Stressor One) to generate stress-related increases in glucocorticoids (e.g., cortisol) and stress-related decreases in neurotrophic factors (supporting neuronal growth and survival) and angiogenic factors (regulating growth in the vascular system; Rajkowska & Miguel-Hidalgo, 2007). Figure 15.19 characterized these as key elements of allostasis (Allostasis One), the moment-to-moment response to a current stressor at depression onset ($t + 1$). Allostasis generates allostatic load (Ganzel et al., 2010), which in the R-MH model includes glucocorticoid-related inhibition of oligodendrocyte and

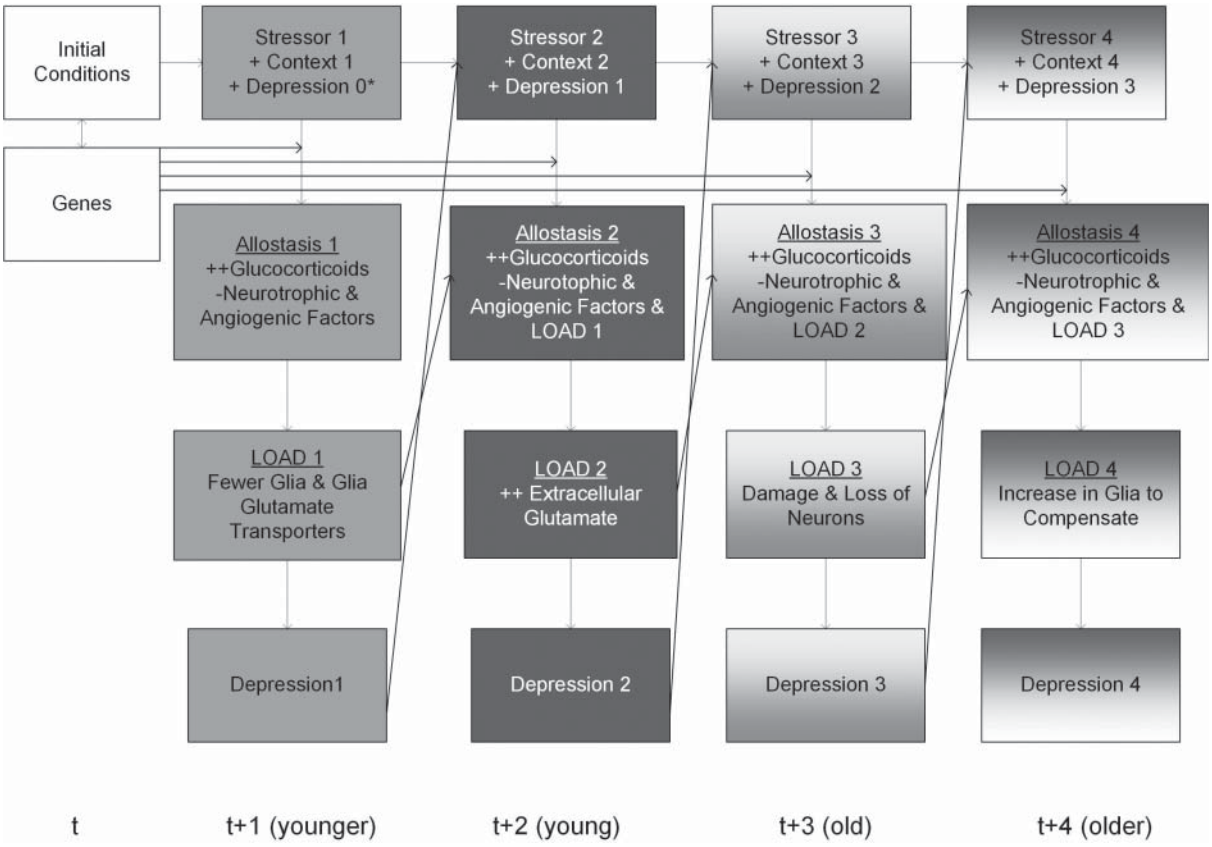


Figure 15.20 Allostatic diathesis–stress model of depression. Interactions between stressor exposure and diathesis (genetic compliment + depression-related cell pathology) drive variation in the underlying mechanisms of depression over the life span (modeled here as younger, young, old, older). *Source:* Adapted from G. Rajkowska & J. J. Miguel-Hidalgo, Gliogenesis and glial pathology in depression, *CNS & Neurological Disorders Drug Targets, 6*(3), 219, 2007.

astrocyte proliferation (Load One). This view is supported by postmortem studies of glial cell density, which show strong decreases in astrocyte density in anterior cingulate, amygdala, hippocampus, and dorsolateral PFC in younger depressed adults (see review by Sanacora & Banasr, 2013). Depression-related pathology of oligodendrocytes (reviewed by Edgar & Sibille, 2012) and microglia (reviewed by Beumer et al., 2012) has been well established, although the R-MH model highlights the role of astroglia. In particular, astrocytes are a crucial regulator of glutamate availability. One astrocyte will serve as the sole regulator of glutamate removal for a large number of synapses, so that "the failure of a single astrocyte could impair glutamate removal at thousands of synapses" (Sanacora & Banasr, 2013, p. 1175). In the R-MH model, stress-related depletion of astrocytes is expected to impair glutamate regulation, which would manifest as increased glutamate in the synaptic cleft. Thus, the carryover of allostatic load from time $t + 1$ to time $t + 2$ includes glial pathology and an associated dysregulation of glutamate uptake and release.

This latter point is critical to the R-HM model, as excessive glutamate exposure causes neuronal damage and death due to excitotoxicity (reviewed by Rajkowska & Miguel-Hidalgo, 2007). At time $t + 2$ in Figure 15.20, the individual is still in the earlier stages of depression. She experiences Stressor Two, but now she is carrying a diathesis that consists of her initial genetic vulnerability plus the acquired allostatic load from her encounter with Stressor One. Her mechanisms of central allostasis will now be trying to operate in a brain that has fewer glia and more extracellular glutamate (Allostasis Two). This is likely to hinder allostasis, resulting in a unique additional burden of allostatic load (Load Two), including fewer glia and an increasing burden of extracellular glutamate. Notably, however, this progression of stress-related glial loss and glutamatergic escalation appears to be limited. Rajkowska and colleagues (Si, Miguel-Hidalgo, O'Dwyer,

Stockmeier, & Rajkowska, 2004) have observed that younger individuals with major depression show minor neuronal pathology but prominent glial pathology (particularly pathology of astroglia). In Figure 15.20, this is represented by our allostatic R-HM model at time periods ($t + 1$) and ($t + 2$). On the other hand, older individuals (>60 years) with major depression show an increase in astroglia, combined with a notable reduction in pyramidal neurons. Because of this, Rajkowska and Miguel-Hidalgo (2007) proposed that many years of stress-related elevation in extracellular glutamate does substantial neuronal damage in aging depressives (Load Three). This exemplifies the life span development of load and an individual's diathesis (genes + load). To explain the age-related increase in glia, Rajkowska and Miguel-Hidalgo invoked the well-established tendency for glial cells to proliferate in response to neuronal damage—in this case, damage due to glutamate excitotoxicity (2007). We note that this model requires repeated stressor exposure (e.g., Stressor Four) to drive the ongoing, changing burden of allostatic load (e.g., Load Four). However, exposure to stress and trauma is relatively common in the general population (Copeland, Keeler, Angold, & Costello, 2007; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995) and psychopathology itself can serve as a stressor (e.g., Bruce, 1998).

Hypothesis Generation

Here, we depart from our reconceptualization of Rajkowska and Miguel-Hidalgo's (2007) glial model of depression to explore some of the ways this model—and our own overall approach to diathesis–stress modeling—might be used in hypothesis generation. For example, earlier we noted that astrocytes regulate non–rapid eye movement (NREM) sleep, as well as modulating sleep need, sleep intensity, and EEG slow waves, i.e., the slow neuronal oscillations that occur during NREM sleep (Fellin et al., 2009; Halassa et al., 2009). If stress-related astrocyte pathology is integral to depression, then these properties of NREM sleep should also be dysregulated in depression. There is a growing body of evidence for this. Dysregulated sleep is a core symptom of depression and there is a recent research focus on the interplay between astrocyte function, sleep (esp. NREM sleep), and depression in humans and in animal models (e.g., Cao et al., 2013; Duric et al., 2010; Florian, Vecsey, Halassa, Haydon, & Abel, 2011; Hines, Schmitt, Hines, Moss, & Haydon, 2013). Also from earlier, recall that EEG slow-wave activity during NREM sleep is argued to play a crucial role in synaptic homeostasis by downscaling LTP-related increases in synaptic weight, thus preserving memory and optimizing learning (e.g., Tononi & Cirelli, 2006). We would therefore expect that learning and memory would be impaired in depressives in direct relationship to their degree of astrocyte pathology and compromised LTP-related synaptic homeostasis. While astrocytes are observed to modulate cognitive declines associated with sleep loss (e.g., Halassa et al., 2009), to our knowledge, Tononi & Cirelli's (2003, 2006, 2012) synaptic homeostasis hypothesis has not been explored as a possible mechanism associating astrocyte pathology and the cognitive impairments observed in depression.

The R-MH model of cellular pathology in depression (Figure 15.20) embraces a life span perspective. Specifically, this model predicts pathological increases in the density of astrocytes and a parallel decrease in pyramidal neurons in key brain areas in aging depressives. It follows from the earlier discussion that we would expect to see progressive changes in NREM sleep biology, sleep-related symptoms, and cognitive deficits as depressed individuals grow old. Similarly, if age-related variation in glial and neuronal density is driven by stressor exposure, then we would expect people who have experienced more stress and trauma in lifetime to show an earlier transition to the aged scheme of depression neurobiology (more glia, fewer neurons), relative to depressed individuals with less lifetime stressor exposure. We leave these questions to future research.

In exploring this example, we do not suggest that astrocyte pathology is the only important factor in diathesis–stress models of depression. Our goal has been to demonstrate a specific use of our diathesis–stress model for hypothesis generation, as well as to emphasize that life span development is likely to underlie at least some of the observed heterogeneity in the neurobiology of psychopathology. We next turn to broader questions raised by our allostatic diathesis–stress model.

TRIPLE NETWORK ALLOSTASIS AND PSYCHOPATHOLOGY

In this section, we incorporate current research on the large-scale organization of the human brain into our allostatic model of response to a current stressor (Figure 15.4). This effort incorporates a neural network approach to psychopathology into our allostatic model of the stress process, discussed in detail in Sections Two and Four. Incorporated into a diathesis–stress framework, this approach serves as the basis for hypotheses about allostatic load within the large-scale neural networks the brain, and

its role in the onset and maintenance of psychopathology. We review emerging evidence for these effects and segue to directions for future research.

Dysfunctional Large-Scale Neural Networks in Psychopathology

A Paradigm Shift in Psychopathology Research

The intrinsic neuronal signaling within the human brain has been compared to the dark energy of the universe (Zhang & Raichle, 2010). New astrophysical evidence suggests that dark energy makes up approximately 68% of the mass energy of the universe, so this recently acknowledged (and largely hidden) component of the universe in fact constitutes *most* of the universe (Ade et al., 2013). This discovery is paralleled by recent findings in human neuroscience that less than 5% of the brain's resources are devoted to processing external stimuli—thus leaving the vast majority of the brain's energy budget devoted to previously uncharted intrinsic activity within brain systems (Raichle & Mintun, 2006). Exploration of this intrinsic activity has resulted in a functional network model of the neural function that is based on stable large-scale networks of synchronized neuronal activity. This model constitutes a paradigm shift in systems neuroscience (Sylvester et al., 2012), with a consequent paradigm shift under way now in clinical neuroscience and neuropsychiatric research (Menon, 2011; Sylvester et al., 2012; Uhlhaas & Singer, 2012).

Neuroimaging studies of psychopathology are increasingly focused on dysfunctions within large-scale neural networks. These dysfunctions can occur via damage to the nodes of a functional network, to the connections ("edges") between nodes, or to a combination of these. For example, changes in the excitation inhibition balance (Figure 15.21) at the local or node level can disrupt the synchronized neuronal activity in adjacent nodes. Thus, damage to a node can propagate to other nodes to which it is linked in a functional network (Carter, Shulman, & Corbetta, 2012; Ewers, Sperling, Klunk, Weiner, & Hampel, 2011). This may also lead to compensatory changes in other parts of the network (e.g., strengthening connectivity between between other nodes; Crofts et al., 2011). Even if the nodes of a network are healthy, network function is compromised if the connections between nodes are damaged. This can happen, for example, through age-related degeneration of white matter integrity. Damage to axonal myelin results in increased signal degradation between nodes and this, in turn, is associated with disruptions in neuronal synchrony (e.g., Mander et al., 2013; Rajkowska & Miguel-Hidalgo, 2007; Ringli & Huber, 2011). Aberrations in nodes or edges can derive from initial genetic loading or they can be acquired through experience, insult, or disease at any point in the life span. Analysis of abnormalities in functional neural networks provides a common quantitative framework for a novel synthesis of findings in psychopathology research, as well as highlighting fruitful directions for clinical research. This, in turn, has been productive in providing new insights into the neural underpinnings of schizophrenia, autism, anxiety disorders, and a wide range of other major forms of psychopathology, as we discuss later.

A Triple Network Model of Psychopathology

There is a groundswell of new research suggesting that some, if not all, psychopathologies are associated with more or less unique abnormalities in the functional connectivity of large-scale neural networks (for reviews, see Menon, 2011; Seeley, Crawford, Zhou, Miller, & Greicius, 2009; Uhlhaas & Singer, 2012; Zhang & Raichle, 2010). This suggests the alluring prospect that functional connectivity MRI (fcMRI) may be diagnostic at some point in the future. Meanwhile, research in fcMRI is driving new theorizing about neuropsychiatric disorders as pathologies of networks rather than brain regions. We will focus our discussion on an integrative model of large-scale neural network dysfunction in psychopathology, the *triple network model* (Menon, 2011). The core elements of this model are the three canonical neurocognitive networks discussed in **Section Three**—the default mode network (DMN), the salience network (SN), and the central executive network (CEN). As discussed, these three networks serve as the framework of the brain's intrinsic functional architecture, and there is growing consensus that disturbance in the function or organization of these three networks are fundamental to many neuropsychiatric disorders (e.g., Menon, 2011; Seeley et al., 2009; Uhlhaas & Singer, 2012).

Menon (2011) placed the salience network in general—and the right anterior insula in particular—at the core of triple network theory. As such, the salience network has a pivotal role in the onset of affective and cognitive dysfunction. In support of this hypothesis, he points to a robust pattern of structural or functional abnormalities in bilateral or right insula in schizophrenia (Glahn et al., 2008; Palaniyappan & Liddle, 2012; Palaniyappan, Mallikarjun, Joseph, White, & Liddle, 2011; Sommer et al., 2008; White, Joseph, Francis, & Liddle, 2010), bipolar disorder (Bora, Fornito, Yücel, & Pantelis, 2010), frontotemporal dementia (Seeley et al., 2006; Zhou et al., 2010), addiction (Naqvi & Bechara, 2009; Scott & Hiroi, 2011), anxiety

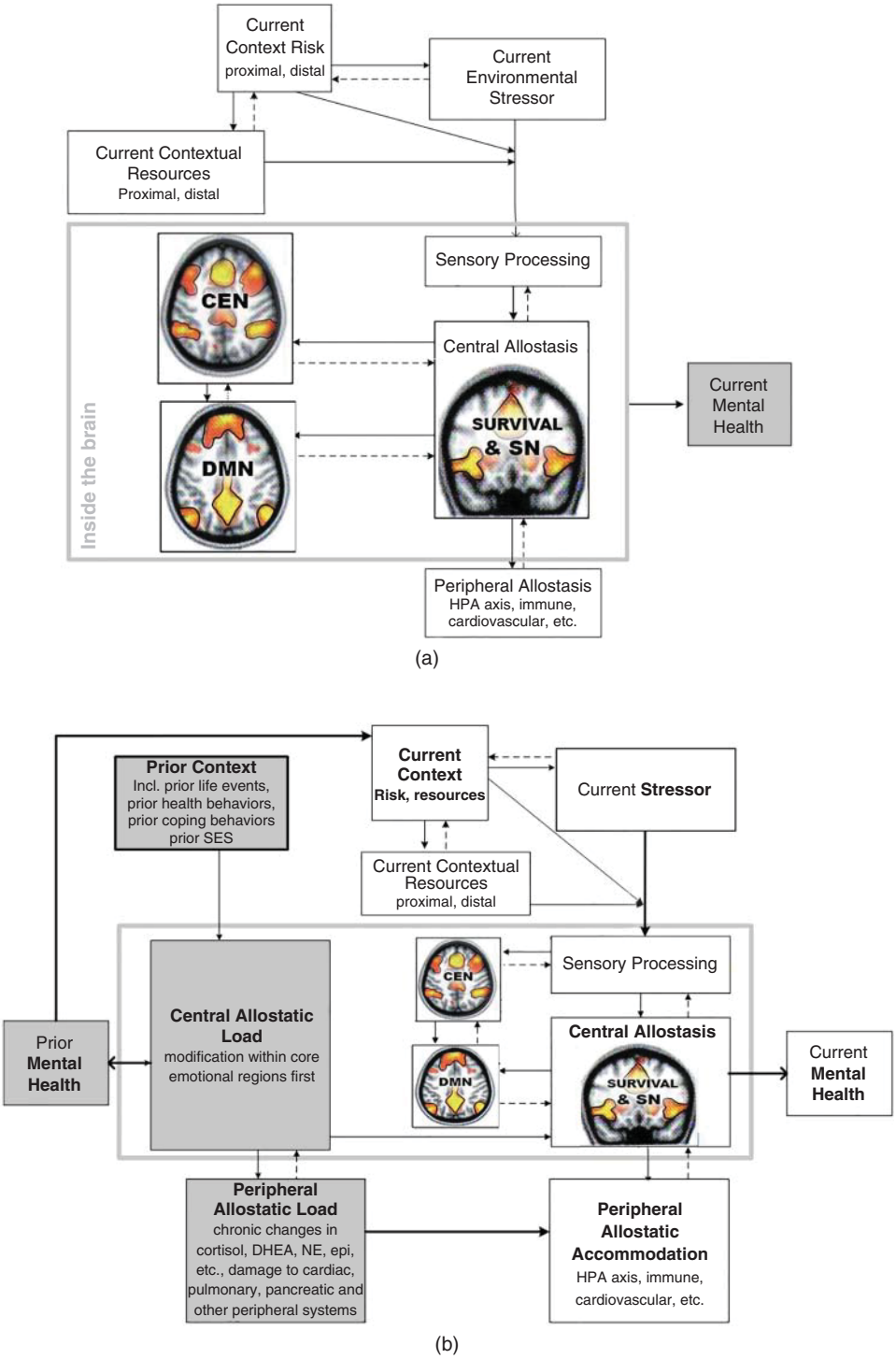


Figure 15.21 Triple network allostasis, including (a) the role of the canonical large-scale neural networks in the response to a current stressor and (b) the role of prior experience and prior allostatic load. Interaction would be expected between allostatic load and major pathways in central allostasis (not shown). DMN = default mode network; CEN = central executive network; SN = salience network; Survival = survival circuits (LeDoux, 2012). See footnote 1. *Source:* Adapted from B. L. Ganzel, P. A. Morris, & E. Wethington, Allostasis and the human brain: Integrating models of stress from the social and life sciences, *Psychological Review, 117*(1), 134, 2010; V. Menon, Large-scale brain networks and psychopathology: A unifying triple network model, *Trends in Cognitive Sciences, 15*(10), 483–506, 2011.

(Etkin, Prater, Schatzberg, Menon, & Greicius, 2009), autism (Allman, Watson, Tetreault, & Hakeem, 2005; Santos et al., 2011), and pathological pain processing (e.g., chronic migraine; Hadjikhani et al., 2013; irritable bowel syndrome; Hong et al., 2013).

Menon's (2011) proposal is based on the role of the anterior insula and the rest of the salience network in (1) detecting salient stimuli and (2) recruiting the central executive network or the default network to generate adaptive behavioral response, as discussed earlier. In his triple network model, abnormal salience detection of external stimuli or internal mental events is a core feature of psychopathology. In anxiety disorders, for example, overactive salience detection may result in misattribution of salience to relatively neutral or minor events. Atypical salience mapping could also stimulate atypical engagement of activity in the other canonical neurocognitive networks, including attention and executive control via the CEN or self-referential processing via the DMN (e.g., autobiographical memory; assignment of personal value to a stimulus). In depressed individuals, atypical salience control signals may prompt pathological rumination through hyperactivation of the default network (Berman et al., 2011; Menon, 2011; Sheline et al., 2009). In individuals with addictions, salience may be incorrectly mapped, resulting in heightened salience of drug-related cues and decreased CEN-based cognitive control of response to these cues. There is now evidence for this model of addiction through lesion studies (Naqvi & Bechara, 2009, 2010; Naqvi, Rudrauf, Damasio, & Bechara, 2007) and functional connectivity studies (Cisler et al., 2013), which have identified a crucial and unique role for the right insula in addiction.

Salience mapping may also play a key role in psychotic disorders. In schizophrenia, bilateral anterior insula volume is reduced relative to healthy controls, and these volume reductions are correlated with increasing symptoms of psychosis (Palaniyappan et al., 2011). Node-level dysfunction within the anterior insula may result in impaired connectivity within the salience network itself, and this may produce hallmark symptoms of schizophrenia. For example, disruptions in the synchrony between anterior insula and the dorsal ACC/presupplementary motor area (preSMA) could disregulate motor planning and motor execution, resulting in the psychomotor poverty or motor overflow associated with schizophrenia (Menon, 2011). Atypical activation of anterior insula is also associated with auditory verbal hallucinations, suggesting that abnormal processing of salience plays a role in these symptoms. It has been suggested that salience network dysfunction in schizophrenia underlies both the positive and negative symptoms of this disorder through disrupted recruitment of the DMN and the CEN, which together engender hallucinations and delusions and deficits in information processing (Palaniyappan et al., 2011).

In the triple network model, abnormal salience detection may have reverberating consequences not only within the salience network, but within either or both of the other canonical networks as well (Menon, 2011). Depending on diatheses and life experience, these downstream effects in other networks may be larger than the initial deficit in salience processing. Moreover, the small-world structure of each network will uniquely constrain the manifestation of these effects. In this way, the distinctive constellations of symptoms associated with particular neuropsychiatric disorders may arise out of characteristic perturbations/malfunctions within the functional architecture of the brain.

While there is some disagreement regarding whether the amygdala and ventral striatum are core elements of individual survival circuits or if they belong to the general-purpose salience network, Menon (2011) included them in the salience network (which we are calling the survival/salience network for clarity).[15] Menon contended that these nodes are particularly relevant to psychopathology. Amygdala dysfunction plays a consistent role in anxiety disorders (e.g., Etkin & Wager, 2007) and shows atypical function or structure in a number of other psychiatric disorders, while ventral striatum function is clearly aberrant in addiction and schizophrenia, among others (e.g., Barch & Dowd, 2010; R. W. Morris et al., 2011; Volkow, Wang,

[15]Recall from earlier that the amygdala and ventral striatum are key elements of two major survival circuits (LeDoux, 2012) associated with defense/avoidance and reward/approach, respectively. We also previously noted that the literature has been ambiguous about distinguishing the survival circuitry from the salience network. The distinction between these circuits depends on the type of study paradigm used. As discussed previously, activity in the salience network can be studied at rest but co-activation of survival circuitry is sporadic and highly variable. Reliable activation of any given survival circuit requires exposure to an appropriate circuit-specific trigger stimulus (e.g., Bachis et al., 2008; Ganzel et al., 2008; Kang et al., 2012; LeDoux, 2012; Phan et al., 2004; Phan et al., 2002). In experimental paradigms that do include these trigger stimuli, there will be activation of relevant survival circuitry in addition to the salience network. For clarity, then, we have elected to use the term *survival/salience network* in discussing co-activation of the salience network and one or more of the survival circuits in salience processing. Under stress, there will activation of this combined network.

Fowler, Tomasi, & Telang, 2011). As previously discussed, the amygdala and ventral striatum are highly connected with one another and with the anterior insula, with which they share many functional similarities. For example, Pessoa and Adolphs (2010) argued that the function of the amygdala in many cortical networks is primarily modulatory, in that it processes the biological value of stimuli (including ambiguity, salience, unpredictability) and serves to allocate and prioritize processing resources to generate adaptive behavior. If this sounds similar to the functions described for the anterior insula, discussed previously, it should be noted that studies of nonhuman primates indicate that the insula and amygdala are tightly linked, as well as being physiologically adjacent. The amygdala consists of multiple separate nuclei, and the insula has reciprocal connections with nearly all of them (Mufson, Mesulam, & Pandya, 1981), which helps to explain why the two structures appear functionally similar. Like the anterior insula, the amygdala is highly interconnected with much of the cortex, particularly medial and orbital PFC, but also much of the rest of the PFC. Studies from macaques indicate that amygdala inputs are able to reach approximately 90% of the PFC after a single connection (Averbeck & Seo, 2008) and that the amygdala constitutes a core brain area in terms of global brain connectivity (Modha & Singh, 2010). As previously discussed, however, the differing circumstances under which the insula, amygdala, and ventral striatum are functionally connected suggest that these three brain regions each play very different roles in the onset and maintenance of psychopathology.

As previously noted, functional connectivity between anterior insula and the rest of the salience network is observable all of the time, even at rest. On the other hand, the amygdala and ventral striatum and their respective survival circuits join robustly with the salience network only upon exposure to an appropriate circuit-specific trigger stimulus (e.g., Bachis et al., 2008; Ganzel et al., 2008; Kang et al., 2012; LeDoux, 2012; Phan et al., 2002, 2004). Menon (2011) argued for the unique integrative role of the right anterior insula in linking interoceptive/homeostatic information with the central processing of salient/survival related stimuli, including its command role in switching between the default and central executive networks. For this reason, the right anterior insula is the fulcrum, the pivot point, of the triple network model.

Triple Network Allostasis: A Novel Diathesis–Stress Model

Menon's (2011) triple network model of psychopathology provides a valuable heuristic for conceptualizing the process by which dysfunction within the large-scale neural networks of the brain predicts mental disorder. We incorporate this approach in developing an allostatic diathesis–stress model that takes the large-scale functional architecture of the brain into account. We refer to the resulting model as *triple network allostasis,* the core components of which are the canonical large-scale neural networks discussed earlier. This is an expansion of Menon's (2011) approach to include current contextual risk and resources, prior experience, life span development, peripheral stress physiology, and a dynamic diathesis into a working model that predicts mental state, psychopathology onset, and future mental health.

Triple Network Allostasis

Previously, we argued for the core affective[16] systems of the brain as the central mediator of allostasis (Ganzel & Morris, 2011; Ganzel et al., 2010). This followed from a growing body of evidence indicating that these regions are the main organizing factor in the translation of environmental stimulus into behavioral or physiological response (e.g., LeDoux, 1996; Ohman & Mineka, 2001; Rosen & Schulkin, 1998). In light of recent research on large-scale neural networks, we update this prior model by placing the survival/salience network in this key mediating role. As with Menon's (2011) triple network model, this proposal is based on the role of the survival/salience network in detecting the biological significance of external stimuli or internal events. The salience network is positioned to integrate information from the survival circuits (Cameron et al., 1993) with interoceptive information (e.g., Damasio, 2003; Rakic, 2009) to facilitate threat evaluation, selection of motor and homeostatic response, as well as response modulation (Touroutoglou et al., 2012). Moreover, the ability of the anterior insula/dorsal ACC hub to switch among canonical networks (Kempermann et al., 1998) provides flexible access to autobiographical memory, prospection, and semantic memory via the default network, and to executive control and goal-directed planning via the central executive network. Thus, the survival/salience network is the most current and precise representation of an organizing force linking salient stimuli with behavioral and physiological outcome. As such, the survival/salience network necessarily constitutes the primary regulator of allostasis, to which all other physiological and behavioral allostatic accommodation is secondary.

[16]Previously referred to as the "core emotional regions of the brain" (Ganzel & Morris, 2011; Ganzel et al., 2010).

It follows from this that the survival/salience network will be the first and primary site to show evidence of long-term wear and tear (central allostatic load) as a part of the cost of physiological accommodation to environmental demand. Accrual of allostatic load in the brain will, in turn, have consequences for peripheral physiology, psychosocial adaptation, and mental health. Identification of the specific neural circuitry that is most likely to undergo long-term change or outright damage from ongoing allostasis will allow better understanding of the physiological and behavioral consequences of environmental adversity. This will, in turn, allow more precision in intervention strategies to aid populations at risk.

The survival/salience network is a subset of synchronized nodes within the core affective systems of the brain, as those systems are currently delineated (Barrett & Satpute, 2013; Lindquist & Barrett, 2012), so that this update does not change the fundamental relationships within our prior model (Figure 15.4). In arguing that the survival/salience network is the central mediator of allostasis, we gain greater specificity in our understanding of the mechanisms of allostasis. We also acquire new and broader perspectives on the neural underpinnings of diathesis–stress processes in psychopathology. This model replaces our previous schematic of the organization of information flow and influence during moment-to-moment allostasis. Compared with the life span models discussed previously (e.g., Figure 15.19), triple network allostasis as depicted in Figure 15.21 represents a moment in the ongoing stress process—one point in time in which the salience of a current stressor is being computed, and processing resources are being mobilized in response. In a world with perfect graphic representation, progressive developmental variations of triple network allostasis would be incorporated as individual columns of a life span model like that we discussed in the previous section (e.g., Figure 15.19). With mental health as our outcome of interest, this becomes a novel articulation of the classic diathesis–stress model.

Peripheral Allostasis and Allostatic Load

In triple network allostasis, the salience network is the central mediator of allostasis, so that this neural network would be expected to accrue allostatic load at a faster pace than surrounding tissue (Ganzel et al., 2010). Said differently, the function and structure of the salience network is likely to be critically influenced by individual differences in life experience, which would, in turn, drive differences in accumulated central and peripheral allostatic load. This is an emerging area of stress research; to our knowledge, there are no studies that link prior life stress with canonical network integrity and autonomic, endocrine, or immune function in nonclinical humans (although see Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007; Ganzel, Kim, Altemus, Voss, & Temple, 2007; Gianaros, Marsland, Sheu, Erickson, & Verstynen, 2012). Yet from our allostatic model, we would predict that individual differences in central allostatic load influence almost all peripheral allostatic regulatory functions (McEwen, 2004), and we would expect this to be a key predictor of long-term health and mortality. It may also be a key predictor of emotion, feelings, and sense of self, as it has been argued that these fundamentally derive from interoceptive information conveyed up from the physiological periphery, through the spinal cord and the thalamus, to the anterior insula—which then disseminates this information to the functional networks of the brain (e.g., Damasio, 1999; Damasio & Carvalho, 2013). This is the substance of the iterative feedback loop depicted in Figure 15.21a between central and peripheral allostasis. In this perspective, the irate boss is seen with the eye, perceived in the brain, felt in the gut, and acted upon using integrated brain/body input. Under allostasis, the physiological mechanisms underlying perception and feeling in this model are subject to central and peripheral allostatic load respectively (Figure 15.21b).

Stress Vulnerability Within the Functional Architecture of the Brain

We previously reviewed evidence for selective stress-related damage or long-term change in individual nodes of the survival/salience network and the default mode network in nonclinical adults and juvenile humans and animals. In this section, we focus on the impact of stress on large-scale neural network function and structure in nonclinical adults, with some reflection on the role of development.

In the Laboratory

In the laboratory, healthy/nonclinical adults show robust reconfiguration of salience network activity during exposure to highly aversive cinematographic stimuli (Hermans et al., 2011). When viewing aversive stimuli relative to neutral ones, study subjects' functional connectivity robustly increased in anterior insula, dorsal ACC, amygdala, ventral striatum, ventromedial PFC, and other regions associated with the survival/salience network. Increased synchronized activity within this network was correlated with heightened cortisol and alpha amylase production, as well as with increases in negative affect (Hermans et al., 2011; also see van Marle, Hermans, Qin, & Fernández, 2010). Interestingly, pharmacological manipulation during

exposure to these aversive stimulus showed that these effects were mediated by stress-related production of norepinephrine, but not cortisol. Norepinephrine (NE) neurons project from the locus coeruleus to salience-related brain regions, and firing in these projections varies to support focal attention during mild arousal, and hypervigilance and distraction during extreme arousal (Arnsten, 2009; Corbetta, Patel, & Shulman, 2008; Valentino & Van Bockstaele, 2008). This is consistent with a model of norepinephrine function as the means through which neural network activity—particularly salience network activity—is quickly co-opted in response to a stimulus and then reorganized to support adaptive response (Bouret & Sara, 2005; also see Olson et al., 2011). Also in the laboratory, a similar network reconfiguration favoring salience processing has been observed in response to sustained deep-tissue pain in humans (J. Kim et al., 2013). Moreover, there is evidence in animal models that exposure to uncontrollable stressors can produce generalized sensitization of NE-producing neurons, so that future stressors of different types will drive exaggerated production of NE and behavioral disturbance (for the potential roles of serotonin and BDNF, see Anisman, Merali, & Hayley, 2008; Olson et al., 2011). This suggests one mechanism through which stressor exposure may generate allostatic load (sensitization of NE-producing neurons) that in turn influences future stress reactivity.

Laboratory stressors also impact resting state functional connectivity within the default mode network (e.g., Vaisvaser et al., 2013; Veer et al., 2011). In one study, nonclinical adults exposed to a social stress test showed immediate, but transient, increases in resting state functional connectivity between the posterior cingulate cortex (PCC) and medial PFC, inferior parietal lobule, caudate, and thalamus, along with decreased connectivity between the PCC and bilateral posterior insula and lingual gyrus (Vaisvaser et al., 2013). Immediate post-test increases in amygdala-hippocampus functional connectivity were also observed. Among the regions of interest selected for this study, only the stress-related alterations in amygdala-hippocampal connectivity persisted for more than 90 minutes after the stress test. Self-reports of increased subjective stress during testing were related only to increases in amygdala-hippocampal connectivity, and not to alterations within the default network (Vaisvaser et al., 2013). In a RSFC study employing a similar social stress test but different regions of interest, persistent (>90 minutes) increases in functional connectivity were observed between amygdala and medial PFC, and between amygdala and PCC/retrosplenial cortex/precuneus (Veer et al., 2011). This latter finding is consistent with research identifying a direct ascending anatomical projection between the basal nucleus of the amygdala and the retrosplenial cortex in the macaque brain (Buckwalter, Schumann, & Van Hoesen, 2008). Direct reciprocal anatomical connections between amygdala and medial PFC have been previously established (e.g., Ghashghaei, Hilgetag, & Barbas, 2007).

Brain development will also play a key role in the interplay between the survival/salience network and the default network during stress. This, in turn, has implications for the accrual of allostatic load and the developmental timing of the emergence of psychopathology. For example, there is a full developmental reversal in functional connectivity between the amygdala (of the survival/salience network) and the medial PFC (of the default network) (Gee et al., 2013). Children younger than ten years of age demonstrate positive connectivity between amygdala and medial PFC during a laboratory stressor, such as viewing fearful faces; However, there is a linear decrease in the valence of this connectivity between the ages of 10 and 22, and amygdala-medial PFC connectivity in nonclinical young adults is robustly negative (Gee et al., 2013). Change in the valence of this association has been shown to mediate the decreases in separation anxiety that normally occur with increasing age, and this is argued to follow from increasing top-down control of amygdala reactivity by the maturing medial PFC (Gee et al., 2013). We note that this is yet another profound alteration in brain function that occurs between 10 and 20 years of age, along with the reversal of the global excitatory/inhibitory (E/I) balance of the brain, the winnowing of synapse density during the massive second wave of pruning, and the abrupt downward shift in brain energy metabolism and amplitude of slow wave EEG activity during NREM sleep that accompanies the migration of the peak amplitude from the back to the front of the brain (and which may underlie the optimization of learning and memory). While these considerable changes are all complex outcomes of brain maturation, their interrelationship is only loosely understood and their impact on the diathesis–stress process is, as yet, unclear.

In the Wild

There are very few ecologically valid studies of the impact of stress/trauma on functional neural connectivity in nonclinical human adults. Of the studies that do exist, most highlight aberrant connectivity within regions of interest in the default network. Exceptions do exist, though. One such study examined resting state functional connectivity in nonclinical adults with recent exposure to the great Sichuan earthquake of 2008 (Lui et al., 2009). Relative to a

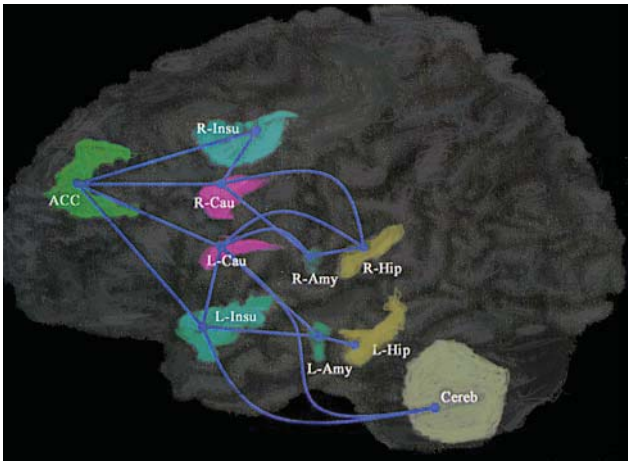


Figure 15.22 Survival/salience network disruption after the great Sichuan earthquake of 2008. In earthquake survivors, decreased functional connectivity was observed in salience-related circuitry (light-colored lines). Increased regional activity at the nodes of the salience circuit was correlated with increased distress (more symptoms of anxiety and depression). See footnote 1. *Source:* From S. Lui, X. Huang, L. Chen, H. Tang, T. Zhang, X. Li, . . . A. Mechelli, High-field MRI reveals an acute impact on brain function in survivors of the magnitude 8.0 earthquake in China. *Proceedings of the National Academy of Sciences of the United States of America, 106*(36), 15412–15417, 2009.

control group scanned prior to the earthquake, nonclinical adult earthquake survivors showed strong evidence of disrupted survival/salience network activity. Specifically, survivors showed decreased global resting state functional connectivity across bilateral insula, ACC, amygdala, hippocampus, striatum, and cerebellum (see Figure 15.22). Global decreases in functional connectivity across the salience network were accompanied by local increases in the amplitude of low frequency [synchronized] activity at nodes of the salience network, including insula, amygdala, hippocampus, and striatum. In the survivor group, this increased regional activity correlated with increased distress (more symptoms of anxiety and depression; Lui et al., 2009). This research provides convergent behavioral and neuroimaging evidence for stress-related change in the salience network in nonclinical adults. (We note that this convergence of findings helps to support the study's conclusions in the face of recent statistical concerns about group comparisons in resting state studies; e.g., Tononi & Cirelli, 2003.)

Functional connectivity studies of nonclinical adults who have experienced early life stress/trauma are also rare. One recent effort, however, used a graph analysis approach to examine the impact of early life stress on an emotion processing/emotion regulation network, which included bilateral insula, amygdala, hippocampus, and striatum, and PFC (Cisler et al., 2012). This was a rare three-group study that included women with a history of early life stress *and* a history of psychopathology (depression-susceptible individuals), women with early life stress *and no* psychopathology (resilient individuals), and a control group without histories of early life stress or psychopathology. Overall, this study found that more severe early life stress was associated with fewer connections between nodes, and fewer hubs. Interestingly, one of the network traits that best differentiated the three groups was the hub-like nature (the *betweenness centrality*) of left amygdala connectivity. Women in the nonclinical/resilient group had amygdalae that were less hub-like than controls, whereas women in the susceptible group had amygdalae that were more hub-like than controls. Increased centrality of the amygdala in information processing may lead to more affectively biased processing in susceptible women with early life stress (Cisler et al., 2013) and a greater vulnerability to affective disorders over time. If so, then a question for future research concerns the social, contextual, or biological factors that may moderate the hub-like qualities of the amygdala in children and adults who have experienced early life stress. This, in turn, may pave the way for more effective interventions.

Reverberating Effects

The survival/salience network is the neural front-line responder in initiating and supporting adaptive behavioral response to environmental challenge and (as argued here) the central mediator of allostasis (Ganzel et al., 2010). Earlier, we reviewed some of the early evidence that suggests this network is selectively vulnerable to stress, and that this influences its ability to respond to future stressors (allostatic load). We hypothesize that this stress-related damage or plasticity in the survival/salience network will drive disruptions in the other two canonical networks over time. For example, we have noted that the amygdala is extensively connected with other brain regions, serving as a connector hub that links other hubs (Pessoa, 2008). This provides ample means for the salience network, via the amygdala, to influence nodes in other networks. For example, the amygdala has direct ascending connections to the PCC and the mPFC, as previously discussed. These are the primary nodes of the default network, so that stress-related amygdala hyperactivity has a direct means of influencing default network function. Default activity is anticorrelated with activity in the dorsal attention network (which makes up half of the CEN), suggesting that stress-related disruption in one may well propagate to the

other via the amygdala. Most tellingly, the anterior insula and the dACC are included in the frontoparietal control network (which makes up the other half of the CEN), so that stress-related change in the salience network *equals* stress-related change in these key nodes of the CEN. Thus, we argue that stressor exposure can impact neural network function on a global scale, in a manner that (following our models) can be expected to be deeply influenced by individual diathesis.

Central allostasis drives peripheral allostasis (Ganzel et al., 2010). Stress-related disruptions in central allostasis can therefore be expected to drive disruptions in the stress response in physiological systems peripheral to the CNS. It is difficult to overstate the scope of these responses. Stress-related activation of both the HPA axis and the sympathetic nervous system produces glucocorticoids (cortisol, in humans) and catecholamines (e.g., epinepherine and norepinepherine; e.g., Feldman, Conforti, Itzik, & Weidenfeld, 1995; Pacák & Palkovits, 2001; Schulkin, 2003). These have profound preparative and modulating effects throughout the body, creating extensive short- and long-term stress-related alterations in peripheral physiology (e.g., McEwen, 2004, 2007; Sapolsky et al., 2000). These, in turn, feed back on brain function and structure via multiple pathways, including interoceptive input to the salience network (e.g., Critchley et al., 2004; Farb, Segal, & Anderson, 2013) and the effects of cortisol on hippocampal function and structure (McEwen, 2004, 2007; Pruessner et al., 2008). Individual differences will modulate this feedback, providing yet another avenue through which diathesis may influence the long-term impact of stress on brain and behavior.

Triple Network Allostasis in Context

The individual is embedded in a multilevel dynamical system that includes a current context, which influences the relationship between the current stressor and sensory processing, allostasis, and, ultimately, mental health (Figure 15.21). Consistent with our interest in specifying the multiple ecological levels of influence on mental health outcomes, we draw from psychosocial stress research to conceptualize the special conditions of contextual risk in this model. We also draw from dynamic systems theories in modeling the context of stress as an important source of input into physiological allostasis. Dynamic systems theory helps us understand the structure of context, how context interacts with other ecological and individual levels, and how contextual effects may play out across time. First, as shown in Figure 15.21, we conceptualize contextual risk as including both proximal and distal risk factors. While not shown on the figure for the purpose of efficiency, we do consider them as nested and interacting influences on the stress process. The direct arrow from current context to environmental stressor reflects the recognition that low-resourced environments are likely to result in higher levels of stressor exposure (Brooks-Gunn, Duncan, & Aber, 1997; Earls & Buka, 2000; Shonkoff & Phillips, 2000). In some cases, there is feedback (as indicated by the reverse arrow) from stressor to the current social or physical context. This accounts for the selection of individuals into environments, as well as the constraint on opportunities that stressors create in the choice of such contexts. Given the interactive nature of this system, we posit that prior and current risk will moderate, or shape, the effects of environmental stressors on sensory processing, as well as on the canonical large-scale neural networks and downstream peripheral physiology. In other words, the meaning of the stressor to the individual interacts with information about the physical and social context in which the individual is embedded (e.g., Hobfoll, 2001) to drive perception of the emotional intensity of the stressor and the resulting behavioral response. In short, the individual (mind, brain, peripheral physiology, and behavior) is highly influenced by extraindividual context.

Moderators of Triple Network Allostasis

Triple network allostasis also suggests approaches for predicting important moderators of the stress process. If the brain is the central mediator of allostasis, the biological capacities and organization of the brain can help to determine the properties of a stressor that are likely to influence mental and physical health outcomes in the allostatic model. For example, a stressor must have sufficient *magnitude* to activate the emotional circuitry of the brain or the stress response will not be invoked by the organism; conversely, stressors that are of a magnitude sufficient to overwhelm the mechanisms of allostatic accommodation will produce greater allostatic load. A stressor's *duration* or *chronicity* is also likely to modify the allostatic response; a stressor of sufficient persistence to exhaust (or render toxic) the biological processes of accommodation can produce profound effects on allostatic load, as previously discussed. We have also noted the expanding evidence that stressors of different *types* may be processed differently within the emotional circuitry of the brain, as, for example, with the neural processing of social pain versus physical threat (for reviews, see Alleva & Santucci, 2001; Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009; Depue

& Morrone-Strupinsky, 2005; Eisenberger & Lieberman, 2004; Lieberman, 2007). Likewise, there is evidence that the *developmental timing* of stressor exposure can moderate central allostasis (e.g., Liu et al., 1997; Susser & Stein, 1994). We have reviewed evidence here that significant amounts of central and peripheral allostatic load may be acquired in adulthood; thus, when long-term biological effects of stressor exposure are observed in children, it remains to be determined what is different about the mechanisms of allostasis and allostatic load in early human development and how the long-term health consequences of allostatic load acquired in childhood may be distinct from the consequences of load acquired in adulthood. This special role of developmental timing in allostasis may derive from the development of knowledge of emotion (Tottenham, Leon, & Casey, 2006), from differences in maturation time across the emotional circuitry of the brain (Casey, Getz, & Galvan, 2008), from a biological stress-sensitive period (analogous to the well-established stress sensitivity in the first ten days of a rat pup's life; e.g., Levine, 2001; Liu et al., 1997), or a combination of these. It remains for future research to distinguish the impact of all of these potential moderators of triple network allostasis.

Distinction between the differing impact of developmental timing and stressor type is of particular importance for studies of the consequences of early stressor exposure. The most frequently studied stressors of childhood involve separation from (or conflict with) the primary attachment figure (e.g., parental loss, neglect, rejection, or conflict). These are stressors that fit the description of social pain. As previously discussed, there is evidence for qualitative physiological differences in the neural processing of physical threat relative to that of social pain, regardless of age at time of stressor exposure (e.g., Dedovic et al., 2009; Eisenberger & Lieberman, 2004). If the processing of social pain and physical threat are biologically distinguishable within the core emotional systems of the brain, then the allostatic model would predict that central and peripheral allostatic load accrues in distinguishable physiological systems for each type of stressor. This, in turn, should lead to different long-term health outcomes for each type of stressor (there is preliminary evidence for this, e.g., Post, Leverich, Xing, & Weiss, 2001). If stressor type indeed moderates the stress process in a way that is independent of developmental timing, it will be important to include stressor type as a separate variable in models of early stress. Furthermore, the effects of stressors of different types may change across the course of development, so that developmental timing and stressor type interact with one another (a three-way interaction).

Together, these considerations point to the need for attention to likely moderators of triple network allostasis in studies of stress, as well as highlighting opportunities for new research. These may include, for example, further research into differences over time in the physiological processes underlying central and peripheral allostasis and allostatic load in response to stressors of different intensity, chronicity, type, and developmental timing, which in turn would be expected to drive multifinality in outcomes associated with long-term health and behavior. Longitudinal studies of amygdala responsiveness over time in samples of different ages and with different types and levels of stressor exposure would shed light on these points. Such work would also clarify the time frames for the development of stress-related alteration in brain structure and function, and their possible reversal. This is precisely the kind of work that can be built from the model we present.

FUTURE DIRECTIONS

Triple Network Allostasis as a Dynamic System

When we undertook this theoretical work (Ganzel et al., 2010), we aimed to model a dynamic bioecological system that fully penetrates physiology (gets under the skin). In doing so, we followed Bronfenbrenner and Morris (1998) in requiring this model to include "the joint, interactive, mutually reinforcing effects" of person, proximal process, context, and time (Bronfenbrenner & Morris, 1998, p. 996).

We also incorporated many of the principles of dynamic systems theories (Bronfenbrenner & Morris, 1998, 2006; Ford & Lerner, 1992; Sameroff & Chandler, 1975; Thelen & Smith, 1998; Waddington, 1957) that are integral to a multilevel approach to understanding behavior and development (Cacioppo & Berntson, 1992). For example, two principles of dynamic systems theories helped us to consider the relations between the levels of a multilevel system. The first is the principle of multiple nested and interacting levels, which states that the person is embedded in an ecological system that represents the influences of more distal systems through the most proximal system (e.g., a current stressor, as modified by contextual resources and risks). Individual behavior is moderated, or shaped, by the context in which that individual is embedded (interaction across systems). The second of these principles is the transactional relationships between levels of the system, which states that the relations between individuals and their environment, or between proximal and distal contexts, are transactional instead of unidirectional. That is, causality

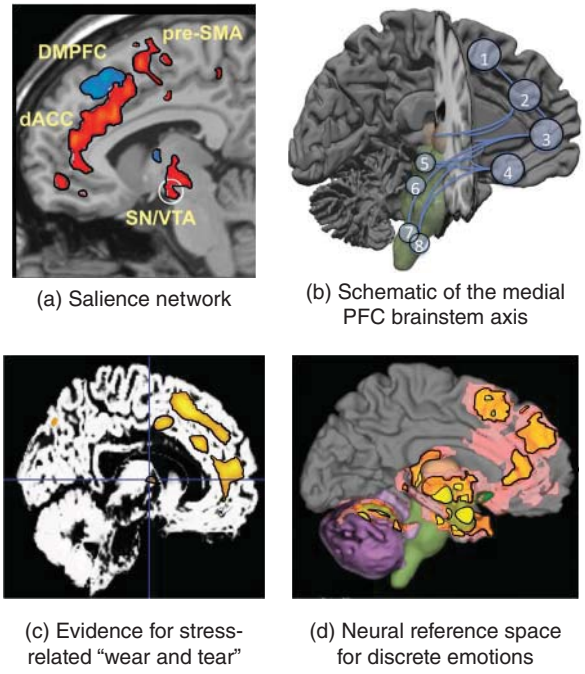


Figure 15.23 Triple network allostasis as an organizing concept. (a) Salience network. (b) Schematic illustration of the brain–body axis that runs along the medial PFC and into the brainstem. (c) Regional gray matter decreases in nonclinical adults exposed to the World Trade Center disaster, 3 years after September 11, 2001. (d) The core affective systems of the brain. See footnote 1. *Source:* Adapted from W. W. Seeley, V. Menon, A. F. Schatzberg, J. Keller, G. Glover, H. Kenna, . . . M. D. Greicius, Dissociable intrinsic connectivity networks for salience processing and executive control, *Journal of Neuroscience, 27*, 2349–2356, 2007; (b) R. D. Lane & T. D. Wager, The new field of brain–body medicine: What have we learned and where are we headed? *NeuroImage, 47*(3), 1135–1140, 2009; (c) B. L. Ganzel, P. Kim, G. Glover, & E. Temple, Resilience after 9/11: Multimodal neuroimaging evidence for stress-related change in the healthy adult brain, *NeuroImage, 40*(2), 788–795, 2008; (d) K. A. Lindquist, T. D. Wager, H. Kober, E. Bliss-Moreau, & L. Barrett, The brain basis of emotion: A meta-analytic review, *Behavioral and Brain Sciences, 35*(3), 121–143, 2012.

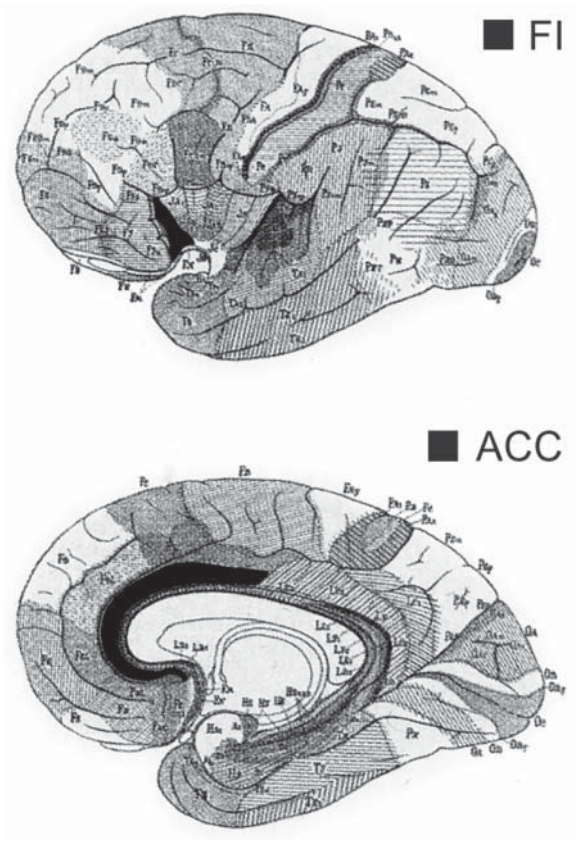


Figure 15.24 Primary location of von Economo neurons in the human brain. See footnote 1. *Source:* Adapted from P. C. Williamson & J. M. Allman, *The human illnesses: Neuropsychiatric disorders and the nature of the human brain*. New York, NY: Oxford University Press, 2011. Color plate 3.1 (page 116)]

works in both directions (e.g., as in modulated allostasis; Figures 15.23 and 15.24).

Three more principles of dynamic systems helped us to consider how life span development plays out across time. The first, multifinality and equifinality, indicates that there are many paths to a single outcome and a single pathway can lead to a diverse set of outcomes. The second, attractor states constrain possible pathways, suggests that development proceeds on a small number of trajectories and is subject to a small number of possible influences, with biological and ecological constraints that limit possible outcomes. The third, continuous and discontinuous change, posits that change can occur through continuous developmental processes as well as through large changes (e.g., threshold effects).

These concepts have provided structure for our application of life span developmental neuroscience to the allostatic models we have presented here. These concepts may also be used in future research to aid in hypothesis generation about the form and nature of model outcomes. Integration of life span development and triple network allostasis into a diathesis–stress model suggests several avenues for future research, along with a number of predictions.

Is Triple Network Allostasis Universal?

Within a developmental psychopathology perspective, the study of normality and pathology are understood to be mutually informative. Nonetheless, study of the long-term effects of environmental and social stressors on the nonclinical human brain is still a newly emerging

topic of investigation in human neuroscience. The nonclinical human brain is of critical interest to these questions because this is where the basic mechanisms of allostasis will be the least confounded with disease processes. If allostatic load is to be a general mechanism underlying the "long-term carry forward of stress and adversity" (Rutter, 1996, p. 37), it must also have significant consequences for nonclinical adults and children, i.e., if allostasis is to be a useful replacement of classical homeostasis, it must apply to everyone (Ganzel & Morris, 2011; Ganzel et al., 2010). In preceding sections, we have reviewed evidence for the accrual of central allostatic load from stressors that occur in nonclinical humans both earlier and later in development. This is a pivotal concept in defining our model of the stress process because it suggests that allostasis and costs of allostatic load are not confined to a special clinical population or a particular developmental sensitive period.

Nevertheless, studies linking neural networks and long-term effects of prior stress have typically focused on clinical populations or early childhood. In addition, few studies link life stress and large-scale neural network integrity/function with measures of socioemotional adaptation/mental health in nonclinical humans. Still fewer studies blend these factors with a developmental component (although see Thomason et al., 2013; Thomason et al., 2011) and none, to our knowledge, include a broader life span perspective. However, our life span model of modulated allostasis (Figure 15.19) combined with the novel triple network approach to allostasis presented here (Figure 15.21), leads us to predict that the salience/survival network will be the first brain areas to show evidence of long-term plasticity or wear and tear as a consequence of accumulating stressor exposure, and that this will be the case for all populations. Via the salience network, individual differences in central allostatic load can be expected to robustly influence the other canonical neural networks in an age-dependent manner across the life span and in all populations, regardless of clinical status. Happily, these predictions are testable and results will lead to important refinements of the model.

We also argued here for inclusion of central and peripheral allostatic load in an individual's diathesis, thus rendering diathesis to be a dynamic force arising out of the confluence of an individual's initial genetic loading and their ongoing life experience. This allowed us to propose an allostatic diathesis–stress model that has triple network allostasis at its core. In this model, past and current stressor exposure interacts with a constantly changing diathesis to predict psychopathology onset, with robust implications for future mental health. As previously, we predict that this model is applicable regardless of an individual's age or current clinical status, and earnestly hope that this work prompts expansion of the research on stress, neural networks, and mental health beyond the circumscribed study of clinical populations or childhood stressors.

Can Triple Network Allostasis Serve as an Organizing Concept?

Next, we call attention to the considerable overlap between the salience network (Figure 15.22a; Seeley et al., 2007) and the brain areas that have key brain-body regulatory functions (Figure 15.22b; Lane & Wager, 2009). Identification of remarkable commonalities in the brain mechanisms that regulate the human autonomic, endocrine, and immune systems has been an exciting step forward in brain–body medicine (e.g., Gianaros & Sheu, 2009; Ohira et al., 2010; Urry, van Reekum, Johnstone, & Davidson, 2009; Wager et al., 2009). The neural loci of these brain–body interfaces fall along an axis that starts at the superior medial PFC and descends along the midline of the PFC and down into the brainstem. Thus, these neural brain–body regulatory mechanisms share significant common ground with the survival/salience network. Moreover, both the salience network and the brain–body "medial PFC-brainstem axis" (Lane & Wager, 2009, p. 1136) overlap with brain areas showing evidence of long- and short-term stress-related change in humans (Figure 22c; e.g., Ganzel et al., 2008; Gianaros, Horenstein, et al., 2007; Gianaros, Jennings, et al., 2007; Liston et al., 2009) and animals (Cerqueira et al., 2005; Vyas et al., 2002). While this three-way overlap is highly consistent with our theoretical models, there is relatively little research that examines the linkage between central and peripheral allostasis in the context of large-scale neural networks. We commend this topic to future research.

In the context of a constantly changing brain and our life span model of modulated allostasis (Figure 15.19), we argue that *all* allostatic functions will be influenced by life span development, i.e., they would be expected to vary with age. In triple network allostasis, central allostasis (as initiated and directed by the survival/salience network) is hypothesized to drive short-term stress-related alterations in autonomic, endocrine, and immune function, and peripheral/visceral physiology (peripheral allostasis), which are modified by prior accumulations of peripheral allostatic load (Ganzel et al., 2010). This somatic/visceral response feeds back via the insula to influence salience network function and the experience of emotion (Damasio & Carvalho, 2013) or affect (Figure 15.23d; Lindquist,

Wager, Kober, Bliss-Moreau, & Barrett, 2012). In the context of a constantly and systematically changing brain, age- and stress-related change in central allostasis can be expected to reverberate through this feedback loop to generate age- and stress-related change in the peripheral stress response (and in the quality and quantity of peripheral allostatic load), with subsequent feedback effects on the salience/survival network itself. Thus, this model predicts that there will be age-related change in the experience of salience, and indeed of affect. As a corollary to this, we would predict that life stress interacts with age to impact the experiences of salience and affect, and the activities of emotional cognition (e.g., emotion regulation, emotional decision making; Burri et al., 2013; Marsh, Nagengast, & Morin, 2012; Tsolaki et al., 2010).

Ongoing work in psychology, psychiatry, and human neuroscience tie together many of these themes in pairs (stress and emotional cognition; stress and development; development and functional neural networks; neural networks and psychopathology, neural networks and affect). The models presented here suggest novel combinations of these factors for future investigation, as well as the additional need for deployment of these factors as statistical controls.

Is Triple Network Allostasis Only Human?

We have argued that the triple network model of allostasis is common to all humans, regardless of age or clinical status. We have also suggested ways in which this model may serve as an organizing concept to unite theories of stress and diathesis–stress with brain–body medicine and research on emotion. In this section, we present the suggestion that this organizing concept may apply uniquely to humans and perhaps some of the higher primates and other big-brained species. This is not for grandiosity, but rather to outline possibilities—including possible limitations—for future research. The pivotal role of the salience network in our allostatic triple network model raises some broad questions about the nature and origins of psychopathology. We note that this point has implications for how appropriate traditional animal models are for studying some major mental disorders.

Von Economo Neurons

As discussed previously, the right anterior insula/dorsal ACC subnetwork is a hub of information traffic within the salience network and it is argued to play a unique and pivotal role in switching between all three canonical neural networks (Kempermann et al., 1998). It is therefore notable that the right anterior insula and ACC are the two primary locations of a unique type of neuron—the *von Economo neuron* or *spindle* neuron (Maroun & Richter-Levin, 2003; Vyas et al., 2004; Williamson & Allman, 2011). These large projection neurons have one apical axon and one primary dendrite, giving them a spindle shape (Olson et al., 2011). The von Economo neurons appear to be exclusive to the brains of humans, other great apes, elephants, and cetaceans, leading to the hypothesis that they are an adaptation necessary for the rapid flow of communication within large brains (e.g., Cui et al., 2008; Evrard, Forro, & Logothetis, 2012; Stimpson et al., 2011).

Concentrations of von Economo neurons are lateralized in the human brain, with populations being denser on the right side of the brain than the left. These neurons are also highly localized, occurring almost exclusively in layer five of anterior insula and anterior cingulate, with much smaller concentrations recently observed in human dorsolateral PFC (Hill et al., 2012; Vyas et al., 2006; see Figure 15.24). In keeping with their large and streamlined structure, von Economo neurons provide rapid relay of simple signals from anterior insula and dACC to target regions that, in animal models, include PFC, orbitofrontal cortex, temporal cortex, and subcortical survival systems (Hill et al., 2012). A recent resting state functional connectivity study has observed that von Economo-containing regions in the human brain activate in synchrony with individual nodes in the salience network, the dorsal attention network, the sensorimotor network, and portions of the default mode network (Hill, McLaughlin, et al., 2010) suggesting that von Economo neurons may project to nodes in each of these networks (also see Fischer et al., 2005). Thus, the network switching capabilities of the right anterior insula/dorsal ACC subnetwork may be, at least in part, due to the unique properties of von Economo neurons (Sridharan et al., 2008).

Von Economo Neurons Across the Life Span

In humans, von Economo neurons begin to appear by the thirty-fifth week of gestation; at birth, the density of these neurons is approximately 15% of the eventual total (Hill et al., 2012). The full complement and typical rightward anatomical distribution of this neuronal population is reached by the age of four years (Cui et al., 2008; Tsolaki et al., 2010). It is argued that this developmental timing renders von Economo neurons vulnerable to disruption during the third trimester of pregnancy, and in the perinatal and early postnatal period (Hill et al., 2012). Moreover, the immunocytochemistry of these neurons suggests that they play a role in social bonding (expression

of the vasopressin 1a receptor), reward under uncertainty (dopamine D3 receptor expression), monitoring of visceral response and possible amplification of threat-related signals (unique serotonin 2b receptor expression within the human CNS), and cognition (robust expression of DISC1, the primary product of the disrupted in schizophrenia [DISC] gene; Allman et al., 2011; Allman et al., 2005). Due to their unique cytochemistry and distinctive phylogeny, von Economo neurons have been proposed to play a role in human capabilities, such as rapid intuitive decision making in complex sociocultural contexts (Chick & Reyna, 2012; Cui et al., 2008; Williamson & Allman, 2011). Abnormal development of von Economo neurons is therefore hypothesized to underlie multiple neurodevelopmental disorders in which aberrant social conduct or emotion regulation are diagnostic features, including autism (e.g., Campolongo et al., 2009; Freund et al., 2003), and schizophrenia (e.g., Cui et al., 2008; Tsolaki et al., 2010).

Less is known about age-related change past midlife in von Economo neurons, except in the context of Alzheimer's disease and behavioral variant frontotemporal dementia (bvFTD; Tsolaki et al., 2010). In Alzheimer's disease, there appears to be a relative sparing of von Economo neurons, whereas bvFTD is characterized by a profound and specific early loss of these neurons (66 to 75% of the expected total; Cui et al., 2008; Fischer et al., 2005; Gross et al., 1997; Tessitore et al., 2005). The degree of selective degeneration of von Economo neurons in bvFTD is correlated with decreases in behavioral and functional indicators of empathy, self-control, and social awareness (e.g., Gross et al., 1997). This, in turn, is hypothesized to result from a catastrophic failure to integrate visceral-autonomic, social-affective, and cognitive cues as the anterior insula/dorsal ACC network hub degenerates (Gross et al., 1997; Tsolaki et al., 2010).

Allostatic Load and von Economo Neurons

This suggests questions for future research. As we reviewed previously, recent trauma exposure appears to selectively reduce gray matter volume in the anterior insula and ACC (Blair et al., 2013; Ganzel et al., 2008; Monohan et al., in preparation) suggesting that von Economo neurons may be uniquely vulnerable to life stress.[17] However, when traumas are farther in the past, the neural functional and structural correlates of trauma exposure vary more widely (Andersen et al., 2008; Blair et al., 2013; Monohan et al., in preparation). These data are consistent with the hypothesis that von Economo neurons are at or near the initial locus of impact of stress and trauma in the human brain, and that stress-related disruption subsequently propagates through the salience network, the default and central executive network, and the systems of peripheral allostasis. Developmental stage and individual differences in diathetic vulnerability would determine the direction and extent of the propagation of stress-related change in neural networks or nodes over time. Under this hypothesis, von Economo neurons would play a pivotal role in triple network allostasis and the onset of psychopathology. If so, further research into the stress-vulnerability of von Economo neurons may shed new light on the mechanisms of allostasis and allostatic load, and the origins of psychopathology. Investigation of possible age- and sex-specific effects in stress vulnerability of these neurons would then also be fruitful in this regard.

[17]This does not necessarily mean that they are a target of glucocorticoids, although they may be.

CONCLUSION

Diathesis–stress models of the origins of psychopathology have been a major organizing framework in mental health research and practice for the past half-century (e.g., Meehl, 1962). At their inception, these models were open to criticism on the grounds that they lacked specificity (McLaren, 1998) and considered stress and diathesis as a distinct (even if interacting) processes. However, such models have benefitted greatly from the development of new scientific tools that allow specification and measurement of processes that span levels of analysis from genes and brains, to cognition and behavior, and to broader contextual influences. Simultaneously, this work has benefited from disparate lines of inquiry into the origins of psychopathology and the sequelae of stressful experiences that spans the fields of biology, medicine, social neuroscience, and psychology. Together, these allow us to build a developmentally informed diathesis–stress model of psychopathology onset that reflects the individual's past history of adversity and that strongly draws on the core tenets of a developmental psychopathology perspective (e.g., Cicchetti & Toth, 2009).

We stand on the shoulders of three major contributions to the study of stress and psychopathology in the development of our new model.

First, the last two decades has seen a paradigm shift in thinking about how humans respond physiologically to stress. As a major revision of the classical theory of homeostasis, allostasis identifies the brain as the executor and central mediator of ongoing system-wide adjustment to meet environmental challenge (Sterling & Eyer, 1988).

Two points are critical from this work: (1) the brain's survival/salience network becomes the primary, physiological targets of stress, bringing stress well into the brain (and not merely as an external force influencing cognition or behavior); and (2) stress has long-term physiological costs in the form of allostatic load that affect later responses to stress, allowing stress to become a diathesis of sorts for the next stressful experience.

Second, we build on new research on the constantly changing brain, citing evidence for brain development and senescence across the life span. The central premise of our thesis is as follows: if the brain is the central mediator of a stress/diathesis-psychopathology relationship, and the brain is not static but represents a constantly changing neural landscape across the life span, then the stress/diathesis-psychopathology process itself must vary across development as well. That is, variations in stressor timing across the life span must have very different implications for brain processes if the neural circuitry of the salience network that is serving as the front lines of stress is changing as well (said another way, stressors at different ages may have different neural sequelae). And if the central mediators of allostasis are changing, then the accretion of allostatic load must be changing as well (i.e., stressors at different ages would have different effects on the development of this form of diathesis). With differential physiological consequences both for the sequelae of stress and the development of diathesis to future stress, it is not hard to see why psychopathological outcomes may also differ across the life course. This thinking has implications for a number of findings, including why the effects of stress and trauma might vary for children and adults; why a critical period approach to stress during early life might be insufficient; and why there are effects of trauma exposure in adulthood even in nonclinical/low risk individuals, to name a few. Making this argument allows us to build a theory of modulated allostasis, in which both the stress process and the diathesis (in part due to load from prior periods) contribute to different psychopathological outcomes, across developmental time from the prenatal period to older adulthood. In this way, diathesis–stress becomes a *developmental* model.

Third, Menon's (2011) triple network model of psychopathology is enormously useful addition to our diathesis–stress model. With this addition, deficits in the functional *connectivity* of neural networks (rather than specific brain regions alone) are key predictors of psychopathology. For example, while the right anterior insula in the salience network is key in the emergence of psychopathology, Menon adds the reasons why—for example, that the insula is critical in the recruitment of the executive network and the default network in generating adaptive behavioral responses. As a result, downstream effects on other networks may be even larger than those in the initial deficits in the salience network. In prior work, we argued that the core affective systems of the brain were central to the translation of stress into physiological and then behavioral response. Menon allows us to improve the neural specificity of this model—that it is synchronized *nodes* in the affective core system (i.e., the survival/salience network)—that produces allostatic responses in the context of stress, and results in the deficits in processing of information that results in deficits in mental health. The resulting model is termed triple network allostasis and represents our new proposed diathesis–stress model of psychopathology.

Having built a new diathesis–stress model of psychopathology onset, the question now arises: can it be used to better design intervention approaches aimed at reducing psychopathology? Indeed, a key principle of a developmental psychopathology perspective is its commitment to translation (Cichetti & Toth, 2009), and a central benefit of identifying the neural underpinnings of the stress–psychopathology relation is to support the development of more effective interventions for individuals at risk (Ganzel & Morris, 2011). However, research in this area is only in its infancy. The question is whether population-scalable, cost-effective, social and behavioral interventions can be developed that target the large-scale neural networks as key mediators of the diathesis/stress-psychopathology relationship. While research on brain architecture has strongly informed pharmacological treatment strategies, it has less often been utilized to inform social and behavioral interventions.

The hope here is that if we were to design and effectively implement promising social and behavioral interventions targeted at relevant brain processes, they would drive longer lasting changes in psychopathological outcomes. But the challenge is that we do not yet have a body of research to draw on about the physiological effects of community-based interventions. A number of research teams are forerunners in this research in their inclusion of physiological assessments in intervention efforts (e.g., Cicchetti, Rogosch, Toth, & Sturge-Apple, 2011; Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008; Fisher, Stoolmiller, Gunnar, & Burraston, 2007). However, we are a far cry from being certain about which interventions are most likely to mitigate the risks of psychopathology because of their effects on neural networks. That is the next frontier for this area of research—translating

neuroscience from the lab and the clinic into the community, thus fully realizing the translational commitment of the developmental psychopathology perspective.

One promising, but still nascent, area of intervention includes mindfulness-based interventions. Mindfulness interventions are aimed at altering the experience of the stress process for the individual by addressing the individual's response to stressors, which should, in turn, result in alterations in the underlying stress–response system. Mindfulness-based interventions have been most often implemented with adults, and have shown some successes with moderate effect sizes (although more methodologically rigorous work is warranted; Baer, 2003; Grossman, Niemann, Schmidt, & Walach, 2004). Another approach to these interventions aims at improving the regulatory capacity of youth exposed to stress and risk. These use mindfulness-based training to focus attention and awareness and reducing rumination that can contribute to the physiological and psychological costs of stress as we have described here. The first work using these approaches for children and adolescents has demonstrated that these interventions are feasible to implement and are well received, but efficacy evidence is only now emerging (Burke, 2010; Mendelson et al., 2010). Further work in this area is currently under way (Greenberg & Harris, 2012) and is needed to determine if this approach can effectively build resilience in children exposed to stress and trauma by reducing the physiological and psychological costs of stress.

In contrast to the relatively new work on mindfulness-based strategies, social-emotional learning programs in schools have a much longer history and these sometimes also target the self-regulatory capacity of children and youth at risk. As such, these programs *may* have implications for building the social-emotional skills that underlie successful coping in the context of stress. As we have discussed, the brain's survival/salience network underlies the processing of salient (survival-related) information and serves as the central mediator of allostatic accommodation to environmental demand (Menon, 2011). We have argued that these systems of the brain underlie the translation of a stressor into a behavioral or physiological response, and are thus key to the onset of mental disorder. Then it stands to reason that interventions that target these same systems might be important in the prevention of such disorders. An extensive meta-analysis of over 200 social-emotional learning programs studied in the context of experimental and quasi-experimental studies shows moderate effect sizes on outcomes like emotional distress and conduct problems that may be the precursors to psychopathology (Durlak, Weissberg, Dymnicki, Taylor, & Schellinger, 2011). But because these studies rarely if ever include physiological assessments, it is not at all clear if such interventions support the theory we have proposed here, or whether they effectively support children's development through other neural mechanisms.

While not typically considered as interventions aimed at psychopathology per se, a number of policy experiments have been conducted that are intended to directly reduce stressors in the external environment by targeting the contextual precipitators of that stress process. Some of the most well-studied of these are employment-based antipoverty programs, that directly target family income (Morris, Duncan, Huston, Crosby, & Bos, 2001; Morris, Gennetian, & Duncan, 2005). These programs provide low-income families with resources either from within or outside the welfare system. They typically tie that increased income to work by providing monthly cash or in-kind supplements to earnings, or by allowing welfare-recipient parents to keep more of their welfare benefits when they transition from welfare into employment. A relatively large and promising research base shows that these programs (known as Conditional Cash Transfers, or CCTs; Fiszbein, Schady, & Ferreira, 2009) can effectively raise income of families in ways that should reduce stressor exposure (Bloom & Michalopoulos, 2001; Morris et al., 2001). These condition cash assistance on parents' participation in some program or institution (historically, school or health visits). Indeed, findings demonstrate that CCTs might be especially good at encouraging participation in services and institutions that might benefit high-risk individuals, even while the increased resources going to families might reduce that risk exposure in the first place. In this way, CCTs could be effectively paired with supply side services to boost the emotional skills of high-risk children (e.g., mindful meditation or social-emotional learning programs). At the same time, they support key demand side adjustments (parents' and children's take-up of those services, which can be notoriously low for voluntary programs). These programs have the added benefit of simultaneously reducing family stress through a key contextual target—increasing income. Future work should certainly explore these opportunities to reduce the risk for psychopathology, although rarely do large-scale randomized trials include the careful measurement of physiological processes that would enable us to move forward in this line of work.

As we have discussed elsewhere (Ganzel & Morris, 2011), we strongly support the inclusion of physiological measurement in community intervention studies that hold promise for reducing psychopathology. Measuring change

in neural processes and in concomitant mental health outcomes in randomized control trials can dramatically advance our understanding of the sensitivity of systems to induced environmental change (Cicchetti & Gunnar, 2008), as well as providing us with information to refine and expand our theoretical models. And by offering such interventions to children at differing periods of development, such research can also tell us about points in development in which the system is plastic and open to change from intervention. Notably, however, caution is in order: interventions may be limited in their contribution to the understanding of risk and resilience if the neural processes deriving from *positive* events are not merely the mirror image of those precipitated by *negative* events. Indeed, it is even possible that the windows of sensitivity to *stress* of physiological processes and mental health outcomes do not always coincide with windows of sensitivity to the *positive* aspects of intervention. In effect, it is not clear whether developmental periods are plastic or merely vulnerable. Or if the neural effects of *positive* contextual change (intervention) are the same as the effects of *negative* contextual change (stress). If they are not, then learning about periods of plasticity to intervention may not tell us all we need to know about periods of sensitivity to stress. They certainly will tell us about one side of plasticity (the sensitivity of neural systems to positive inputs) but may leave us still wondering about the other. That said, such research can still provide sorely needed information about how to best reduce the risk of psychopathology.

In this paper, we draw from research across the disciplines of biology, medicine, neuroscience, and psychology to present a new diathesis–stress framework for the development of psychopathology across the life span. The field is at a pivotal moment—new work is coming on line rapidly, dramatically increasing our understanding of neural processes in ways we could not have imagined a decade ago. It is imperative that we use this new information to develop a cross-disciplinary life span perspective on the emergence of psychopathology—one that highlights our deepening understanding of the neural processes underlying the stress/diathesis process. And, perhaps most importantly, it is critical that this information be used for the design of interventions that can most effectively mitigate the negative effects of psychopathology. In doing so, we will fully realize the commitment of a developmental psychopathology perspective (Cichetti & Toth, 2009) in leveraging the interdisciplinary-informed study of normality and psychopathology across the life span to more fully inform effective intervention at scale for those who are most at risk.

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CHAPTER 16

Typical and Atypical Human Functional Brain Development

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INTRODUCTION

The human adult neocortex contains approximately 20 billion neurons, each connected to about 1,000 other neurons, resulting in networks involving trillions of connections. For the most part, these neurons have already been created and travelled to their correct positions by the time of full-term birth. They will, however, continue to differentiate and refine their patterns of connection over a prolonged period stretching into late adolescence. Relating changes in the developing brain to the remarkable changes in motor, perceptual, and cognitive abilities during the first decade or two of human life is the main focus of the field of *developmental cognitive neuroscience*. This includes normal development of brain–behavior relationships as well as how factors such as brain injury, neurodevelopmental disorder, or atypical environments affect these relationships.

While developmental cognitive neuroscience is still a relatively young field, several general perspectives have emerged that often frame the kinds of research questions asked and how results are interpreted. In this chapter we will outline three perspectives on human functional brain development: (1) a maturational viewpoint; (2) skill–learning viewpoint; and (3) interactive specialization viewpoint. We then focus in more detail on the interactive specialization viewpoint, assessing its application and implications for understanding empirical evidence from (1) functional brain imaging, (2) the effects of early acquired brain damage, and (3) the consequences of atypical early experience.

[1]Color versions of Figures 16.1 are available at http://onlinelibrary.wiley.com/book/10.1002/9781119125556

THREE PERSPECTIVES ON THE FUNCTIONAL DEVELOPMENT OF THE HUMAN BRAIN

As stated earlier, relating evidence on the neuroanatomical development of the brain to the changes in motor, perceptual, and cognitive abilities during infancy, childhood and adolescence presents a considerable challenge. We now briefly introduce three distinct, but not necessarily incompatible, approaches to this issue (Table 16.1): (1) a maturational viewpoint; (2) skill–learning viewpoint; and (3) interactive specialization viewpoint. Next, we go on to examine the assumptions and predictions of one of the three, the interactive specialization viewpoint, in more detail.

Maturational Viewpoint

According to the maturational viewpoint, newly emerging sensory, motor and cognitive functions are related to the maturation of particular areas of the brain, usually regions of cerebral cortex. An area is said to be mature

TABLE 16.1 Three Perspectives on Human Functional Brain Development

	Brain-cognitive mapping	Primary locale of changes	Plasticity	Cause
Maturational	One-to-one mapping Static over development	Intraregion connectivity matures	A specialized mechanism invoked by stroke or injury	Brain changes cause cognitive development
Skill–learning	Changes during acquisition of skill		Life-long; No clear sensitive period	
Interactive	Networks/neural systems Dynamic changes during development	Interregional connectivity changes and shapes intraregional connectivity	An inherent property—the state of having not yet specialized Sensitive—period determined by state of specialization	Bidirectional relations between structure and function

when it achieves the adult state of functioning, with any different state of functioning classified as being immature. This view tends to emphasize discontinuity, or step-like changes. Abilities are viewed as being suddenly switched on at the time the related brain area becomes adult-like. It is a deterministic epigenesis approach that assumes that development involves a unidirectional causal path from genes to structural brain changes to psychological function, in which the influence of the environment plays little role.

According to the maturational viewpoint, the time when a brain region matures should predict the age when a particular behavior or skill emerges. Conversely, emergence of a new behavior or skill at a given age can be attributed to the maturation of a new brain region previously not functioning due to immaturity. One problem with this approach is that it is circular: emergence of new abilities is evidence of a cortical region becoming mature, and the cortical region's maturation accounts for the emergence of the new skill. For example, the development throughout adolescence of the ability to detect error-related conflict in action monitoring tasks has been attributed to maturation of anterior cingulate cortex over this time (Ladouceur, Dahl, & Carter, 2004), and at the same time changes in children's error detection have been taken as evidence of changes in anterior cingulate function (Epsinet, Anderson & Zelazo, 2013). Functional brain development is, in this sense, depicted as the reverse of adult neuropsychological studies of patients with brain damage: specific brain regions are being added in during development instead of being subtracted out by damage. This view thus sees a static, one-to-one mapping of brain–behavior relations over development: when new structures come on line, the existing (already mature) regions continue to support the same functions they did at earlier developmental stages. This assumption that brain–behavior relationships are static over development is partly why the maturational viewpoint considers it acceptable to study developmental disorders in adulthood and then extrapolate results back in time to early development.

Despite the intuitive appeal and attractive simplicity of the maturational approach, it does not successfully explain all aspects of human functional brain development. One aspect that is difficult to account for within this view is that some of the cortical regions that are slowest to develop by neuroanatomical criteria show activity from shortly after birth and appear to mediate cognitive functions even before they would be considered anatomically fully mature. For example, while prefrontal cortex continues to mature into the teenage years according to neuroanatomical criteria, functional imaging studies show evidence that it can be activated during the first months (see Johnson 2011 for review). Thus, the emergence of new behaviors is not necessarily linked to a previously immature, silent neural region suddenly becoming active when it matures. For example, working memory shows a protracted course of development, which has been attributed to the prolonged development of the frontoparietal network mediating this skill. However, one study of 12-year-old children and young adults showed that 6 weeks of practice can considerably reduce the differences in functional activation between children and adults during working memory tasks (Jolles et al., 2012). This pattern of findings is inconsistent with the idea that brain structures cannot be engaged in a skill before they are fully structurally mature.

Another difficulty for the maturational viewpoint is that associations between neural and cognitive changes based on age of onset are theoretically weak due to the great variety of neuroanatomical and neurochemical measures that change at different times in different regions of the brain. Thus, it is nearly always possible to find a potential neural correlate for any behavioral change.

Skill Learning

The skill–learning view of human functional brain development proposes that the brain regions active in infants during the onset of new perceptual or motor abilities are

similar, or identical, to those involved in complex skill acquisition in adults. While the nature of the skills to be acquired change with development (from basic sensory and motor skills, to complex cognitive ones), the challenge to the brain at a given point in development may be equivalent. For example, Gauthier and colleagues showed that extensive training of adults to identify individual artificial objects (called greebles) eventually results in activation of a cortical region previously preferentially activated by faces, the fusiform face area (Gauthier et al., 1999). This suggests that the region is normally activated by faces in adults, not because it is prespecified to do so but because of our extensive expertise with that class of stimulus. Extended to ontogeny, this view would argue that development of face processing during infancy and childhood could proceed in a similar manner to acquisition of perceptual expertise for a novel visual category in adults (see Gauthier & Nelson 2001). While the degree to which parallels can be drawn between adult expertise and infant development remain unclear, to the extent that the skill learning hypothesis is correct, it presents a clear view of a continuity of mechanisms throughout the life span.

Interactive Specialization

The interactive specialization (IS) viewpoint represents a probabilistic epigenesis approach (Gottlieb, 1982), in which development involves a process of interactions among genes, structural brain changes, and psychological function that are viewed as bidirectional, dynamic, emergent, and influenced by the environment. This sharply contrasts with the maturational approach described previously, in that the latter assumes deterministic epigenesis whereby region-specific gene expression is assumed to effect changes in intraregional connectivity that, in turn, allows new modular functions to emerge.

The interactive specialization viewpoint assumes that postnatal functional brain development, at least within cerebral cortex, involves a process of organizing patterns of interregional interactions (Johnson 2000, 2011). One key idea is that of brain *specialization*: cortical regions may begin with poorly defined, general-purpose functions (and consequently are partially activated in a wide range of different contexts and tasks) but during development their functions sharpen such that their activity becomes restricted to a narrower set of circumstances (e.g., a region originally activated by a wide variety of visual objects may come to confine its response to upright human faces). A second key idea of the interactive specialization viewpoint is that *interactions* between cortical areas are critical for this process of specialization and for emergence of new skills. Thus, the response properties of a specific brain region are partly determined by its patterns of connectivity to other regions, and their patterns of activity. During development, changes in the response properties of cortical regions occur as they interact and compete with each other to acquire their role in new computational abilities.

In the IS view, the emergence of new skills is thus associated with changes in activity over several regions, and not just by the onset of activity in one or more additional regions. Similarly, when a new computation or skill is acquired, there is also a reorganization of interactions between different brain structures and regions (Johnson, 2001). In fact, where functional activity has been assessed by fMRI during a behavioral transition, multiple cortical and subcortical areas appear to change their response pattern (Luna et al., 2001) rather than a few specific areas becoming active. This reorganization process could even change how previously acquired cognitive functions are represented in the brain. Thus, the same behavior could be supported by different neural networks at different ages during development. For example, the prefrontal cortex contributes to working memory in both early and late adolescence and adulthood (Finn, Sheridan, Kam, Hinshaw, & D'Esposito, 2010). However, the hippocampus is also recruited in early adolescence regardless of task demands and performance, whereas in late adolescence and adulthood, the two regions are only co-active under high task demands (Finn et al., 2010). Thus, different neural networks underlie working memory at different points in development. This contrasts with the maturational viewpoint previously described, which assumes that the relation between brain structure and cognitive function is unchanging during development.

The view that cognitive functions are the emergent product of interactions between different brain regions follows views in adult functional neuroimaging. For example, Friston and Price (2001) pointed out that it may be an error to assume that particular functions can be localized within a certain cortical region. Rather, they suggest that the response properties of a region are determined by its patterns of connectivity to other regions as well as by their current activity states. By this view, "the cortical infrastructure supporting a single function may involve many specialized areas whose union is mediated by the functional integration among them" (p. 276). Similarly, in discussing the design and interpretation of adult fMRI studies, Carpenter and collaborators (2001) argued, "In contrast to a localist assumption of a one-to-one mapping

between cortical regions and cognitive operations, an alternative view is that cognitive task performance is subserved by large-scale cortical networks that consist of spatially separate computational components, each with its own set of relative specializations, that collaborate extensively to accomplish cognitive functions" (p. 360). Extending these ideas to development, the IS approach emphasizes changes in interregional connectivity, as opposed to the maturation of intraregional connectivity. While the maturational approach may be analogous to mosaic cellular development, the IS view corresponds to the regulatory development seen in higher organisms in which cell-cell interactions are critical in determining developmental fate. While mosaic development can be faster than regulatory, the latter has several advantages. Namely, regulatory development is more flexible and better able to respond to damage, and it is more efficient in terms of genetic coding. In regulatory development genes need only orchestrate cellular-level interactions to yield more complex structures (see Elman et al., 1996).

Stating that structure–function relations can change with development is all very well, but it lacks the specificity required to make all but the most general predictions. Fortunately, the view that there is competitive specialization of regions during development gives rise to expectations about the types of changes in structure–function relations that should be observed. These predictions are outlined in more detail in the following section.

PREDICTIONS OF THE INTERACTIVE SPECIALIZATION FRAMEWORK

The IS viewpoint expects that widespread networks of brain regions will change their patterns of activation in association with the onset of new behavioral abilities. In addition, regions will become more specialized (finely tuned) in their response properties with experience. A consequence of this specialization is that, on at least some occasions, fewer brain regions are activated with development in certain tasks. Thus, while the exact nature of changes in brain activation will depend on the degree of specialization achieved in different component structures, the IS view predicts a general trend for a *decrease* in the extent of cortical activation and an increasing specificity of the cortex that is activated with increasing development/experience. This stands in contrast to the maturational approach, which would expect that, if we compare two age groups in a task for which they show identical behavioral performance, then we should also expect to see identical patterns of brain activation. The skill–learning view would expect reactivation of one or more skill–learning circuits when a task is first being learned, followed by a different pattern of activation after the skill is acquired and becomes more automated. In this case, in many comparisons between age groups, the younger group will have acquired the skill in less depth than the older group, giving rise to different patterns of underlying brain activation. Interestingly, however, patterns of changing brain activation while adults acquire new skills should mirror the changes seen during development as infants and children acquire simpler skills. Moreover, patterns of activation across age should be the same if the differently aged participants have attained the same level of performance. This stands in contrast to the IS viewpoint, as the state of specialization and interaction of brain regions would be different in the adult and infant brain, which would influence how the learning itself influenced the brain.

The predictions of the IS view can more specifically be divided into those relating to the specialization part of the hypothesis, and those related to the interactive part of the hypothesis (for more detail, see Johnson, 2011). The developmental predictions regarding specialization are (1) that there is an increased neural tuning with age, so that more selective or narrow response patterns are seen; (2) that there is a shrinkage or contraction of the cortical region responsive to a particular type of stimulus; (3) that the increased neural tuning and shrinkage of cortical regions activated will be correlated, since they reflect two sides of the same underlying process; and (4) that the degree of functional plasticity will depend on the degree of specialization attained at a given time, with greater specialization resulting in less plasticity and vice versa. The developmental predictions regarding the interactive aspects are (1) developmental change in cognitive skills or behavior will be accompanied by widespread changes across multiple regions rather than changes in single isolated areas, (2) the process of specialization will scale up from individual brain regions to multiregion networks, and (3) the specialization of individual regions will be shaped by their involvement in one or more functional networks.

In the sections that follow, we focus on evaluating these hypotheses of the IS viewpoint by examining evidence from brain imaging studies of typical development, the effects of early acquired brain damage, and the consequences of atypical early experience. Contrasts with the maturational and skill–learning viewpoints will also be made where they highlight a contrast between the viewpoints.

BRAIN IMAGING OF TYPICAL DEVELOPMENT

In this section we review evidence from the functional neuroimaging of normal development that pertains to the predictions of the IS view described above. We will focus mostly on three of the IS hypotheses for which there is most available evidence: (1) there is an increased neural tuning with age; (2) there is a shrinkage of cortical regions active for a particular type of processing with age; and (3) developmental changes in cognitive skills or behavior are accompanied by widespread changes in multiple regions, because there is the most evidence available for these predictions. The predictions of the IS framework for typical development have been studied in several domains (Johnson, 2011), but perhaps most extensively in face processing, through studies of the emergent core face network, a subnetwork of the cortical social brain. These studies have provided evidence supporting the IS prediction that there is a shrinkage of the cortical area active for a particular type of processing with age. One line of evidence comes from event-related potential experiments with infants, which have indicated that there is increasing localization of processing with age and experience for face processing (de Haan et al., 2002; see Neville, Mills, & Lawson, 1992, for a similar pattern in word learning). That is, scalp recordings reveal a wider area of processing for faces in younger infants than in older ones, whose processing has become more specialized and localized. Within the interactive specialization framework, such developmental changes are accounted for in terms of more pathways being partially activated in younger infants prior to tuning resulting from experience with a class of stimuli. With increasing experience, the increasing localization of one or more of those pathways occurs over time. Changes in the extent of localization can be viewed as a direct consequence of increased specialization, hence the aforementioned prediction that these two developmental changes both reflect the same underlying process. Initially, multiple pathways are activated for most stimuli. With increasing experience, fewer pathways become activated by each specific class of stimuli, and these more limited pathways themselves become more tuned to specific functions and are therefore no longer engaged by the broad range of stimuli as was the case earlier in development. Additionally, there may be inhibition from pathways that are becoming increasingly specialized for that function. In this sense, then, there is competition between pathways to recruit functions, with the pathway best suited for the function (by virtue of its initial biases) usually winning out.

Further evidence comes from studies using fMRI to study the development of cortical activation patterns during childhood involved using the same stimulus array for two different tasks, a face matching task and a location matching task (Passarotti et al., 2003). For the face-matching task, younger children (10–12 years) showed more extensive areas of activation than did older children and adults. In general, the activation shown by the youngest group included the areas activated in adults (such as bilateral activation of the middle fusiform gyrus) but additionally extended to more lateral and anterior regions. In the location matching condition, the children also showed more extensive activation than did adults. While adults had strong right superior parietal activation, children displayed more bilateral activation of this structure, as well as additional activation in right superior frontal gyrus. These results are consistent with a shrinkage or contraction of the cortical region active for a particular type of processing.

Predictions of the IS view about the shrinkage of cortical regions involved in a skill have also been supported in other domains, such as response inhibition. Luna and colleagues (2001) tested participants aged 8 to 30 years in an oculomotor response-suppression task. Their behavioral results showed that the adult level of ability to inhibit prepotent responses developed gradually through childhood and adolescence. The difference between pro-saccade and anti-saccade conditions were investigated with functional MRI, and revealed changing patterns of brain activation during development. Both children and adolescents had less activation than adults in a few cortical areas (superior frontal eye fields, intraparietal sulcus), and several subcortical areas, a finding broadly consistent with maturational hypotheses. However, both children and adolescents also had differential activation in regions not found to show differences in adults. Children displayed increased relative activation in the supramarginal gyrus compared to the other age groups, and the adolescents showed greater differential activity in the dorsolateral prefrontal cortex than children or adults. These findings illustrate that the neural basis of behavior can change over developmental time, with different patterns of activation being evident at different ages, a pattern consistent with both the IS and the skill–learning viewpoints.

A final example of how fMRI studies support the prediction of shrinkage of cortical regions involved in a skill over childhood comes from studies of verbal fluency tasks in which participants are asked to generate words in response to a cue (e.g., to generate examples of a target category, or generate a verb that relates to a cued noun).

Several studies have shown that adults (Lehericy et al., 2000) and school-age children (Gaillard et al., 2000; Hertz-Pannier et al., 1997) typically activate left hemisphere frontal cortical networks including Broca's area, premotor, prefrontal, and supplementary motor areas as well as, less consistently, temporal cortical areas including superior temporal, middle temporal, and supramarginal gyri. In addition, some degree of activation in homologous right frontal regions is almost always found both in adults (Pujol et al., 1999; Springer et al., 1999) and in children (Gaillard et al., 2000; Hertz-Pannier et al., 1997). Two studies have found that both the degree to which activation is bilateral (rather than left dominant) and the extent of this activation is greater in children than in adults (Gaillard et al., 2000; Holland et al., 2001). Thus, as in the other examples discussed before, typical development is associated with a reduction in the extent of activation of cortical areas and, as a consequence, an increased lateralization of activation to the left hemisphere with age (Berl et al., 2014; Holland et al., 2001). However, it should be noted that not all developmental imaging studies have reported decreases in extent of activation with age. For example, in the case of verbal fluency, two studies have reported that laterality and extent of activation did not differ between children and adults (Gaillard et al., 2000; Schlaggar et al., 2002), with one even showing a greater number of pixels activated in left frontal regions in adults compared with children (Gaillard et al., 2000).

Studies of face processing have also addressed the IS prediction that there is an increased neural tuning with age or experience, so that a more selective or narrow response pattern is seen. In functional MRI studies with older children, several investigators have traced the gradual emergence of a high degree of tuning to faces in a particular cortical region; FFA—the fusiform face area. For example, Scherf et al. (2007) used naturalistic movies of faces, objects, buildings, and navigation scenes in a passive viewing task with children (5–8 years), adolescents (11–14 years), and adults. They found that the children exhibited similar patterns of activation of the face-processing areas commonly reported in adults (such as the FFA). However, this activation was not selective for face stimuli only, as the region was equally strongly activated by other complex visual stimuli such as objects and landscapes. Thus, young children had a less narrowly tuned cortical response to faces than did adolescents and adults, who exhibited a more selective pattern of activation. Experience can also induce this type of change, as shown in a study where an individual with developmental prosopagnosia (a congenital disorder of face processing) was trained to recognize faces. As behavioral performance improved, so did the selectivity of the cortical processing of faces as measured by the N170 component of the event-related potential (DeGutis et al., 2007).

While such experiments provide evidence for the increasing specialization (or tuning) of individual regions of cortex during human postnatal development, from the IS viewpoint the next step is to understand how *networks* of different regions, each with their own different specializations, emerge. A key prediction of the IS view is that the process of specialization will scale up from individual brain regions to multiregion networks, and that the specialization of individual regions will be shaped by their involvement in one or more functional networks. Again, face processing provides a good test as a core face network of cortical regions has been well established in adults, and activity in this network is known to be modulated by task demands in adults. To explore these issues, Cohen Kadosh et al. (2011) examined the emergence of the core face network in younger (7–8-year-old) and older (10–11-year-old) school-age children as well as in young adults and found that children showed substantially weaker and more fragmented connectivity within this face network. Further, no evidence was found for the influence of task demands on the effective connectivity within the network in the two children groups. That is, while both child groups exhibited similar overall network structures, these weaker networks were not influenced by top-down task demands.

The IS view argues that emergence of new behaviors requires changes in interregional cortical interaction, thus the finding different patterns of activation in children even in tasks where behavioral performance is similar to that of adults is compatible with the IS viewpoint. In fact, comparing activation in cases where behavioral performance is equated is critical for distinguishing the IS view from both the skill–learning view and the maturational view, as only the former predicts that the pattern of brain activation may differ with age even when performance is equated. Which of the three approaches is adopted has not only theoretical implications but also practical implications for data collection. For example, if one adopts the maturational approach, and is expecting a particular area to become active during development for a particular task, then brain imaging may be focused on that region rather than on the whole brain. As a consequence, any possible changes in more distant brain structures would not be detected. By contrast, if one adopts the interactive specialization approach, then the importance of whole-brain imaging is clearly apparent.

Functional imaging studies also provide support for the IS prediction that younger and older participants will show different patterns of task-related brain activation even in the absence of performance differences. For example, Casey and colleagues (Casey et al. 1997; Thomas et al. 1999) administered a go/no-go task to assess inhibitory control and frontal lobe function to healthy volunteers from 7 years of age to adult. The task involved participants responding to a number of letters, but withholding their response to a rarely occurring X. More than twice the volume of prefrontal cortex activity (in the middle and superior frontal gyri) was observed in children compared with adults (see also Booth et al., 2003; Bunge et al., 2002; Durston et al., 2002; Tamm et al., 2002, for similar results). One explanation of this finding is that children found the task more difficult and demanding than adults. However, children with error rates similar to those in adults showed some of the largest volumes of prefrontal activity suggesting that task difficulty was not the important factor (Casey et a., 1997; Thomas et al., 1999). It is difficult to account for these decreases in the extent of cortical activation in terms of the progressive maturation of these areas. A similar pattern was observed in a study of dimensional shifts of attention (Morton, Bosma, & Ansari, 2009). For both children and adults, dimensional shifting was associated with activity in a distributed frontoparietal network, including superior parietal cortex, dorsolateral prefrontal cortex, inferior frontal junction, and the presupplementary motor region. However, even though children and adults showed comparable behavioral performance, there were still age-related differences in brain activity, with children but not adults showing an effect of dimension shifting in the right superior frontal sulcus, and adults but not children showing an effect of dimension shifting in the left superior parietal cortex and the right thalamus. The finding that children and adults appeared to show different patterns of activation in both studies even when performance was similar is inconsistent with the skill–learning viewpoint, but not unexpected according to the IS viewpoint.

In evaluating fMRI evidence for decreasing or increasing extent of cortical activation underlying a particular skill with age, it is important to be aware that factors other than dynamic changes in the interregional patterns of activation per se could be contributing to the observed differences. Importantly, technical aspects of data collection including coil characteristics, head motion, and physiological age-related differences that could affect the fMRI BOLD signal, could contribute to apparent age-related differences in activation (see Gaillard et al., 2003). For example, a surface coil might identify more activated regions in children than adults because children have thinner skulls and scalp and thus the coil is closer to the brain and can read the signal more clearly than in adults. By contrast, use of a head coil might lead to a finding of greater activation in adults than children, as most head coils are designed for adults and thus children's head position in the coil would not be optimal. Thus, when interpreting the results of functional MRI studies, it is important to keep in mind that technological and developmental factors may affect signal and noise detection that, in turn, may influence an interpretation of age-based differences in activation patterns (for further discussion of these issues see Gaillard et al., 2003; Poldrack, 2002).

Understanding brain networks and the interactions among their component regions is an important aspect of the IS view. It has been hypothesized that the resting state of the brain (when not apparently engaged in a specific task) may provide a critical bridge between structural and functional brain development (Johnson, 2011). The resting states of the brain as measured by fMRI are slow oscillations (under 1 Hz) in which the activity of particular regions cohere into networks (e.g., the default mode network). These patterns of activation appear to reflect averages of sensory and task driven activation patterns over a time period, and consolidation of experience-driven co-activation patterns between regions may require the prolonged activation patterns that resting or default states can provide. Regions that show coherent (in phase) oscillatory activity may maintain or strengthen anatomical connections between them. Other regions that may oscillate at similar frequencies, but that are out of phase, may lose or reduce synaptic connections with the emerging coherent network. Consistent with the Interactive Specialization model, evidence suggests that task-related networks, such as the anterior attention network, develop by increasingly diverging from the resting state or default networks (Gao et al., 2012).

Networks of resting state activity have been used to trace developmental changes in human brain networks, and have even been suggested as the basis for a maturational index (Schlagger et al., 2002). While several studies have shown a developmental shift from local to more long-range connectivity during postnatal development (e.g., Fair et al., 2007), these studies are currently under question for methodological reasons associated with greater motion artifact at younger ages (Deen & Pelphrey, 2012). Another change in network structure during development is that adult networks tend to have a more hierarchical structure that is optimally connected to support top-down relations

between one part of the network and another (Supekar et al., 2009). While hierarchical networks have a number of computational advantages, they are also known to be less plastic and more vulnerable to damage or noise in the particular nodes at the top of the hierarchy. Thus, the less hierarchical network arrangement of children may be more adaptable in response to unusual or atypical sensory input or environmental context.

A final aspect of the transition from child brain network to the adult one is the greater connectivity between cortical and subcortical structures seen at younger ages (Supekar et al., 2009), an observation that may be fundamental for our understanding of the emergence of the social brain and memory systems, as it implies that the specialization of some cortical areas may be initially more dominated by structures such as the amygdala and hippocampus.

Overall, the pattern of findings across studies provides little support for the maturational viewpoint, only partial support for the skill–learning view and is more consistent with the series of predictions from the IS viewpoint. The balance of evidence to date suggests that (1) new behavioral skills, or developmental changes in existing skills, are often accompanied by widespread changes across many regions of cortex, and (2) functional brain development involves the twin processes of increasing stimulus selectivity of the brain's response and increasing localization of regions that respond to a stimulus.

BRAIN IMAGING OF ATYPICAL DEVELOPMENT

In this section, we will examine how the IS viewpoint applies to developmental disorders, acquired brain injury, and atypical childhood experiences. We will focus on four IS hypotheses: (1) there is an increased neural tuning with age, and (2) there is a shrinkage of cortical regions active for a particular type of processing with age, (3) the degree of plasticity following brain injury or atypical experience relates to the degree of cortical specialization attained at the time, and (4) developmental changes in cognitive skills or behavior are accompanied by widespread changes in multiple regions.

Developmental Disorders

Much of the neuroimaging work on developmental disorders to date has been aimed at identifying gross abnormalities in discrete brain regions, structures, or systems. While there have been some specific claims made with regard to such deficits, reviews of the field tend to find instead that evidence regarding developmental disorders is consistent with diffuse damage to widespread parts of the brain. For example, Rumsey and Ernst (2000) summarize their review of functional imaging of autistic disorders as "... studies of brain metabolism and blood flow thus far have yet to yield consistent findings, but suggest considerable variability in regional patterns of cerebral synaptic activity" (p. 171). Other authors reviewing work on autism concur with this conclusion. Deb and Thompson (1998) stated that "various abnormalities of brain structure and function have been proposed, but no focal defect has been reliably demonstrated" (p. 299), and Chugani (2000) concluded that "... data from the various imaging modalities have not yet converged to provide a unifying hypothesis of brain mechanisms" with a range of cortical (frontal, medial prefrontal, temporal, anterior cingulate) and subcortical (basal ganglia, thalamus, cerebellum) structures implicated in different studies. According to Filipek (1999), a similar situation obtains with respect to attention-deficit/hyperactivity disorder (ADHD). She concluded that neuroimaging studies "... have, in fact, confirmed the lack of consistent gross neuroanatomical lesions or other abnormalities in attention deficit" (p. 117). For ADHD, there are abnormalities in widespread cortical areas including, at a minimum, the frontostriatal, cingulate, and parietal regions. In sum, for at least these two disorders there is little support for the notion that discrete lesions to functional cortical areas can be observed in developmental disorders. This is consistent with the IS prediction that developmental changes in cognitive skills or behavior are accompanied by widespread changes in multiple regions, as from this point of view, atypical developmental of cognitive skills or behaviors would be associated with widespread rather than focal cortical abnormalities.

There may be some examples of developmental disorders that show a more focal pattern of brain abnormality. For example, some argue that dyscalculia, a developmental difficulty in understanding simple number concepts and learning number facts and procedures, can be a consequence of a core numerical deficit attributable to dysfunction of a single brain area, the intraparietal sulcus (Rubinsten & Henik, 2009; Wilson & Dehaene, 2007). While evidence supports atypical activation of the IPS in individuals with dyscalculia, it is important to note that the IPS is just one component in a large-scale cortical network that subserves mathematical cognition (Butterworth, Varma, Laurillard, 2011). Moreover, recent evidence suggests that the neural specialization for arithmetical

processing may arise, at least in part, from a developmental interaction between the brain and experience. While adults typically demonstrate activation primarily in the IPS during simple arithmetic tasks, children show significantly lower levels of activity in the IPS arithmetic network but more in frontal regions (Ansari et al., 2005). The observed increases in the recruitment of parietal regions in numerical processing are taken as evidence for a specialization of parietal functioning during ontogeny (Ansari & Dhital, 2006; Holloway & Ansari, 2010). The decreasing involvement of prefrontal areas, on the other hand, is assumed to reflect a developmental disengagement of domain-general processes related to executive control and working memory (Ansari et al., 2005). These results highlighted the possibility that dyscalculia may not result simply from a single, damaged brain region. An important factor may also be that the typical school environment does not provide the right kind of experiences to enable the dyscalculic brain to develop normally to learn arithmetic (Butterworth et al. 2011).

In another example where a focal injury may account for developmental deficits, the KE family shows a genetic disorder of speech and language involving a point mutation of the FOXP2 gene. Behaviorally, the affected members appear to have a deficit in sequencing articulation patterns that results in speech output that is often agrammatical and unintelligible (Vargha-Khadem et al., 1998; Watkins et al., 2002). This impairment is evident from childhood and persists into adulthood. Reports indicate that the brains of affected family members differ from those of unaffected members and controls in several particular regions involved in speech and motor control. Among these, the evidence is most striking for the caudate nucleus, which shows reduced gray matter density and volume (Watkins et al., 2002) and shows abnormalities in activation during language tasks (Vargha-Khadem et al., 1998). While this result might suggest that, at least in some genetic disorders, there may be discrete brain lesions that result in specific behavioral impairments, it is important to note that the caudate nucleus is not the only brain area affected in this family and that imaging studies have not been conducted developmentally to determine whether the pattern of damage is already present and unchanging from early in life (as the maturational or skill–learning views might predict) or evolves with development (as the IS view would predict).

Given the assumption of the maturational approach that there is a static structure-function mapping in the brain during development, it is perhaps not surprising that the vast majority of neuroimaging studies with developmental disordered groups involve participants from middle childhood to adulthood, and that patients are often grouped together over a wide age range (e.g., Kesler et al., 2004; Turner syndrome; 7–33 years; Pinter et al., 2001; Down's syndrome; 5–23 years). For the interactive specialization approach, however, age of testing is critical, and it is especially important to study infancy to understand partial causes of subsequent outcomes (Karmiloff-Smith, 1998; Paterson et al., 1999). For this issue to be assessed, there need to be longitudinal imaging studies of clinical groups, or at least cross-sectional study at different ages**.** Due to the difficulties mentioned earlier, there are very few examples of studies of brain function in infants with developmental disorders. Where these have been investigated, there is evidence that abnormalities in brain structure and function may appear differently at different ages. For example, Karrer et al. (1995; see also Hill Karrer et al., 1998) conducted an ERP study of infants with Down syndrome at 6 months using an oddball paradigm for face recognition and concluded that atypicalities in the responses of infants with Down syndrome were milder than those observed in adults with Down syndrome. There are few MRI studies of developmental disorders that have compared different age groups in infancy or childhood. One recent study of autism found evidence of hippocampal enlargement at all ages but amygdala enlargement only in children (7.5–12.5 years) but not adolescents (12.75–18 years; Schumann et al., 2004). Studies of children with ADHD have reported a decrease in cortical thickness that tends to normalize with development (Narr et al., 2009). There is even evidence that normalization of cortical thinning is related to long-term outcomes. In one longitudinal study, children with more atypical outcomes had a persistent thinning of the left medial prefrontal cortex, whereas children with more typical outcomes showed a normalization of the right parietal cortex (Shaw et al., 2006). In a final example, autism has been related to brain overgrowth, children with autism have abnormally large brains by the second year of life, and, for several years thereafter, their brain size can be multiple standard deviations above normal values. The greater conduction delays and cellular costs presumably associated with the longer long-distance connections in these larger brains are thought to influence developmental processes, giving rise to an altered brain organization with less communication between spatially distant regions (Lewis et al., 2013). Thus in the IS view, autism may in part reflect a failure of the normal process of specialization of multi-region networks. These examples are consistent with the IS view that brain abnormalities in developmental disorders are not necessarily like static lesions but can change as the brain develops.

The interactive specialization view considers that, even if areas of behavioral competence are examined, there will still be differences in the neural processing underlying this performance between children with developmental disorders and those developing normally (Karmiloff-Smith, 1998). This question has been examined in studies of Williams Syndrome, a syndrome portrayed by some theorists as involving islands of sparing (normal performance) amidst clear deficits. Mills and colleagues (2000) focused on an area of behavioral competence in this disorder, face processing, and recorded event-related potentials during a face-matching task. Despite their intact behavioral performance in the task, WS participants displayed different patterns of ERPs including a lack of the normal right-hemisphere asymmetry. Similar findings were obtained in another area of behavioral competence for this syndrome, where the normal left hemisphere asymmetry for words was not observed (Mills et al., 1993; Neville et al., 1994). Event-related potentials in response to faces have also been recorded in participants with autism or Asperger syndrome (McPartland & Panagiotides, 2001). However, in this case face processing is an area of behavioral deficit. Compared with controls, the autism group made more errors on a test of face recognition. Performance on the face recognition task was found to be related to the ERPs in several ways: in controls, a face-sensitive ERP component was larger in amplitude to faces compared with objects, and was more predominant over the right hemisphere. In contrast, the autistic group showed longer latencies of this component to faces compared to objects, in the absence of any clear lateralization. These findings suggest that the poorer performance on face recognition tasks by the autism group is reflected by slower and less lateralized processing (i.e., less specialized) of faces as indicated by their ERPs. In addition, the different distribution of the response to faces between the autistic group and controls may reflect qualitatively different processing strategies. With regard to the IS view, this might reflect an absence of the normal process of localization, so brain processing remains more distributed and less focal than in typical development.

Effects of Early Acquired Brain Damage

The maturational and skill–learning views would both predict that early brain damage should have long-lasting detrimental effects, because the neural substrates through which an ability emerges or is learned and retained are destroyed. While the maturational view allows for some plasticity in response to such damage, it makes no clear prediction that the extent of such plasticity should be greater for children compared to adults. The skill–learning view might predict, at least under some circumstances, more negative outcomes for early lesions to areas involved in skill acquisition, because adults would have previously learned, retained skills to fall back on while children would have fewer established skills. In the interactive specialization view, however, there may be compensation for early damage. Although the damage may affect the areas that under normal circumstances would be most suitable for the task and become specialized for it, if the area is damaged in early life then there is still scope for alternative neural circuitry to be recruited for the task. Thus, the IS view predicts that plasticity following brain damage will be related to the degree of functional specialization already achieved in a given region. A region that is already well specialized will be less plastic in response to later life injury, while a region that is less specialized will have more options for future specialization. It is possible that this compensation could come at some price, however, since the overall amount of brain area that can take on specialized functions would be reduced (e.g., the notion of crowding; for discussion see Vargha-Khadem & Mishkin, 1997). If brain area is damaged later in life, then the outcome may be less optimal, as brain areas would already have specialized for particular skills and there would be less scope for alternative neural circuitry to be recruited, as it will already be taken up by other tasks. In the following sections, we will evaluate evidence relating to these hypotheses from studies of the effects of early lesions in three cognitive domains: face processing, memory, and language.

Face Processing

In adults, damage to the occipito-temporal cortex can result in prosopagnosia, a selective impairment in face processing. Several cases of selective deficits in face processing attributed to damage sustained in infancy have been reported (developmental or congenital prosopagnosia; e.g., Bentin, Deouell, & Soroker, 1999; Farah, Rabinowitz, Quinn & Liu, 2000; Jones & Tranel, 2001; Nunn, Postma & Pearson, 2001). On the surface these results are consistent with both the maturational view (early damage to the cortical face-processing system would result in a similar functional impairment as in adults with similar damage), and the skill–learning view (early damage to the system involved in learning about faces will result in a persistent impairment in this ability). However, there are some characteristics of developmental cases of prosopagnosia that do not seem to fit either of these views. If the maturational view is correct, then it would be expected that the location of damage causing prosopagnosia would

be the same in both early and adult-onset cases (Damasio, Tranel, & Damasio, 1990). However, of the few early-onset cases where structural imaging was obtained, there was no observable structural damage (Nunn et al., 2001) or diffuse rather than focal abnormalities (Laeng & Caviness, 2001). If the maturational view or the learning view were correct, then one would also expect the nature of the face-processing deficit to be similar in early and adult-onset cases. Although some authors have concluded that the two disorders are basically similar in terms of an impairment in encoding for spatial arrangement of facial evidence (Barton et al., 2003), there is some evidence for differences related to age of onset: (1) residual discrimination abilities are more limited in developmental cases (Barton, Cherkasova, & O'Connor, 2001) and (2) covert recognition is absent in developmental cases (Barton et al., 2001; but see Jones & Tranel, 2001). Thus, the impairments in face processing observed in early-onset cases appear to be neither identical in nature to those observed in adult-onset cases, nor a direct consequence of focal damage to brain areas involved in face processing in adults. Finally, if the skill–learning view is correct, and face processing represents a specific example of a more general system for acquiring perceptual expertise, then impairments in face processing might be expected to co-occur with more general impairments in acquiring perceptual expertise. However, a study of two individuals with developmental prosopagnosia showed normal acquisition of perceptual expertise for greebles (Rezlescu et al., 2014). Overall, the pattern of results across these studies is most consistent with the IS view, which would predict that the nature of the deficit would depend on the age of injury.

There is some evidence to support the idea that the problem underlying developmental prosopagnosia is a failure of the normal process of brain specialization and localization. One functional MRI study of face perception in four adult developmental prosopagnosics (Avidan et al., 2005) showed that these individuals recruited the inferior frontal gyrus. This area was not commonly activated during face perception in typical adults, but is activated during face perception in children (Passarotti et al., 2003; Scherf et al., 2007). The difference between children and adults is consistent with the IS prediction that the cortical regions that respond to a given stimulus or task will decrease with age. The finding of additional areas of activation in adult developmental prosopagnosics compared with typical adults suggests that the condition may reflect a delayed or impaired specialization process (see Johnson, 2011, for further discussion).

Other studies have taken a different approach, and instead of finding individuals with face-processing deficits that could be attributed to early lesions, have found children who sustained lesions to areas known to be involved in face processing in adults and investigated the consequences for face processing. In one study of face-processing abilities in 5- to 14-year-olds who had experienced perinatal unilateral lesions, the effects were fairly mild: fewer than half the children showed impaired performance relative to controls on tests of face or object identity recognition (Mancini et al., 1998). Furthermore, (1) face-processing deficits were no more common than object processing deficits following a right hemisphere lesion, (2) face-processing deficits were no more common after right-sided than left-sided damage, and (3) a face-processing deficit never occurred in the absence of an object processing deficit. This general pattern is similar to that reported in other studies (Ballantyne & Trauner, 1999; Mancini et al., 1994), and contrasts with the severe impairments in face or object recognition observed in adults with damage to similar brain regions (Farah, 2000). Together, these results suggest that the infant face-processing system is more widely distributed or more plastic following damage than is the adult system. These results fail to provide convincing evidence for the maturational view or skill–learning view. Instead, they are more consistent with the IS view that, when brain areas that typically mediate a function in adults are damaged early in life, there may be greater recovery of function than following similar damage in adults.

Memory

Memory is among the most fundamental aspects of cognitive development, enabling individuals to amass knowledge about the world (semantic memory) and to recall everyday events (episodic memory). In adults, bilateral damage to the medial temporal lobe results in a global amnesia, reflecting this region's essential role in explicit memory. However, until recently there were virtually no reports of memory impairments following temporal lobe damage in children. This was assumed to be either because the results of such damage were so devastating to the developing child that a global severe mental delay resulted (consistent with skill–learning view) or because the greater plasticity of the developing brain allowed sufficient recovery to prevent clinical appearance of memory impairments (consistent with interactive specialization view). In recent years, however, there have been reports that very early damage to a specific medial temporal lobe structure, the hippocampus, does result in amnesia (Gadian et al., 2000;

Isaacs et al., 2003; Vargha-Khadem et al., 1997, 2003). On the surface, this finding appears consistent with the maturational view, in that early focal damage to a brain region believed to mediate a particular ability in adults results in a specific failure of that skill to develop. Indeed, the pattern of memory impairment observed in these children, where episodic memory is relatively impaired and semantic memory relatively spared, has been used to argue that the hippocampus is necessary for episodic memory in adults (Vargha-Khadem et al., 1997). However, the results of selective, bilateral hippocampal damage occurring in childhood appear to differ from those of similar damage occurring in adulthood (Baddeley et al., 2001; Gadian et al., 2000; Vargha-Khadem et al., 1997). The deficits following early injury appear more subtle: while hippocampal damage in adulthood typically results in deficits in both semantic (facts) and episodic (events) memory, damage during childhood results clear deficits only in episodic memory, showing relatively normal development of semantic memory. For example, they score in the low average to average range on indices of semantic memory, such as general intellectual abilities and academic attainments, but they are severely impaired on indices of episodic memory, such as remembering a name, a message, or where a belonging was placed (Gadian et al., 2000; Vargha-Khadem et al., 1997; 2003; see also Cooper et al., 2014). Also, in cases with neonatal damage, the memory deficits that these children do display become apparent only about the time they first enter school or even later. Lastly, while a study comparing performance in those sustaining damage before 1 year of age and those sustaining the damage between 6–14 years (Vargha-Khadem et al., 2003) found no difference in the degree of episodic memory impairment, there was evidence that those with early damage performed better on tests of immediate memory than those with later damage. This might reflect a greater degree of recovery or reorganization of general memory skills in those with early damage.

Proponents of the maturational or skill–learning view might argue that this difference in outcome can be explained by a difference in the selectivity of the medial temporal lobe (MTL) between the two conditions, such that whereas the hippocampus is damaged in both, only the patients with DA show substantial sparing of the subhippocampal cortices. This possibility is in line with the suggestion that the hippocampus and the subhippocampal tissue serve different components of explicit memory, with the hippocampus mediating episodic recollection and the subhippocampal cortices mediating semantic memory and familiarity-based recognition (Baddeley et al., 2001; Mishkin et al., 1998). However, in the IS view this difference in outcome can be explained by the fact that the degree of postinjury compensation and reorganization differs between the developing and the mature brain, such that only early damage allows for recovery of the functions found to be spared in early-onset amnesia. As there has currently been no published report directly comparing early-onset with adult-onset amnesia controlling for extent of damage, it is difficult to decide between these two possibilities. Interestingly, a functional imaging study of one patient with developmental amnesia (injury neonatally, tested at 22 years of age; Maguire, Vargha-Khadem & Mishkin, 2001), showed that, although his hippocampi are severely damaged (approximately 50% reduced in volume bilaterally), they are activated in tasks in which controls also activate the hippocampus. Specifically, during retrieval of real-world memories, the patient Jon activated the same brain regions as controls, including the hippocampus. Also like controls, activation in Jon's hippocampus was greater for the few autobiographical events he could recall compared to public events and general knowledge. However, in spite of these qualitative similarities, his activation was actually greater than controls. Specifically, he activated many homologus areas on the right which the controls did not, and he also showed a different pattern of connectivity between areas compared to controls (controls showed increased connectivity of hippocampal with parahippocampal regions during retrieval of autobiographical events, whereas Jon showed increased connectivity between the hippocampus and retrosplenial cortex and the medial frontal cortex and retrosplenial cortex). These results are consistent with the IS view, as they suggest that Jon activates a different network because his early lesions have allowed for reorganization and compensation. Similarly to the interpretation of performance in cases of developmental prosopagnosia, Jon's wider spread pattern of activation suggests that there is a delayed or impaired specialization process for brain memory systems.

Language

In adults, left hemisphere lesions that involve perisylvian areas result in a dramatic impairment of speech and language that is typically chronic despite rehabilitation. By contrast, damage to these regions during childhood appears to have no or only subtle effects on ultimate language abilities, and there appear to be no or only subtle effects of side of injury (in cases uncomplicated by epilepsy; e.g., see Vargha-Khadem, Isaacs, Watkins &

Mishkin, 2000; also reviewed in Bates & Roe, 2001). For example, one direct comparison of children (5–8 yrs) and adults found the classic association of left-sided damage with aphasia in adults, but found that children performed within the normal range, with no effect of lesion side (Bates, Reilly, Wulfeck, Dronkers, Opie, Fenson, Kriz, Jeffries, Miller & Herbst, 2001). This result is inconsistent with the maturational view, which would predict a similar pattern of impairment in cases of childhood injury. It is also difficult to reconcile with the skill–learning view, unless the damaged areas are not involved in language learning and are only critical once the skill is fully acquired.

There is some evidence consistent with the idea that the left perisylvian areas critical for language in adults may not be key in language learning in children. This comes from data showing that even in early damage there are significant effects of lesion side and site on first stages of language development, but not involving the left perisylvian areas. For example, early delays in word comprehension and symbolic gesture are somewhat more common with perinatal right hemisphere damage but only between 10–20 months of age (Vicari et al., 2000) and deficits in expressive vocabulary and expressive grammar are more common with perinatal left temporal lobe damage, but only from 10 months to 5–6 years (Thal, Marchman, Stiles, Aram, Trauner, Nass & Bates, 1991). One interpretation is that, when children are struggling to reproduce familiar sounds from their input language for the first time, they have to extract a great deal of perceptual detail from the input. This might normally rely on the left temporal cortex, since it is known to be involved in extracting detail from perceptual inputs.

Overall, evidence suggests that younger children may have less consolidated and more bilateral representations of language processing areas, which derives mostly from increased activation in the right frontal lobe (Gaillard et al., 2000; Holland et al., 2001). For example, PET studies of children who had neurosurgery to treat intractable epilepsy indicate that, especially for language perception tasks, early left hemisphere lesions are associated with enhanced activation of right hemisphere areas, whereas recruitment of regions ipsilateral to the lesion side is limited. Studies with children born preterm support the idea that interhemispheric connections are key in typical language development. One diffusion tractography study of adolescents who had been born preterm showed that 38% showed a language impairment and that a combination of anatomical measures of temporal interhemispheric connectivity (through the splenium of the corpus callosum and anterior commissure) explained 57% of the variance in language abilities (Northam et al., 2013). Thus, a more diffuse, less consolidated distribution of language networks has been proposed as an explanation for recovery from dominant hemisphere brain injury in children that extends, with diminishing capacity, into adolescence (Boatman et al., 1999; Gaillard et al., 2000; Vargha-Khadem et al., 1992). It has been argued that, by adulthood, the functional role of the RH in aphasia recovery may be more limited compared with that of the peri-lesional structures in the LH (Karbe et al., 1998; Weiller et al., 1995).

Effects of Atypical Early Experience

The three perspectives on human functional brain development differ in their views as to the effects of early atypical experience. In the maturational view, differences in experience might influence the speed at which a function matures or the ultimate level of performance; in the skill–learning view any nonoptimal, atypical early experiences can potentially be compensated for later in development as the mechanisms for learning remain in operation in the same way; in the IS view atypical early experiences could have long-lasting effects because they could affect the specialization and localization of function, which may not be able to be altered later in life when there is less scope for plasticity. Recovery from nonoptimal atypical experience will relate to the degree of specialization already achieved for that region—if the region has become atypically specialized, there will be less scope for recovery than if the region is still relatively unspecialized when typical experience resumes.

There have only been a limited number of studies examining the effects of atypical early experience in humans. Several studies have examined the influence of early experience on processing of facial information. For example, Pollak and colleagues have found that perception of the facial expression of anger, but not other expressions, is altered in children who experienced the culturally atypical environment of parental abuse. Specifically, they report that, compared to nonabused children, abused children show a response bias for anger (Pollak, Cicchetti, Hornung, & Reed, 2000), identify anger based on less perceptual input (Pollak & Sinha, 2002), show altered category boundaries for anger (Pollak & Kistler, 2002) and show atypical responding to anger in tasks of selective attention (Pollak & Tolley-Schell, 2003). These results suggest that atypical frequency and content of their emotional interactions with their caregivers results in a change in the basic perception of emotional expressions in abused children. Specifically, in this case children seem to show a hypersensitivity to anger, a finding also supported by ERP

studies with this population (Curtis & Cicchetti, 2011; 2013; Pollak, Cicchetti, Klorman, & Brumaghim, 1997; Pollak, Klorman, Thatcher, & Cicchetti, 2001), even in infants as young as 15 months (Curtis & Cicchetti, 2013). However, whether these effects would disappear with sufficient exposure to a normative environment, as the skill–learning view might predict, or reflect more lasting effects, as the IS view might predict, is not clear.

ERPs in response to facial expressions of emotion have also been assessed in institutionalized children who have experienced extreme neglect and deprivation. In one such study, ERPs to happy, sad, angry and fearful faces were recorded in 5- to 31-month-old institutionalized Romanian children and a similarly aged group of Romanian children who had never been institutionalized (Parker et al., 2005a, b; but see Moulson, Fox, Zeanah, & Nelson, 2009). Institutionalized children showed overall decreased amplitudes of the N170 Nc and PSW responses and, unlike controls, did not show a decrease in Nc amplitude with age. These results appear consistent with the notion that institutionalized children show brain hypoactivation, as well as a distinctive trajectory of brain development. Institutionalized children also showed an absence of hemispheric lateralization for the positive slow wave, whereas controls showed a larger response over the right hemisphere. Moulson and colleagues (Moulson, Westerlund, Fox, Zeanah, & Nelson, 2009; Moulson et al., 2009) also found evidence of hypoarousal in institutionalized children who displayed smaller amplitudes for the P1 bilaterally and the N170 and P400 components over the right hemisphere compared to the never-institutionalized group. Latencies for the P1 and P400 components were also longer among the institutionalized children relative to the never-institutionalized children, thus chronicling slower information processing in children with a history of institutionalization (Moulson, Fox, et al. 2009; Moulson, Westerlund, et al., 2009). After these initial baseline measures were collected, the institutionalized children, as previously noted, were randomly assigned to be placed into foster care or to remain in the institution. At 30 and 42 months of age, ERPs were once again collected during presentation of emotion face stimuli. Results revealed that P1 and P400 amplitudes of children in the foster care group were midway between the institutionalized and never-institutionalized children, suggesting that foster care may be normalizing these components. Interestingly, neither age at placement in foster care nor duration of time there contributed to this outcome. Overall, the results of these studies suggest brain hypoarousal and lack of hemispheric specialization.

Interestingly, while the ERP studies just described provide evidence of cortical hypoarousal, fMRI studies highlight subcortical hyperactivation during face processing in previously institutionalized children. Children who were previously institutionalized have larger amygdalas than those who were never institutionalized and also show hyperactivation of the amygdala to fearful faces and distractor stimuli, but not neutral faces (Tottenham et al., 2011; Figure 16.1). While control children showed no difference in amygdala activation for fearful compared to neutral faces, previously institutionalized children showed greater activation to fearful faces, a pattern similar to that observed in adults and suggesting precocious development of the amygdala. Moreover, while control children showed a coupling of amygdala activity with medial prefrontal cortex activity, previously institutionalized children failed to show this link, a finding consistent with other reports showing reduced white matter between these two areas in this group (Govindan et al., 2010).

Sensory deprivation is another form of atypical early experience. Some studies have investigated the perception of facial information in children who experienced deprivation of patterned visual input in the early months of life due to bilateral, congenital cataracts. These patients were tested years after their cataracts were removed and they were fitted with contact lenses (i.e., years after visual input had been restored), thus any effects of the few months of deprivation following birth would likely be absent or very minimal according to the maturation or skill–learning views. However, investigation of these patients reveals persistent deficits in selective aspects of face processing. One study found that patients showed impairments in matching facial identity over changes in viewpoint (and tended to show an impairment in recognising identity over changes in emotional expression), but performed normally on tests of lip-reading, perception of eye gaze and matching of emotional expressions (Geldart, Mondloch, Maurer, de Schonen & Brent, 2002). A second study demonstrated that this difficulty in processing facial identity may be due to deficits in processing the spacing among facial features, since patients performed normally in discrimination of faces that differed only on individual features (e.g., mouth) but they were impaired in discrimination of faces that differ only in the spacing of the features (Le Grand et al., 2001; see also Le Grand, Mondloch, Maurer, & Brent, 2003, 2004). This was not due to a general impairment in perception of spacing of features, as they performed normally in discriminating non-face patterns whether they differed by the shape of the features or the spacing of the features. These patients also show impairments in holistic

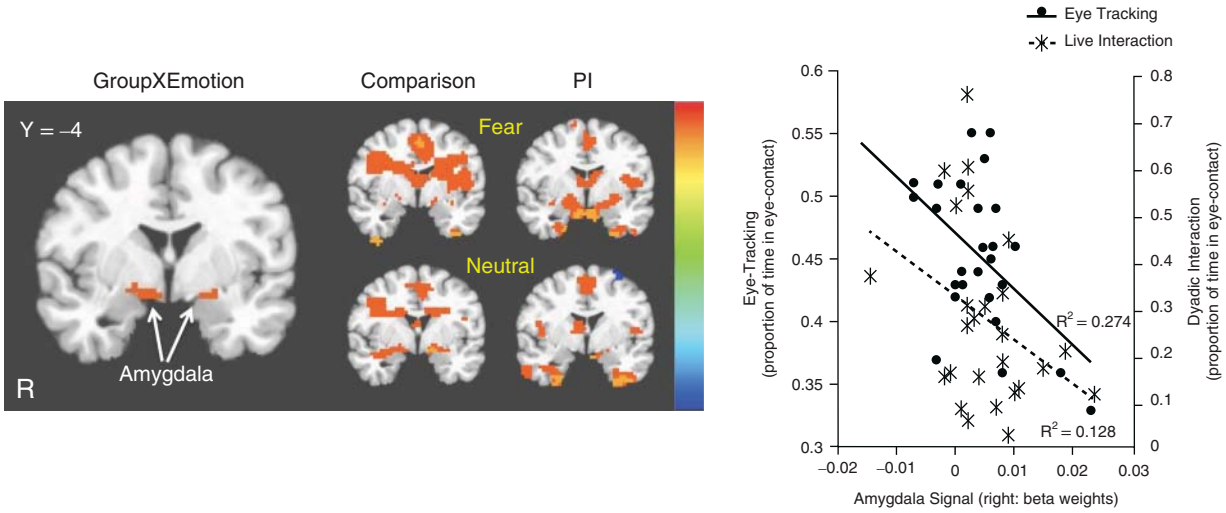


Figure 16.1 Elevated amygdala response to faces following early deprivation. Amygdala signal change to fearful faces and eye contact. Left: A Group × Emotion interaction showed that PI children exhibited greater signal change than the comparison group for fearful faces. Middle: Post hoc *t* tests showed the results for each emotion relative to baseline separately for PI and comparison children. Right: BOLD signal (beta weights) from the group × emotion amygdala ROI was inversely correlated with amount of eye contact children made during eye-tracking (proportion of frames spent looking at the eye region). *Note:* The negative correlation between amygdala signal change and eye-contact during a live dyadic interaction (proportion of time making eye contact) was not statistically significant. See footnote 1. *Source:* From N. Tottenham, T. A. Hare, A. Milner, T. Gilhooly, J. D. Zevin, & B. J. Casey, Elevated amygdala response to faces following early deprivation, *Developmental Science, 14,* 190–204, 2011.

processing of faces, which actually allows them to perform better than controls on certain tasks where optimal performance relies on ignoring the whole and focusing on the features (Le Grand et al., 2004). The fact that these impairments persist even after years of visual input to compensate for the early deprivation is not consistent with the maturational or skill–learning views but is consistent with the IS view that early atypical experience may have long-lasting consequences.

Early experience has also been studied in the context of language development. One question of interest here has been, when adults acquire a second language, does this activate the same network as the primary language learned during childhood (consistent with the skill learning and maturational views) or does it activate a different network (consistent with IS view). Some early reports indicated that bilinguals who learned their second language late showed different activations for the two languages while bilinguals who learned their second language early showed overlapping activations (e.g. Kim et al., 1997). However, subsequent studies have suggested that level of skill in the second language, rather than age of acquisition, is the more important variable in determining the degree of overlap of regions activated by the two languages (e.g., Chee et al., 1999; Dehaene et al., 1997; Perani et al., 1998;), a result consistent with a skill–learning view.

A slightly different approach has been taken by other studies, where the question of whether early exposure to a language has any long lasting consequences has been asked. These studies have examined adults who early in life were exposed to one language for a few months or years but then were removed from that language and exposed to another one either because of adoption or emigration. One study examining Korean adults adopted between 3–8 years of age by French families found no evidence that the subjects could identify Korean words and no differences in brain activation to Korean compared to unknown languages, but did find that the brain activation for French, while it involved the same basic network, was more widespread in the native speakers than the adoptees (Pallier et al., 2003). Another study found that children who had heard or heard and spoken Korean during the first years of life later showed benefits from this limited early experience in learning Korean during the first-year of college (Oh, Jun, Knightly, & Au, 2003). These lasting effects of limited periods of early exposure are difficult to explain in the maturational or skill–learning view points, but can be explained in the IS view as the effects of early experience on the specialization of the areas involved in processing speech and language.

TRANSLATIONAL CONSIDERATIONS

Understanding the dynamic transactions between risk and protective factors plays a central role in building developmentally informed models of prevention. Through increasing the relative balance of protective factors over risk factors, there is greater potential for normalizing developmental trajectories and achieving adaptive outcomes that minimize the emergence of psychopathology. The interactive specialization viewpoint emphasizes the importance of understanding these factors and intervening from early on in development, as with age the brain becomes increasingly specialized and has potentially less scope for alteration. The interactive specialization viewpoint also highlights the need for understanding brain–behavior networks: altering one aspect of risk or protection can have wide-ranging, and potentially unintended, implications for other brain areas or behaviors as a result. Overall, the interactive specialization view points to the importance of (1) obtaining brain–behavior profiles from early in development rather than focusing only on disorders once they are manifest; (2) focusing more on understanding differences in interregional neural interactions in developmental disorders rather than searching for localized, discrete lesions; and (3) moving away from studying only deficits in young children with disorders to also understanding brain-behavior relations for skills in which atypical participants perform as well as typically developing participants (see Johnson, Halit, Grice, & Karmiloff-Smith, 2002). Viewed from an interactive specialization perspective, key diagnostic features of some developmental disorders may even be the result of the brains adaptive responses to an atypical early internal environment (e.g., noisy processing resulting from poor-quality synaptic function), rather than the result of an ongoing neural pathology (Johnson et al., 2015).

CONCLUSIONS

In this chapter, we outlined three perspectives on human functional brain development that have different implications for our understanding of developmental disorders, and the effects of brain damage over the first years of life. By the maturational view, genetic disorders could potentially lead to focal cortical damage, and consequently to selective cognitive, motor, or perceptual disorders. Symptoms of these disorders would be first become evident at the normal age of maturation of the regions concerned. However, reviews have concluded that there are few, if any, human developmental abnormalities of genetic origin that affect only one or two specific regions of cortex (e.g. Johnson et al. 2002). Rather, structural and functional neuroimaging usually reveal subtle but widespread differences in the brains of groups with developmental disorders. Relatedly, claims of domain specific cognitive deficits in syndromes such as autism and Williams syndrome have been challenged, and replaced with hypotheses about different styles or modes of processing (e.g., Karmiloff-Smith, 1998). Finally, it is difficult to explain reports of recovery of functions following early brain damage by the maturational view, without recourse to additional special mechanisms of plasticity.

According to the interactive specialization view, developmental disorders of genetic etiology will often involve disruption of the typical biases and interactions between regions that give rise to adult patterns of cortical functional specialization. By this view, subtle symptoms may be evident from birth, but these will become compounded through the infant's abnormal interactions with its environment. While there are currently few behavioral studies of developmental disorders during infancy, those that do exist suggest discontinuities in the patterns of behavioral and cognitive deficits through postnatal development. For example, in one such disorder, Williams Syndrome, adults present with behavioral deficits in number tasks, but show surprising proficiency in some aspects of language. One study investigated whether this pattern of specific deficits is also observed in Williams Syndrome infants, as would be expected if they have a damaged innate module for number. Standard infant paradigms for assessing number and object naming skills were used with toddlers with Williams Syndrome (Patterson et al. 1999). The toddlers did not show the same behavioral profile as observed in adults with the syndrome, indicating that the profile of behavioral deficits in developmental disorders can change during ontogeny, and that it is not appropriate to characterize such deficits in terms of damage to specific domain-specific modules. In another example, while children and adults with autism show impairments in face processing, infants at risk for autism show a clear orienting response to faces in an array of distracters irrespective of their later outcomes (Elsabbagh et al., 2013) but show atypically quick processing of objects (McCleery et al., 2009). From the interactive specialization perspective it may also be easier to understand recovery of function following early damage since the same mechanisms that ensure specialization during the typical developmental trajectory could also ensure a different pattern of specialization.

The IS view includes a series of predictions about the role of brain specialization and interactions among brain regions in development. Studies reviewed in this chapter support the specific predictions regarding increased specialization and localization of brain response and changes in the dynamics of brain networks with age. However, fewer studies directly address some of the view's other predictions, including the idea that specialization scales up from regions to networks, and that changes in the degree of brain plasticity with functional specialization and localization, and these remain important avenues for further research.

FUTURE DIRECTIONS

Further assessment of the three perspectives on human functional brain development presented in this chapter will require more improved methods for non-invasive functional imaging methods, and more detailed computational models that generate predictions about both neuroanatomy and behavior. With regard to new functional imaging methods, forms of optical imaging (Near InfraRed Spectroscopy—NIRS) offer promise for studying brain function in human infants (Lloyd-Fox et al., 2013). Like functional MRI, NIRS can measure changes in blood oxygenation in the brain that occur following the activation of groups of neurons within an area. While currently lacking the spatial resolution of functional MRI, the method does not involve the exposure to high magnetic fields, noise, and motion sensitivity that make using functional MRI with typical awake infants difficult.

From the age of 6 or 7 years MRI can be routinely used. Recent advances in MRI analysis techniques will allow the investigation of both structural and functional changes during development. The recent studies using diffusion tensor imaging (DTI) to track the development of white matter demonstrate its usefulness for understanding not only structural brain development but also the functional development of brain networks underlying emerging cognitive skills. For example, one study used DTI together with fMRI to study the development of the frontoparietal network involved in working memory. These authors found that DTI measures of frontoparietal white matter correlated with the fMRI response in closely located gray matter in the superior frontal sulcus and inferior parietal lobe. These results suggest that development of white matter could account for increases with age in level of activation of frontoparietal gray matter observed during working memory tasks (Olesen et al., 2003).

While the basic method of EEG/ERP has been available for over 50 years, recent advances in technology and analysis methods have opened up new possibilities for the exploration of brain function in infants and young children. In one such advance, high-density recording systems along individual structural MRI or age appropriate templates allow for improved source localization of ERP activity (Bathelt et al., in press). In another advance, the relation of bursts of high-frequency oscillatory activity in the brain to cognitive and perceptual tasks has begun to be studied in infants, children, and adults (e.g., Csibra et al., 2000). In one experiment, high-frequency oscillations occurred during periods of time when previously visible objects became occluded, potentially providing a neural correlate of object permanence (Kaufman et al., 2003). Advances in wireless EEG/ERP recording systems may also facilitate acquisition of data in a wider range of context and populations.

In order to relate findings on brain structure and development to those on perceptual or cognitive functions we need the explanatory bridge that can be provided by computational modeling of neural networks. While there are currently major efforts to use connectionist models to explain aspects of typical and atypical cognitive development (Thomas et al., 2011), very few of these efforts currently allow interpretation of data from functional imaging or neuroanatomy. These types of investigations will provide information regarding which of the three viewpoints best describes the developmental process, and whether the answer to this question depends on the cognitive domain under study and the context in which it develops. Whatever the outcome of these investigations, a better understanding of functional brain development in human infants and children may have profound consequences for educational, clinical, and social policies (see Casey & de Haan, 2002).

While advances in neuroimaging acquisition and analysis methods will undoubtedly be important for future work in developmental cognitive neuroscience, it will also be useful to better integrate these measures with other levels of analysis, including psychosocial and environmental-contextual ones. The interactive specialization view discussed in this chapter is compatible with this view, but in the future it might be informative to relate its predictions about developing brain-behavior relations with other broad frameworks for understanding child development. For example, multiple levels of analysis (Cicchetti, 2010) and relational developmental systems (Overton & Lerner, 2012) are broad frameworks that emphasize the bidirectional nature of brain–behavior development and

highlight the need to consider biological measures within the broader psychological context in holistic rather than componential, reductionistic way. It is difficult for individual researchers to tackle the many levels of analysis, and thus these approaches also emphasize the future need for collaborative research on a broader scale.

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CHAPTER 17

The Neurodevelopmental Process of Self-Organization

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Increasingly, the science of human development may be informed by a neurodevelopmental analysis, with questions of psychological growth and adjustment seen in the new light of the evidence on neural mechanisms. Moreover, advances in understanding the epigenetic regulation of neural development have shown that genetic control of the brain's growth and differentiation is achieved only as life experiences shape the epigenetic regulation of gene transcription. The traditional controversy of nature versus nurture no longer makes sense when genetic control is so strongly mediated by epigenetic regulation, which is, in turn, highly responsive to the child's life experiences.

Considering the new insights into the neural basis of psychological development, we will suggest that it is now possible to consider a single theory in which mind and brain are studied as the same process. Within this theory, the control of neural activity and the resulting growth and differentiation of the brain's connectional architecture can be understood as identical to the child's processes of motivation and self-regulation of psychological development. The process of life is achieved through the ontogenetic coordination of disparate genetic influences required for biological self-organization. The growth and differentiation of the brain are exactly isomorphic to the differentiation and refinement of the self in the context of social relations.

Before outlining this integrated analysis, we first describe the neurodevelopmental process in biological and then in psychological terms. At the biological level, self-organization of the human brain involves not only the instructions of the genome, but the epigenetic modification of those instructions to adapt the genetic code to two related factors: (1) the organism's adaptation of feedback to developing systems to achieve coherent self-organization (classically termed *canalization*); and (2) the organism's ongoing adaptation to environmental conditions (the process of *plasticity*). The recent progress in understanding the molecular mechanisms of gene transcription has offered a new understanding of how each child's genetic endowment must be shaped by the set of life experiences that determine the *epigenetic* control that actualizes the code of the genome. Epigenetic control is highly active in the specification of cells from their pluripotent stems in embryonic differentiation. It remains important in the development of the central nervous system, even after many organ systems have become fully specified. Importantly, epigenetic mechanisms have been discovered to be particularly important to the regulation of neural plasticity that is in turn essential to the child's growth and adaptation.

The implication of these findings is that genetic variations are common, and their impact on the child's

development are strongly regulated—for better or worse—by life experiences. Furthermore, because it is cumulative, and captured in the progressive differentiation of neural architecture, neural plasticity is not necessarily reversible. As a result, both genetic defects and early experiences create patterns of neural and psychological self-regulation that may impair future developmental adaptation. The task is then to appreciate how the genetic and epigenetic variation experienced by a given person interacts with the major control systems regulating neural plasticity and the normal developmental process. These control systems engage mechanisms of activity-dependent synaptic organization that are isomorphic with the process of behavioral learning. In this way, the development of psychological function through motivated learning can be seen as identical to the growth and organization of the brain.

Having outlined this biological model of organismic development in the first section, we then consider the psychological process of developmental self-regulation in the second section. Increasingly, researchers are characterizing the control of development not just through fixed biological maturation, nor just through family and social influences as separate factors, but through the child's capacities in self-organization that mediate the synergistic interactions between social influence and maturational competence. Consistent with this theoretical account, we review evidence that mental disorders can be understood not as diseases but as variations in normal psychological development. Not only the familiar personality disorders, but the spectrum forms of more severe psychopathology such as autism, schizophrenia, and manic-depressive illness are found to vary more or less continuously in the normal population. Recent research on disorders of motivation and self-regulation in psychopathology is providing insight into the ways these disorders diverge from optimal development.

At a certain level of dysfunction, of course, mental disorders may show a precipitous and progressive decline from normal adaptive function. Furthermore, certain genetic neurodevelopmental disorders, such as fragile X syndrome or Rett syndrome, produce unique and discrete neurodevelopmental defects (Day & Sweatt, 2011). Nonetheless, we suggest that theoretical insight into the nature of psychopathology may be advanced most importantly through studying the way that normal developmental controls become disordered, leading to psychopathological outcomes. Many of the genetic variants of critical developmental control mechanisms, including dopamine, serotonin, or oxytocin, produce variations in temperament that are largely within the normal range. Given these general insights, we can appreciate that psychopathology is often a developmental phenotypical, rather than invariant genotypical, result.

Recognizing the continuity of psychopathology with normal neural development can lead to a theoretical analysis of the normal developmental control processes—of motivation, learning, and self-regulation—that become exaggerated or dysfunctional in persons with psychopathology. At the same time, these developmental control processes still confer important capacities for adaptation. In a third and final section of this chapter, we attempt to provide a theoretical analysis of normal developmental self-regulation that helps to explain how the biological vectors of growth and differentiation of the brain are shaped—often irreversibly—by the interaction between the child's social support systems and the child's personal capacity for self-regulation in the context of life stress. We propose that the major syndromes of externalizing and internalizing in psychopathology can be understood as exaggerations of normal neurodevelopmental mechanisms of self-organization. These control mechanisms first shape the embryonic formation of dorsal (externally directed, visceromotor) and ventral (internally directed, viscerosensory) divisions of the telencephalon, and then continue to determine neural activity-dependent specification of cerebral architecture after birth, in the key developmental processes of learning and memory consolidation.

Thus the mechanisms of psychological development that mediate cognitive maturation, through processes of motivation and self-regulation, are literal neurodevelopmental mechanisms, reflecting the ongoing morphogenetic processes shaping the connectional architecture of the brain. Neural morphogenesis begins in the embryo, and it continues to organize the brain's growth throughout life. Cognition is neural development, continued in the present moment.

Because the child's capacity for self-regulation determines the activity-dependent specification of neural plasticity—and thus the growth and differentiation of both cortical and subcortical networks—it controls the process of *self-organization* in a literal sense. In this sense, the personality is not a disembodied mental construct, but the individual's unique pattern of brain development. To understand the epigenetic specification of the endophenotype—the individual child—it is necessary to consider not just the genetic coding for traits, but the full context of developmental self-regulation that shapes the growth of the brain and the personality within the complex social and cultural environment.

The essential mechanisms of self-regulation in normal development can be described broadly as externalizing and internalizing. These mechanisms reflect the operation of the major, dorsal and ventral, divisions of the limbic system, respectively. Through close integration with neocortical representational capacities, the dual limbic circuits in turn elaborate more primitive controls on neural activity emerging from the striatum, diencephalon, and brain stem. In normal brain development, externalizing and internalizing reflect ways the child comes to regulate arousal to mediate the relation between self and world. In the personality disorders, externalizing and internalizing can be understood to reflect exaggerated variations on the normal neurodevelopmental process. More severe forms of psychopathology reflect more severe deficits in the balance of biological control systems that shape the emergence of the self in the context of social relations. For both biological and psychological levels, the self is an important theoretical construct for understanding the control of the developmental process, whether the specific issue is maintaining arousal, acting with confidence, or actualizing the knowledge of self gained in interpersonal interaction.

THE NEURODEVELOPMENTAL PROCESS

The scientific study of biological development over the last century has ranged between more holistic conceptual approaches, such as those based on observation of morphogenetic differentiation of the embryo (Waddington, 1942), and more molecular approaches, such as those that attempt to explain development in terms of biochemical mechanisms (Gould, 1977). In the modern molecular approach, the goal has been to identify specific genes and their transcription processes that code for the organism's traits and their developmental emergence. The dominance of the molecular approach in the modern era has been bolstered not only by the discovery of DNA and the sequencing of the genome, but the success of the neo-Darwinian explanation of evolution. In this account, evolution has progressed first through random genetic mutations that alter the course of ontogenesis, and second through natural selection for those rare molecular defects that prove adaptive (Gould, 1977).

Modern biological approaches to psychopathology have been dominated by the molecular rationale. A widespread assumption seems to have been that once the genetic cause of a specific mental disorder is discovered, it will be treatable through a molecular or pharmacological manipulation. Supporting the molecular approach, there have been important findings of neurodevelopmental disorders such as Rett syndrome in which specific genetic defects lead to symptoms of psychopathology. Furthermore, the alleles or variant forms of certain genes, such as those that regulate serotonin, can be found to be relevant to individual differences in the cognitive and emotional features of mental disorders such as anxiety and depression (Talati, Weissman, & Hamilton, 2013; Tops, Russo, Boksem, & Tucker, 2009).

Without doubt, the remarkable capacity for detailed examination of an individual's genome is presenting powerful new tools for understanding the genetic basis of psychopathology. Researchers naturally take the obvious empirical approach, questioning whether a genetic cause can be found for a disorder such as autism or psychopathy. In psychopathy, for example, genes that regulate oxytocin function have been shown to have specific alleles or variants that are associated with a trait of callousness and non-emotionality that is an important component of psychopathic behavior (Dadds et al., 2009; Moul, Killcross, & Dadds, 2012). Because oxytocin has been found to mediate interpersonal closeness and attachment in both human and animal studies (Tops, van Peer, Korf, Wijers, & Tucker, 2007), this research provides an important implication of a genetic predisposition for psychopathy. Yet the scientific understanding of the role of specific genes—such as those that regulate oxytocin—in psychopathology will require more than an empirical cataloging of associations. Instead, each biological factor must be understood in relation to its contribution to the human developmental process. For example, oxytocin seems to facilitate interpersonal bonding through *suppressing* the anxiety responses of the amygdala (Tops et al., 2007); if anything, psychopathy results from too little anxiety rather than too much. Rather than accepting a simple single cause, scientific insight into developmental factors such the role of oxytocin in psychopathy will require a careful analysis of the interaction between interpersonal bonding and self-regulation in the course of development.

Genetic Control of Ontogenesis

Thus reasoning from genes to psychopathology requires interpreting development. Genes do not control traits of the phenotype; rather, they control the process of ontogenesis that translates from the genome—through what we now appreciate as a complex epigenetic process—into the phenotype of the individual.

Modern biology has recognized the theoretical significance of genetic control of ontogenesis in understanding the mechanisms of evolution. Rather than selecting

for traits, as was often implicitly assumed in the neo-Darwinian modern synthesis of evolutionary theory, genes control the process of ontogenesis, which may result in adaptively significant traits, but only as a result of the developmental process (Gould, 1977). Certain Mendelian traits require little complexity in ontogenesis to be manifested. However, the more complex traits, such as those that regulate behavior and psychopathology, show *reduced penetrance* as a result of complex and probabilistic influences on the phenotype.

Another complicating factor in understanding the genetic control of human development is the extended human juvenile period, during which epigenetic factors operate over long intervals to shape the phenotype. Whereas most mammals achieve maturity in a few months or a few years, humans achieve the capacity for competent adult behavior only after two decades, and even then the capacity for independence is sometimes unclear. Importantly, rather than a defect of the species, human neoteny or developmental delay seems to have been a progressive factor in the evolution of intelligence in a cultural context (Gould, 1977). Recent research in developmental neuroscience continues to illustrate the key role of extended human neoteny.

Cortical thinning is an integral process of brain maturation in adolescence, appearing to reflect a critical stage of synaptic pruning to achieve the adult brain architecture (Mutlu et al., 2013). Remarkably, adolescents whose cortical thinning continues through late adolescence might be thought to suffer from lower intelligence or even mental retardation. Instead, these late bloomers are eventually found to achieve higher levels of intelligence than those who complete cortical thinning earlier (Mutlu et al., 2013). This observation is consistent with the notion that neoteny allows an extended period of juvenile neural plasticity that is integral to human intelligence. Equally remarkably, the individual variability of cortical maturational rate suggests that human evolution has resulted in considerable heterogeneity in the degree of neoteny in current populations.

Epigenetic Canalization and the Cybernetics of Self-Organization

Thus genetic factors creating risk of psychopathology operate through a course of human ontogenesis that is inherently protracted. For example, as the child's development proceeds over decades under the influence of family and cultural influences, a genetic variant influencing serotonin or oxytocin sensitivity does not code for a psychopathological trait, but rather for a regulatory process that shapes the course of ontogenesis, during which the many social and environmental influences interact with the child's capacity for effective self-organization. Genes must therefore act through mediation by the more organismic controls on ontogenesis classically described as *epigenesis* (Waddington, 1942).

At the molecular level, epigenetic mechanisms regulate the process of gene expression. The transcription of the DNA code to specific proteins is modified through processes within the cromatin sheath around the DNA. At each gene locus, epigenetic molecular mechanisms such as methylation act to suppress the transcription of specific genes (Sweatt, 2013). Remarkably, these epigenetic mechanisms may influence not only the immediate transcription process but also may become ingrained in the daughter cells following cell division, thereby propagating through the developmental process for the life of that individual (Sweatt, 2013). It is now clear that environmental influences that shape the epigenetic mediation may include not only chemical insults but also emotional and social experiences of the young animal. Considerable evidence suggests that early experiences, such as maternal licking and grooming for rat pups (Meany, Braike, & Gratton, 2002), may shape a host of biological developmental mechanisms, including epigenetic, hormonal, and immunological processes (Sweatt, 2009).

The increasing evidence of the importance of epigenetic mechanisms has led to renewed theoretical interest in the more global organismic processes that modify the translation from genetic code into the structure and function of the phenotype. In Waddington's (1942) analysis of epigenesis, the genetic control of embryogenesis was seen to require organismic mechanisms that maintained a kind of systems-level continuity in ontogenesis, even in the face of varied discrete effects of specific gene transcriptions. Waddington used the term *canalization* to describe how essential functional channels of embryonic development (*canals*) are maintained, even as the landscape of gene transcription takes on widely varying shapes in response to the code of an individual genome. Waddington's organismic approach is consistent with classical theoretical models of developmental psychology such as those of Jean Piaget (1936/1992) or Heinz Werner (1957), in which broad principles of organismic differentiation and integration establish the context for regulating the developmental process. In modern terms of control theory, the process of canalization can be seen as a *cybernetic* process, in that the individual molecular mechanisms of genetic specification are controlled by feedback within the organ

systems that operate to maintain functional continuity in development.

The essential role of canalization and organismic self-organization can be seen in the process of embryonic neural morphogenesis. In the dominant mode of genetic feed-forward control, the genome provides processes of gene expression that create trophic chemical gradients that guide neuronal migration (Rakic, 2009). An example is the gradient of Emx2 that guides neuronal migration in the dorsal telencephalon. In the modern cookbook model of gene instructions providing the building blocks of life, interlocking patterns of gene expression and trophic factors set the stage for building the brain through each stage of morphogenesis. However, this *feedforward* control from gene expression must be continually modified by *feedback* control from the outcomes of neuronal processes themselves. For example, the migration of precursor pyramidal (spindle) cells from the periventricular region to the cortex is followed by differentiation of middle layers of the cortex under control by the arrival of afferents from the thalamus to layer 4 (Marin-Padilla, 1998). Thus the network's success in functional organization at a systems level guides the connectivity at the molecular synaptic level. Once the gross architecture of the cortex is established—along the lines of the major gradients of trophic factors—it is the spontaneous activity of the neuronal networks themselves that determines the differentiated synaptic connectivity that is retained to support function (Hanganu-Opatz, 2010; Marin-Padilla, 1998).

Embryonic Plasticity and Learning

Activity-dependent self-organization of neural networks in the process of cerebral development is thus becoming increasingly understood at multiple levels, from the epigenetic regulation of gene expression to the ongoing modification of synapses by the consolidation processes of memory and learning. Epigenetic mechanisms are particularly active in the embryo, as cells differentiate from their generic pluripotent forms. These mechanisms are less important once cells achieve the target forms that will remain set throughout development (Sweatt, 2009). However, in the mammalian brain, whereas other organ systems become relatively stable after birth, the brain's continuing developmental process retains a high degree of epigenetic plasticity. This suggests a kind of continuing active development that is described as *neuroepigenetics* (Sweatt, 2013). A remarkable and fundamental realization is that neuroepigenetic mechanisms regulating cerebral architecture are closely related to the neural plasticity that determines functional learning and memory of the juvenile animal.

In general, *neural plasticity* involves changes in brain wiring as a function of experience, wherein inputs, either from the neuronal milieu or external world, influence the functional synaptic architecture. The regulation of neural plasticity is inherently a developmental, self-organizing process, progressing from a somewhat undifferentiated abundance of synaptic connections in the *blooming* stage of the infant brain to a selective differentiation in the *pruning* stage through retaining only those connections that are activated by functional inputs, a process of connection pruning (Greenough & Black, 1992; Greenough, Black, & Wallace, 1987; Markham & Greenough, 2004). Within this overall activity-dependent differentiation, there are critical periods for the development of normal sensory functions, such as vision and audition, when plasticity is prepared for the normal pattern of sensory experience. As a result of critical periods of sensory plasticity, sensory deprivation at these periods impairs the development of sensory maps that are required for normal perceptual functions. Initially, the maps established during these *experience-expectant* periods (Greenough & Black, 1992) were then found to be resistant to change, leading to the concept of a critical period when neuronal adaptation was active. The sensitive neural plasticity during these critical periods was found to be mediated by specialized molecular mechanisms—including neuroepigenetic mechanisms—that are active during these critical periods (Hensch, 2005). The result of successful sensory plasticity is an established neural structure that represents, more or less accurately, the state of the external world (or, more specifically, the effect of the external world on the sensory receptors) that forms the brain's interface with the world during ontogenesis.

Although plasticity is reduced after the critical period, it remains in some form to support learning and reorganization of function in the adult brain. For example, even after the critical period, if sensory inputs are radically altered, such as by amputation of digits, massive reorganization can be induced even in primary sensory cortex (Merzenich et al., 1984).

Neural plasticity thus first appears as a neurodevelopmental mechanism, serving to organize the brain's connectivity in the process of embryological differentiation. It then remains as a neurodevelopmental mechanism after birth, during the critical periods in which environmental interaction adapts the brain's networks to the information in the unique environment that the organism discovers. Finally, neural plasticity continues to support

the brain's functional differentiation throughout life, in the general process of learning and adaptation of behavior and cognition to environmental demands.

Although these developmental stages of neural plasticity have important unique features, in studying humans it may be important to appreciate the continuity in the developmental process, through which the process of ontogenesis involves neural self-organization not only in the differentiation of neural circuitry through mesencephalic, diencephalic, and telencephalic stages of embryonic differentiation, but also through the continued refinement of connectional architecture that marks the maturation of the brain through childhood, adolescence, and adulthood. Psychological development thereby reflects an unbroken continuity with neural development throughout the process of ontogenesis. Cognition and memory continually consolidate the learning process within the fine synaptic architecture of experience (Tucker & Luu, 2012).

This continuity of neurodevelopmental mechanisms can be appreciated by considering how perceptual experience begins with the structure of cortical maps formed in the fetal brain. Recent progress in developmental biology has shed light on the patterns of gene expressions that serve to differentiate cortical maps at specific embryonic stages (Rakic, 2009). Initially, *protomaps* are established in the ventricular zone (VZ). Protomaps appear through the formation of patterning centers. These patterning centers reflect the gradients of expression of neurotrophic molecules across the developing ventricular zone. During the course of fetal development, the patterning centers become more refined as discrete regional genes are expressed. As cells migrate from these centers within the VZ to the cortical plate to form the cortex, their chemical identity, achieved in many cases through epigenetic differentiation, allows these neuronal precursors to attract the appropriate afferents from the relevant thalamic nucleus, as well as to send reciprocal efferents to the same nucleus. It is important to note that the patterning mechanisms that operate on the developing cortex are highly dependent on the morphogenetic mechanisms of subcortical structures. In many ways, the structure of the differentiation of the cortex and telencephalon (limbic structures, basal ganglia) is explained by the earlier developmental differentiation of more primitive subcortical (mesencephalic, diencephalic) levels of development.

After neuronal precursors migrate to the cortical plate, laminar differentiation occurs in two stages. The first stage is the establishment of pyramidal cells in middle layers of the cortex, under control by brainstem norepinephrine projections, with extensive apical dendrites reaching to the superficial cortical layers. A second stage is the development of additional cell types, including the granular layer IV that receives thalamic inputs (Marin-Padilla, 1998). These thalamic inputs are themselves critical organizing influences on the network patterns established in the six layers of the mammalian cortex. Although sensory input will be critical to the differentiation of sensory (and motor) maps in the older brain, much of the protomap is established through spontaneous activity of the developing brain itself, creating a kind of intrinsic activity-dependent cortical map development of the visual, auditory, and somatosensory cortices (Hanganu-Opatz, 2010). An example is the organization of ocular dominance columns. These are not specified during protomap development, yet they are created in the spontaneous activity of primary visual cortex (and thalamus), and are already established prior to the development of functional inputs (photoreceptors) from the retina. Although there are important intrinsic, experience-independent, mechanisms shaping cortical maps, regulated by the expression of specific neurotrophic factors (Rakic, 2009), evidence for the role of spontaneous, self-organizing activity is rather impressive in each species examined.

As reviewed by Hanganu-Opatz (2010), electrical recordings of fetal brain activity show remarkable similarities between species (rats, nonhuman primates, and humans), with periods of activity alternating with periods of little to no activity. The electrical activity is made up of low amplitude higher frequency (higher than delta) activity, superposed on larger amplitude, low frequency (delta and slow wave) activity. As the brain matures, the oscillatory activity increases in duration and amplitude; the quiet periods are correspondingly reduced.

Neural Oscillations, Learning, and Critical Periods

This alternating pattern of electrical activity provides clues to the self-organization of developing networks as it responds to at least three factors. The first is patterned input from sources that are intrinsic to the embryonic brain. In this way, the brain's self-organization is activity-dependent even before much environmental interaction. One of the intrinsic sources is spontaneous inputs from premature sensory organs (such as the retina lacking photoreceptors). Another is spontaneous input from receptors (such as whiskers in rat) that are responsive to initial sensory input but are not organized by mature behavior such as exploration. Removal of sensory receptors reduces the amplitude of the spontaneous electrical activity, but does not eliminate it. This is because there are at least two other contributing mechanisms.

Subcortical regulatory inputs, particularly the nucleus basalis (a source of cholinergic input), appear to be critical. It is well known that cholinergic activity regulates oscillatory electrical activity in the adult brain, but it also regulates spontaneous oscillatory function in the developing brain. In the embryonic brain, cholinergic input is concentrated to the subplate, a layer located above the VZ and intermediate zone but below the cortical plate. This zone eventually develops into layers II through VI of the mature cortex. Cholinergic input synchronizes the activity of cells within the subplate zone (Luhmann, Kilb, & Hanganu-Opatz, 2009). Removal of the subplate eliminates the spontaneous electrical activity noted above. Removal of the subplate also prevents normal cortical organization, such as development of ocular dominance columns. This impairment appears due to the disruption of coupled activity between incoming thalamic inputs and cells in layer IV, and also to removal of inhibitory mechanisms controlled by GABAergic interneurons. In many ways, these same balances of excitatory and inhibitory influences are found to regulate oscillatory activity and cortical plasticity in the adult brain. Specifically, GABAergic interneurons establish oscillatory activity that synchronizes activity from multiple sources in the developing brain. These same GABAergic interneurons serve to synchronize (temporally organize) information exchange among brain regions in the adult brain (Buzsáki, Logothetis, & Singer, 2013).

At birth, sensory systems mature, and the infant's developmental plasticity shifts to the more restricted critical period previously noted as experience-expectant (Greenough & Black, 1992). Environmental inputs then have strong fine-tuning influences on the functional architecture of a given sensory region, such as primary visual cortex (Toyoizumi et al., 2013). During this stage, maturing GABAergic interneurons enable suppression of spontaneous activity and enhancement of external signals to influence synaptic wiring. As noted by Toyoizumi et al., this cortical plasticity mechanism, along with the hierarchical organization of brain regions, can also mechanistically (in addition to other factors, e.g., myelination maturation gradients) account for the maturation gradient (i.e., the later maturation of secondary, association, and limbic regions) of postnatal, experience-dependent brain development.

Some degree of the embryonic and maturational plasticity is retained in the adult animal, such that reorganization of sensory cortices after the critical period occurs in response to alteration of environmental inputs (e.g., Merzenich et al., 1984). The alteration of inputs seems to destabilize the network function of the established circuitry, and thus changes the excitatory–inhibitory balance of the network. As shown by Arckens and colleagues (Arckens et al., 2000), the unresponsive visual cortex that results from retinal lesions shows a reorganizational pattern that starts with an increase in excitability (as indexed by glutamanergic activity) and concordant decrease in inhibitory activities (indexed by GABAergic activity) 2 weeks after the lesion. Over time, GABAergic activity within the reorganizing cortex is gradually restored. Understanding neuropathology and rehabilitation may require a developmental analysis: the change in excitatory-inhibitory balance as a function of altered sensory inputs with the lesion, and subsequent restoration of GABAergic activity, both reflect a similar progression as occurs during the critical period. These processes may be pathological responses to lesions, but when balanced they appear to be the permissive mechanisms that enable cortical reorganization in the adult brain. In fact, Hensch (2005) suggests that a better understanding of the molecular mechanisms that regulate the excitatory–inhibitory balance during development may help explain a variety of psychological disorders that occur when this balance is poorly regulated.

Organismic Mechanisms of Network Self-Regulation

Insight into the specific subcortical circuitry regulating excitatory-inhibitory balance has been provided through the theoretical model of thalamocortical dysrhythmia (Llinas, Urbano, Leznik, Ramirez, & van Marle, 2005). Specific layers of the cortex are connected with both specific and nonspecific thalamic nuclei, including the cholinergic thalamic reticular nucleus. The normal oscillatory control over cortical activity (and thus activity-dependent neural plasticity) may become imbalanced through lesions such as deafferentation, leading to dysrhythmia reflected by abnormal cortical delta and theta activity. Llinas and associates have emphasized that abnormal cortical delta and theta oscillations may be observed in psychiatric as well as neurological disorders. There are interesting parallels between self-organizing mechanisms in embryological differentation of the cortex, regulated by specific neuromodulators, and the thalamocortical dysrhythmia of neuropathology, regulated and dysregulated by the same neuromodulators and intrinsic properties of network synchronization. If they could be extended to explain more complex disorders of cerebral maturation, these parallels may present the opportunity for understanding developmental psychopathology in more explicit neurophysiological terms.

Cortical wiring after critical periods must involve more than just the statistical properties of environmental

inputs, as translated into neuronal signals that influence excitatory–inhibitory dynamics of local circuits. Self-regulation is not just passive reception and organization. Rather, self-regulation, if it is truly adaptive, considers the behavioral relevance or significance of events encountered as an organism explores and learns about the world. It is during this time that the organism learns, and environmental consequences can have adaptive or deleterious effects on cortical organization. By its nature, such organization should involve more than the dynamics of local circuits; it must also include systems that have multiple inputs, from wide ranging areas of the cortex and subcortical structures that are known to be responsive to the internal states of the organism, such as limbic cortices, and project widely throughout the brain. The neuromodulator systems, particularly the cholinergic and monoaminergic systems, are primary candidates for gating the impact of sensory inputs on cortical reorganization. Their projections are widespread, but their influence on cortical plasticity can be highly specific. It has been shown that cholinergic and catecholaminergic (norepinephrine, dopamine) control can facilitate cortical reorganization both at critical periods and later in development (Hensch, 2005). Merzenich and colleagues show that tonotopic maps in primary auditory cortex can be extensively re-organized after the critical period when auditory stimuli are paired with stimulation to the cholinergic nucleus basalis (Kilgard & Merzenich, 1998) or the ventral tegmental area (VTA), a subcortical dopaminergic cell group (Bao et al., 2000). The plasticity of reorganization appears to be spike-timing dependent: the pairing of stimulus presentation with stimulation of the NB and VTA must follow the parameters of learning (i.e., the stimulus must predict stimulation of the NB or VTA) otherwise changes in cortical maps will not be obtained. Bear and Singer (Bear & Singer, 1986a) showed that cholinergic and norepinephrine inputs are critical to cortical plasticity; their removal from the primary visual cortex severely affects cortical plasticity during the critical period. In some way, the local influence of these neuromodulators on cortical plasticity is not just the regulation of activity diffusely; this influence must operate on the local excitatory–inhibitory mechanisms, but exactly how remains to be elucidated.

PSYCHOLOGICAL SELF-REGULATION

Thus the neurophysiology of developmental self-organization is regulated by global controls on plasticity and activity-dependent synaptic specification. In ways that are still not fully understood, the most important global controls may be those regulating arousal of the brain, provided by the monoaminergic and cholinergic brainstem and forebrain neuromodulator systems. These are complemented by the more detailed mechanisms of neural plasticity linked closely to the representational capacities of the cortex, and recognized as the integral operations of memory consolidation (Tucker & Luu, 2006). In psychological terms, these self-regulatory systems—both for global arousal and for representational plasticity—can be seen as integral to the characteristic patterns of arousal and reactivity described in research on temperament and personality. The theoretical challenge is to understand not only the alignment between specific neural maturational processes and specific psychological processes, but organismic patterns of self-representation and self-organization through which arousal and memory consolidation sculpt the individual personality.

There are interesting parallels between the specific corticolimbic networks regulating neuroembryonic differentiation for internal and external processing with the patterns of learning, memory consolidation, and self-regulation that can be described as introversion and extraversion (Tucker, & Luu 2012). In turn, these normal developmental variations can be understood to become disordered in the psychopathological dimensions of internalizing and externalizing (Achenbach, 1982). By reviewing current models of temperament and self-regulation in relation to psychological development in this section, we prepare for the final section in which we attempt to explain how the major dimensions of psychopathology can be understood as disordered exaggerations of what are fundamentally normal variations in the major dimensions of arousal regulation, memory consolidation, and thus neural self-organization.

Dimensions of Temperament

In his review of the literature, Nigg (2006, p. 398) pointed to a growing consensus that temperament and personality are closely linked: "Temperament is viewed as highlighting the psychobiological analysis of traits related to reactivity of core incentive-based neural systems and, in many contemporary models, also their regulation." This account aligns closely with Rothbart and Posner's (2006, p. 466) definition of temperament as "constitutionally based individual differences in reactivity and self-regulation, as observed in the domains of emotionality, motor activity, and attention."

Factor analytic models of temperament and personality have typically identified two to five major dimensions.

There is considerable agreement across the models on the two core affective-motivational dimensions. These dimensions have been referred to as positive emotionality and negative emotionality (Watson & Tellegen, 1985), surgency/extraversion and negative affectivity (Rothbart & Posner, 2006), approach and avoidance (Elliot & Thrash, 2002, 2010), and approach and withdrawal (Nigg, 2006). It is clear these are closely related to the classical personality dimensions of extraversion and neuroticism (Eysenck & Eysenck, 1985; McCrae & Costa, 1987).

Another related model is Gray's (1971) formulation of a behavioral activation system (BAS) and a behavioral inhibition system (BIS). Elliot and Thrash (2002, 2010) found that extraversion, positive emotionality, and BAS loaded above 0.80 on a single factor they termed approach, while neuroticism, negative emotionality and BIS loaded above 0.80 on a single factor they termed Avoidance. When considered in relation to the biological mechanisms of learning and self-regulation, these two opposing dimensions can be seen to form a primitive, reactive control cybernetic that guides behavior, as an organism is motivated to approach positive stimuli and withdraw from potential dangers.

Reactivity of the approach dimension is associated with surgency, extraversion, positive affect, impulsivity, reward sensitivity, behavioral activation, and externalizing behaviors. In contrast, reactivity of the avoidance dimension is associated with negative affectivity, fear, anxiety, withdrawal, anger, frustration, irritability, punishment sensitivity, behavioral inhibition, and internalizing behaviors. Together, these dimensions emerge as controls on learning and motivation that arise from the regulation of cerebral arousal (Tucker & Luu, 2007; Tucker & Williamson, 1984). At the level of learning and memory consolidation, the extraversion or approach dimension describes the motive bias of the dorsal corticolimbic system, whereas the introversion or avoidance dimension describes the motive bias of the ventral corticolimbic system (Tucker and Luu, 2012).

Most models of temperament include a third major dimension related to the ability to self-regulate these reactive tendencies through attention and voluntary control. This has been described as effortful control (Eisenberg, Spinrad, & Eggum, 2010; Rothbart, Sheese, Rueda, & Posner, 2011), or constraint (Depue & Spoont, 1986). A central component of effortful control is the ability to inhibit a dominant response and activate a subdominant one (Rothbart & Posner, 2006), thereby allowing effortful control to modulate both reactive approach/surgency and reactive avoidance/negative affectivity as a function of cognitive evaluation. Read et al. (2010) elaborated a neural network model of personality structure and dynamics, in which approach and avoidance systems provide basic trait biases that become elaborated into more specific motives through the dynamics of psychological experience. Similarly, they include in their model a distinct control system that acts to inhibit or disinhibit baseline activations of the approach and avoidance systems. In contrast to a single higher level control system, Tops and associates (Tops et al., 2009) proposed two additional proactive systems that parallel and overlay the reactive approach and avoidance systems. Thus, building on primitive reactive cybernetics of the approach–avoidance systems, self-regulation comes under additional reflective, proactive regulation mechanisms. Together, both reactive and reflective control mechanisms continue to influence and guide an individual's cognitive and emotional processes and interactions with the internal and external world throughout life.

As reflected in the aforementioned Nigg (2006) and Rothbart and Posner (2006) definitions, temperament is generally viewed as having a genetic predisposition that is expressed in an infant's rudimentary approach and avoidance reactivity biases. These biases continue to influence attention, behavior, experience, and memory during development. When development is successfully organized, these control biases become increasingly differentiated and stabilized in interaction with more volitional self-regulatory mechanisms such as effortful control in the process of forming the child's developing self. In a meta-analysis of 152 longitudinal studies (Roberts & DelVecchio, 2000), the population cross-time correlation estimates (controlling for time interval of longitudinal study) of temperament and trait stability were lowest during early childhood (0–2.9 years = 0.31), increasing to 0.49 from 3 to 5.9 years, dropping slightly into preadolescence (6–11.9 years = 0.43) and adolescence (12–17.9 years = 0.43) and then increasing monotonically throughout adulthood and peaking from 50 to 59 years at 0.74. These correlations indicate considerable stability in temperament overall, alongside opportunities for malleability throughout life, particularly during periods of infancy and adolescence. These are of course the periods of maximal neural plasticity and thus developmental vulnerability.

From birth, individuals differ in their set points along the approach/positive affectivity and avoidance/negative affectivity continua. These differing set points manifest in differing reactivity to the environment in infancy when exposed to appropriate eliciting conditions. For example, Hane and associates (Hane, Fox, Henderson, & Marshall, 2008) found that infants who at 4 months of age displayed strong negative motor reactivity were later

assessed at 9 months of age as more avoidant, whereas those who displayed strong positive motor reactivity at 4 months expressed significantly more approach behaviors at 9 months. In a latent profile analysis of mother ratings of their toddlers' sociability, anger proneness, and activity level at four intervals over the course of 1 year, three profiles emerged: a fearful temperament; high in internalizing problems, an expressive temperament high in externalizing problems; and a typical temperament with well-adjusted behavior (Dekovic, Prinzie, & Asscher, 2010). In a study of 3-year-olds, de la Osa et al. (de la Osa, Granero, Penelo, Domenech, & Ezpeleta, 2014) similarly found a positive relationship of surgency–extraversion with attention-deficit/hyperactivity disorder (ADHD) and externalizing problems, and of negative affectivity with internalizing and emotional disorders. Adolescents who scored high on self-reported behavioral inhibition system (BIS) dimension, also scored high on negative affect, negative emotion regulation style, and anxiety (Balle, Tortella-Feliu, & Bornas, 2013).

From this research, high reactivity set points would appear to place children at risk for either externalizing or internalizing problems (Carver, Johnson, & Joormann, 2008). At the same time, a child's temperament cybernetics, along with effortful control, may provide modulatory, protective effects against maladjustment, depending on the match between the child's temperamental bias and the challenges of the environment. Both fearfulness and frustration are associated with the negative affectivity dimension of temperament, but fearfulness is typically expressed in internalizing, and frustration in externalizing, behavior. A primitive cybernetic analysis of the effect of the child's motive arousal would suggest that frustration may also be related to the surgency–approach dimension, through a reactive response to a blocked goal (Derryberry & Rothbart, 1997). Thus, individuals high in frustration may be high on dimensions of both negative affectivity and surgency, whereas fearful individuals are high in negative affectivity but low in surgency. Consistent with the importance of higher order cognitive regulatory skills, Oldehinkel et al., (Oldehinkel, Hartman, Ferdinand, Verhulst, & Ormel, 2007) found that degree of effortful control at 11 and 13/14 years of age, mitigated the effects of high negative emotionality—fearfulness and frustration—on both internalizing and externalizing problems, respectively (Oldehinkel et al., 2007). Thus, effortful control of negative emotionality can both modulate an internalizing response to fear, and counteract more primitive, reactive response to frustration.

Temperament and the Development of Self-Regulation

The achievement of self-regulation skills thus appears to depend on both the more primitive temperament cybernetics (internalizing and externalizing motive controls) as well as on more sophisticated, cognitive capacities in effortful control. The ongoing interaction with social and environmental factors from infancy onward must be seen to impact both the vulnerability to maladjustment and mental illness, and the resilience to overcoming developmental disorders. Rothbart et al. (2011) proposed that in infancy the regulation of reactive responses is primarily managed through controlling attention, initially guided by the primary caregiver (e.g., distraction from distress) and then through infant-initiated behaviors (e.g., looking away, self-soothing). In the first few months of life, an infant's behavior is characterized primarily by approach or surgency—either positively in smiling and laughing behavior, or negatively in the collapse of the positive affect state with expressions of distress and crying.

Anxiety and inhibitory capacity typically emerge only later in the first year of life, at which time these motives can provide an initial reactive regulation of the approach system. Interestingly, it was reported that infants at 3 months of age who experienced stress by overstimulation could be easily soothed by distraction with novel objects for long periods of time, whereas they began to habituate to caregiver distraction by 6 months (Harman, Rothbart, & Posner, 1997), perhaps through the maturation of increasing anxiety and internal control. Around this same age, infants begin to develop the ability to disengage their attention from distressing stimulation, an ability that stabilizes by the end of the first year and was associated with lower levels of negative affect at 13 months (Rothbart, Ziaie, & O'Boyle, 1992). Thus, it appears that cybernetic control between the approach and avoidance systems develops over the course of the first year, with the habituation bias of the approach system reducing the ability of sustained caregiver soothing at the same time as early self-regulation is enabled by engagement of the avoidance system and the infant's rudimentary ability to withdraw attention from negative stimuli. Factor analysis of parent-report scales of infant temperament identify this as orienting/regulation, a dimension with loadings from scales of low intensity pleasure, cuddliness, duration of orienting, and soothability (Gartstein & Rothbart, 2003). The important theoretical insight is that affective processes are not epiphenomena, but are integral to the motive controls that shape developing cognition and behavior.

At about 3 years of age, a higher level of self-regulation, termed Effortful Control, begins to emerge, appearing to rely on the toddler's developing executive attention system of the frontal and anterior cingulate cortices (Posner & Rothbart, 2009). Factor analysis of the parent-report Children's Behavior Questionnaire (CBQ; Rothbart et al., 2001) shows that scales of inhibitory control, attentional focusing, low intensity pleasure, and perceptual sensitivity load onto the dimension of effortful control (Rothbart, Ahadi, Hershey, & Fisher, 2001). High effortful control is associated with lower levels of negative affect and better adjustment. As it supports increasing cognitive capacity in self-regulation, cognitive control seems to become a protective factor against the development of psychopathology. Components of executive attention, such as the engagement of the anterior cingulate and medial frontal cortex in responding to errors or unexpected outcomes, appear as early as 7 months (Berger, Tzur, & Posner, 2006). Nonetheless, continued development leads to continued sophistication in the ability modify behavior (Jones, Rothbart, & Posner, 2003), as well as to articulate the anatomical connections of the frontal cortex to extended networks for behavioral control well into adolescence (Fair et al., 2009). Grosbras et al. (2007) suggested that it may be the immaturity of interregional connections of frontal cortex that makes it difficult to self-regulate in the face of peer pressure in early adolescence.

Considerable developmental evidence links both the child's reactivity and capacity in early orienting of attention to the subsequent development of executive attention and effortful control. Kochanska and Knaack (2003), for example, found that the development of greater effortful control in children was associated with lower initial reactivity in both anger and joy but greater reactive inhibition to an unfamiliar environment as toddlers. Citing Shulman et al.'s (2009) finding in adults that a novel object appears to activate the executive control network to supplement the attentional orienting network, Rothbart, Sheese, Rueda, & Posner (2011) speculated that the caregiver's presentation of novel objects to an infant may serve to exercise the development of the executive network required for effortful control.

Whereas high reactive inhibition may be associated with subsequent development of higher effortful control, both approach/impulse and avoidance/constraint control mechanisms remain integral to personality and shape the child's flexibility in responding to life challenges. Block and Block (1980) distinguished between ego-control, a reactive inhibitory control over impulsive approach, and ego resiliency, a flexible response to changing situational demands and challenges. This analysis emphasizes the importance of the dynamic balance between impulsivity and constraint for adaptive behavior and adjustment, as well as the role of socialization in shaping this flexibility. Healthy, well-adjusted individuals tend to be high in ego-resilience, with moderate levels of ego-control. They can respond adaptively in varied situations, have high social competence, and are neither overimpulsive nor overconstrained. Individuals with low ego resilience coupled with ego overcontrol tend to exhibit highly constrained emotions, anxiety, and withdrawal, while low ego resilience coupled with ego undercontrol is characterized by impulsive behavior and externalizing behavior problems.

Thus, the ego control construct reflects reactive temperament dimensions, with ego undercontrol descriptive of an individual high on the approach–surgency dimension, and ego overcontrol descriptive of individuals high on the avoidance dimension. In both cases, there is an imbalance in adaptive cybernetics, and inflexibility leading to poor adaptation. In contrast, the more proactive, reflective self-regulation of effortful control characterizes an ego-resilient individual (Rothbart & Posner, 2006). In a recent longitudinal study, Causadias, Salvatore, and Sroufe (2012) found that ratings of ego resiliency, but not ego control, at 3–4 years and 7–9 years of age were strongly predictive of healthy adjustment and of the development of both internalizing and externalizing problems in adolescence and adulthood.

The importance of environment and parenting on the development of self-regulation has received considerable attention. As noted above, parents may scaffold children's emerging self-regulation, exercising the higher-level attention networks engaged in effortful control. They may also provide important modeling of either reactive or reflective self-regulation. However, the interaction between parenting and self-regulation may operate through neurodevelopmental mechanisms as well. In a recent study on the development of self-regulation, Ursache et al. (Ursache, Blair, Stifter, & Voegtline, 2013) found that, in infants with low emotional reactivity, there was no relationship between emotional regulation in infancy and subsequent executive control at 4 years of age, as if these infants had only modest self-regulatory challenges. However, in infants with high emotional reactivity, those who also exhibited high-level regulation skills (orienting, avoidance) had better executive control at 4 years of age than those who exhibited poor regulation skills during infancy. Importantly, the highly reactive infants with high regulation came from homes with positive parenting. Drawing upon a theoretical model

of biological sensitivity to both context and the stress response, Ursache et al. (2013) hypothesized that supportive parenting of highly reactive infants helps to keep stress hormones at moderate levels, thereby promoting synaptic activity and neural plasticity in the prefrontal cortex, whereas negative parenting and adverse environments lead to excessive levels of stress hormone, inhibit prefrontal cortex development, and promote strong, reactive limbic and midbrain responses to perceived threat.

The disruption of attachment and socialization processes between mother and child has been shown to have an important impact on the occurrence of both internalizing and externalizing problems. Positive parenting (supportive, consistent and sensitive behaviors) and negative parenting (hostile, harsh, and negative control behaviors) have been shown to interact with a child's temperament to impact adjustment, but research findings have been mixed. In general, children high in negative affectivity and low in self-regulation appear to be most vulnerable to adverse parenting and environment, usually resulting in externalizing problems.

Kochanska et al. (Kochanska, Kim, & Boldt, 2013), however, showed that effects of adversity were not seen just in children with difficult temperaments. In a study of low-income families, toddlers who initially expressed a willing stance toward socialization, but whose mothers were inadequately responsive due to adverse circumstances, went on to display externalizing problems 10 months later. Adversity also led to internalizing problems, but without the mediating role of undermined maternal responsiveness.

Temperament, Self-Regulation, and Developmental Psychopathology

Because of human neoteny, temperament and self-regulation operate over a protracted developmental course, allowing parental and cultural influences to shape an individual's emerging self and its dynamic mediation between internal motives and needs and external relations. Most often, the developmental process is largely adaptive, with personality variations within the normal range and the experience of only transient adjustment challenges. In many cases, however, initial temperament vulnerabilities and adverse environment can tip psychobiological development toward more serious psychopathologies.

Clark, Watson, and Mineka (1994) distinguished four models relating temperament or personality to psychopathology. The *spectrum model* posits that disorders are extreme expressions of normal temperament development processes. The *vulnerability model* posits that temperament may predispose an individual to a disorder. The *pathoplasty model* suggests that temperament may shape the course of a disorder without being a direct cause. Finally, the *scar hypothesis* suggests that experience of a disorder (e.g., anxiety) causes a change in personality (e.g., increased dependency). Clark and associates emphasize that these models are not mutually exclusive. Considering the development of the self through dynamic psychobiological processes, multiple causal models may interact.

To consider such an interaction, if a child with a more extreme temperament encounters chronic or acute adverse environments, the developmental process—and the resulting self—may become disordered. Vulnerability may be particularly acute during the early childhood and adolescent periods of rapid brain plasticity and reorganization. The developmental disorder involves imbalances in the neurophysiological systems of learning and neuroanatomical differentiation, with corresponding imbalances in the psychological structures of the self and social relations.

An example may be provided by the Ursache et al. (2013) study cited above on the effect of stress hormones on the prefrontal cortex and its role in self-regulation. The most pernicious disorders are those that lead to continued maladaptive responses, such that the developmental process itself results in severe psychopathology rather than adaptive self-correction. Thus, the very dynamics of the psychobiological development of the self may result in chaotic and degenerative feedback mechanisms that permit extreme forms of normal personality differences (spectrum model) to emerge through vulnerabilities (vulnerability model) in the epigenetic process, which may be further shaped by the evolving disorder (pathoplasty model), and be strongly and permanently influenced by highly adverse events and their maladaptive responses (scar hypothesis).

When considering the dimensions of self-regulation that mediate the child's response to vulnerabilities and environmental insults, the typical patterns of developmental psychopathology are sufficiently similar to patterns of temperament to suggest that psychopathology often reflects exaggerations of normal developmental mechanisms. In his influential application of factor analysis, Achenbach (1982) identified two broad clusters of childhood disorders, *externalizing* and *internalizing*. Externalizing problem behaviors are metaphorically described as directed toward others (e.g., hyperactivity, conduct disorder) whereas internalizing problems are described as directed inward (e.g., anxiety, depression). Krueger, Caspi, Moffitt, and Silva (1998) reported that a two-factor model of internalizing and externalizing best explained the relationship between 10 psychological disorders assessed at 18 and 21 years

of age. Specifically, depression and dysthymia, anxiety, phobias, and obsessive-compulsive disorder loaded onto internalizing, whereas conduct disorder, anti-social personality, and alcohol and marijuana dependence loaded onto externalizing.

In considering the development of these disorders, there is considerable empirical support and growing consensus relating externalizing and internalizing personality adjustment disorders to (1) an individual's set points (reactivity) on the approach and avoidance dimensions of temperament; (2) the interplay between these dimensions, and (3) the strength and flexibility of their cognitive self-regulation. In a longitudinal study of children at 6, 7.5, and 10 years, Eisenberg et al. (2009) found externalizing problems to be associated with low effortful control, high impulsivity, and negative emotionality. In contrast, internalizing problems were associated most strongly with low impulsivity and sadness (low approach).

Latent profile analysis of posttraumatic psychopathology revealed that subtypes of a disorder may also be distinguished by variations in temperament (Wolf, Miller, Harrington, & Reardon, 2012). Specifically, while high negative emotionality was associated with both an externalizing and internalizing subtype of posttraumatic stress disorder (PTSD), the externalizing subtype (antisocial, borderline, histrionic and narcissistic elements) was also associated with low levels of constraint (inadequate inhibition due to low anxiety). In contrast, the internalizing subtype of PTSD (with schizoid and avoidant elements) was additionally distinguished by low positive emotionality.

Using latent class analysis in a person-centered, rather than variable-centered, approach to studying the underlying structure of psychopathology, Olino et al. (Olino, Klein, Farmer, Seeley, & Lewinsohn, 2012) identified four major classes: 1) psychologically healthy, 2) externalizing, 3) internalizing, and 4) both internalizing and externalizing. The internalizing class was most likely to suffer from dysthymia, major depressive disorder, social phobia, specific phobia, separation anxiety, posttraumatic stress disorder, generalized anxiety disorder, and panic disorder. This group had higher negative and lower positive affectivity relative to the healthy group. Those in the externalizing class were most likely to meet criteria for conduct disorder, adult antisocial behavior, and substance abuse or dependency. They had higher levels of negative affect and disinhibited temperament compared to the healthy group, though it is unclear whether the disinhibited temperament scale reflects high approach–surgency reactivity or low effortful control. There was an increased probability across a wide range of disorders within the comorbid internalizing and externalizing class, with the exception of conduct disorder and adult antisocial behavior, which were found primarily within the externalizing class only. The comorbid class had higher negative and disinhibited temperament and lower positive temperament than the healthy class. Depression was the most pervasive disorder, significant in all individuals in the internalizing class, appearing in over 90% in the comorbid class, and in over 50% in the externalizing class. Olino et al. (2012) suggested that the high rate of depression in the externalizing class may have occurred because the externalizing problems contributed to repetitive failures, with depression as the eventual result (Burke, Loeber, Lahey, & Rathouz, 2005).

Nigg (2006) stressed the importance of considering multiple levels of analysis in examining the complexity of temperament developmental patterns and outcomes. These levels include behavioral response, psychological experience, neural systems, physiological reactivity, and genetic composition. Nigg considered both a spectrum and vulnerability model of psychopathology, but argued that a vulnerability model is more consistent in explaining a gene × environment interaction. He reviewed evidence on three externalizing disorders emerging in childhood, each of which appears to develop from two different pathways. Type 1 conduct disorder (psychopathy in adults) was found to be related to low withdrawal/fear (and its associated low reactivity to punishment) as well as low affiliation, which then is proposed to interfere with the development of conscience and socialization. In contrast, Type 2 conduct disorder was found to involve high approach, high negative affect/anger, and low reactive or effortful control, resulting in reward and sensation seeking with disregard for others or high reactive aggression. ADHD was found to involve low effortful control, particularly for the inattentive-disorganized symptoms, and very strong approach, as related to the hyperactive-impulsive symptoms. Finally, the influence of anxiety and depression resulted in a more complex pattern, where high withdrawal (avoidance) was associated with a general risk for internalizing behavior. This manifested in depression and generalized anxiety disorder (GAD) when accompanied by low approach and stressful events, and it manifested in GAD specifically when it was accompanied by low effortful control.

As Nigg (2006) pointed out, the failure to develop effective effortful control can contribute to many psychopathologies, depending on the reactivity set point on the approach and avoidance dimensions. The protective influence of high effortful control in psychopathology

underlines the importance of psychological flexibility in healthy adjustment (Kashdan & Rottenberg, 2010). Whereas reactive control is more likely to lead to overregulation and underregulation (Derryberry & Rothbart, 1997), the reflective control of executive processes affords flexibility in response to life events that brings resilience under adversity and adaptive psychosocial functioning. Consistent with this reasoning, King, Lengua, and Monahan (2013) found that in pre-adolescence both effortful control and impulsivity (high approach) were predictors of self-regulation, but that contextual risk factors were related only to the development of impulsivity, whereas positive adjustment was related only to increases in effortful control.

In a major longitudinal study of temperament at age 3 and the development of adult disorders, children who were classified as undercontrolled were more likely to develop a wide range of disorders by the age of 21, including antisocial personality disorder, alcohol dependence, attempted suicide (Caspi, 2000), and gambling disorders (Slutske, Moffitt, Poulton, & Caspi, 2012). Good attention control skills may also buffer children with high dispositional anger from developing externalizing problems (Kim, Deater-Deckard, Mullineaux, & Beekman, 2010). Carver, Johnson, and Joormann (2013) similarly proposed that an individual's emotional reactivity in the absence of cognitive control (reactive versus reflective control) increases vulnerability for either externalizing or internalizing problems. Carver, et al. described this vulnerability as *transdiagnostic vulnerability*. They emphasized that the emergence of the specific type of disorder will depend on an individual's temperament disposition (e.g., high incentive-approach temperament may lead to antisocial impulses). Results from their multiple regression analysis of a wide range of scales indicated that unchecked emotional reactivity was associated with a wide range of psychopathology tendencies, including borderline personality, suicidality, anger, hostility, aggression, and anxiety.

Mineka, Watson, and Clark (1998) proposed an integrative hierarchical model where each disorder is composed of general and unique components of varied weights. Thus, depression shares a common component of negative affect combined with a large specific component of low positive affect that distinguishes it from anxiety. Anhedonic depression is the purest form of this component, and positive affect is most strongly linked to the core symptoms of depression, namely anhedonia, dysphoria, and lassitude (Watson, 2009). This reasoning led to the development of the Inventory of Depression and Anxiety Symptoms (IDAS) for improved assessment of these conditions. Watson and Naragon-Gainey (2010) further argued that whereas social avoidance is indeed associated with low positive affect, it is more specifically associated with the low levels of the closely related personality dimension of extraversion, which encompasses sociability, ascendance, and fun seeking, in addition to positive affectivity.

There is also growing evidence that links temperament to the more extreme psychopathology of schizophrenia. Watson and Naragon-Gainey (2010) reviewed evidence that schizophrenia/schizotypy symptoms are related to both positive and negative affectivity, but in unique ways. Whereas negative affectivity is related to both positive symptoms (e.g., magical thinking, perceptual aberrations, suspiciousness) and negative symptoms (e.g., constricted affect, social aloofness), low positive affect is related most strongly to negative symptoms. Consistent with this observation, schizophrenics have also been found to experience an anticipatory pleasure deficit, leading them to engage in fewer pleasurable activities because they do not expect to enjoy them.

NEURAL CONTROL OF INTERNALIZING AND EXTERNALIZING

Even from the brief overview presented in the first section, it should be clear that a rich set of biological mechanisms regulate neural ontogenesis. These offer ways of explaining the isomorphic dimensions of biological and psychological self-regulation that are reflected in the development of temperament, personality, and psychopathology. Conversely, understanding the psychological challenges of developing the self in the flux of social interactions can help to clarify the context in which biological mechanisms regulate the plasticity of the brain's growth, with dysfunctional as well as adaptive outcomes.

Fusing the biological and psychological levels of analysis, we propose that the dimensions of internalizing and externalizing seen in personality and psychopathology also reflect the major modes of self-regulation in brain development. The embryogenesis of somatic and visceral systems of the brain is regulated differently by primitive control modes of internalizing and externalizing. Continuing in child development, these modes are integral to the internalizing of attention (applying perception and cognition to environmental constraints) and the externalizing of intention (applying perception, cognition, and action regulation to achieve personal goals). Furthermore, these modes of self-regulation are driven by the motives of avoidance—for internalizing—and approach—for externalizing. As we

now propose in this third section, these motives shape not only cognition and behavior but the specific mechanisms of arousal and activity-dependent plasticity that differentiate the major networks of the brain in ontogenesis.

When the motive mechanisms of growth are active and balanced, the development of the brain and personality is also active and balanced. When a bias appears toward one mechanism over the other, the result is the familiar individual differences in personality recognized as Introversion and Extraversion. When these modes of self-regulation are not only exaggerated but also disorganized, the result is the patterns of internalizing and externalizing that have been recognized in the more severe forms of psychopathology (Achenbach, 1982).

The Evolved Structure of Embryonic Development

The neural mechanisms of activity-dependent specification of cerebral development can be seen as mechanisms of self-organization, set in place by the foundations of neuroanatomical differentiation in the embryo, operating to specify the functional connectivity of the embryonic brain, and then continuing to shape the process of learning and self-organization as the child organizes the self in the context of the family, school, and community. As genetic variation changes the substrate for these neurodevelopmental mechanisms, whether through a mutation of a neuromodulator's receptor or a shift in the rate of cortical maturation, the result is imbalanced or ineffective patterns of self-regulation. Nonetheless, even problematic patterns of self-regulation must operate through the fundamental control systems that shape normal development. As a result, understanding psychopathology requires a developmental theory.

In this theory, the major dimensions of developmental self-organization can be understood to be identical with the major dimensions of motive self-regulation. The roots of these dimensions run through the multiple levels of the neuraxis, from the brainstem to the cerebral cortex, such that an evolutionary-developmental analysis is essential to appreciate their functional emergence as control systems for arousal, learning, memory consolidation, and cognitive self-control. The evolutionary-developmental perspective may be novel in psychological science, because our thinking about children is constrained to processes we assume are uniquely human. However, an evolutionary perspective is unavoidable when we consider the developmental anatomy of the brain, as we observe how the process of embryogenesis recapitulates the broad outlines of phyletic evolution (Figure 17.1).

The embryonic brain is first organized through a series of trophic biochemical gradients, before neurons are capable of the activity that organizes the developmental process (Coghill, 1929). As we saw in the first section, these gradients are now understood to be created through developmental patterns of gene expression (Rakic, 2009) that then frame the migrations of neuronal precursor cells, which then organize the architecture of the brain. This pattern of gene expression, migration, and architecture is formed developmentally, through the phyletic progression. Although the process of embryonic morphogenesis is clearly specified by the genome of the species, it involves a complex web of interactions and feedback control mechanisms that require extensive dynamic signaling and epigenetic controls within the individual brain. Even before neurons are active, neural morphogenesis involves patterns of self-organization that reflect primitive functional specialization of both visceral and somatic divisions of the nervous system, and both sensory and motor capacities within each division (Tucker & Luu, 2012). These primitive patterns of functional specialization can be seen as the phyletic developmental foundations of the neurodevelopmental mechanisms of internalizing and externalizing.

The self-regulation of experience and behavior throughout life must build continually on the vertically integrated hierarchy of the neuraxis, as capacities for intention (dorsal limbic) and attention (ventral limbic) integrate the representational capacities of the cortex, which are formed through the memory consolidation and action sequencing from limbic and striatal circuits, which depend in turn on the motive and arousal controls from diencephalic, midbrain, and brainstem projection systems. Because of these interdependencies of the developing neuroanatomy, a biological analysis of the developing mind can be informed by the phyletic architecture of the ontogenetic process, within which the evolutionary history of the organism is integral to a theoretical understanding of current development and function.

As more complex brains have evolved from simpler ones, the more complex circuitry has emerged through progressive mutations of the simpler ontogenetic programs. As a result, there is a continuity of the neurodevelopmental process across evolved levels that may be useful in understanding the continuity of control systems across the multiple levels (rhombencephalic, mesencephalic, diencephalic, and telencephalic) of the neuraxis in child development. The theme of internalizing and externalizing is a fundamental one that can be seen across these multiple levels.

For example, the fundamental input-output specialization—the dorsal organization of sensory functions and

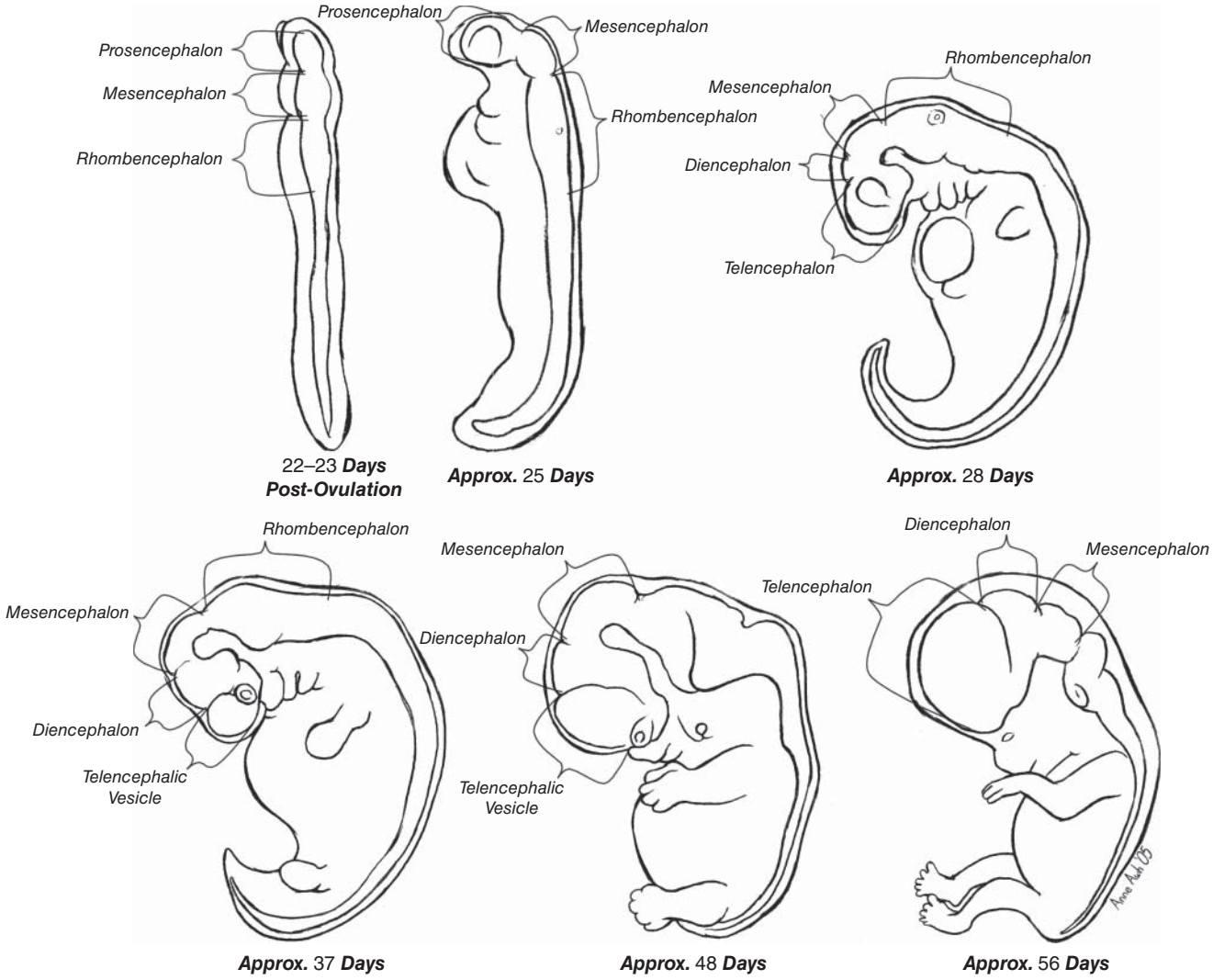


Figure 17.1 Stages in embryogenesis showing the progressive elaboration of more recently evolved (telencephalic and diencephalic) levels of the neuraxis.

the ventral organization of motor functions—can be seen as fundamental to the vertebrate plan. This duality is seen in the topography of the midbrain as examined by Ikemoto (2010). Building on the organization of the spinal cord, sensory processing is carried out in the dorsal regions of the brainstem and midbrain, where the norepinephrine and serotonin neuromodulator controls on arousal and development are particularly important to sensory functions. In parallel, motor processing is carried out in the ventral regions, with dopamine (and acetylcholine) providing arousal controls that are integral to action control and sequencing. The dorsal foundations of externalizing and ventral foundations of internalizing can already be seen at this level of analysis, with approach motivation, for example, reflecting the visceral control circuits of the dorsomedial networks of the ventral tegmental area, operating to set the motive basis for approach. This motive basis is then the foundation for the dopaminergic articulation of action in the more ventrolateral regions of the ventral tegmental area.

This general architecture is replicated in broad outline at the diencephalic and telencephalic levels. At the level of the striatum of the telencephalon, the approach motive appears to be regulated by ventral striatal areas. The articulation and sequencing of actions is then carried out by dorsal striatal (and pallidal thalamocorical) circuits (Ikemoto, 2010).

At the level of the dorsal and ventral divisions of the limbic system, the dorsal division (the Papez circuit of hippocampus, cingulate, anterior thalamus, septum, mammalary bodies) controls the externalizing mode of the approach motive. The dorsal neocortex integrates the holistic, spatial integration of sensory input to the ventral

striatal approach controls through septal and hypothalamic connections. These are the essential motive controls of extraversion, linking the positive motive of approach with the holistic sensory engagement of the environment (Tucker & Luu, 2012).

In contrast, the ventral division of the limbic system appears more important to internalizing, motivated by anxiety and avoidance. Centered on the amygdala, with its links to hypothalamic centers through the stria terminalis—and to perirhinal cortex and frontal lobe through the mediodorsal nucleus of the thalamus—the ventral limbic network organizes the ventral sensory, motor, and object cognition networks of the cerebral hemisphere through negative affect, providing the critical, aversive motive tone of introversion (Tucker & Luu, 2012).

Tucker and Luu (2012) built the case for this general model on several empirical foundations: the animal studies of neurophysiological circuits regulating learning, the effects of lesions on human self-regulation, and several consistent findings in recent neuroimaging research. Equally important is the theoretical explanation for why these global externalizing and internalizing controls are found in these cerebral systems. This explanation is provided by an evolutionary-developmental analysis, in which the continuity of dorsal and ventral divisions at multiple levels of the neuraxis can be observed in the process of embryogenesis. The roots of externalizing, including neuroanatomical, neurophysiological, and cognitive properties, can be traced to the evolution of the mammalian dorsal limbic and cortical networks from the pallium (three-layered cortex) of primitive vertebrates. Even more remarkably, the roots of internalizing can be traced to subpallial origins, the subcortical circuits of the basal ganglia that seem to have been incorporated into ventral limbic and cortical networks with the evolution of the 6-layered mammalian cortex (Tucker & Luu, 2012).

These primordial pallial and subpallial origins can be traced throughout the major phases in the embryogenesis of the mammalian cortex, reflected in the gradients of trophic factors guiding neuronal migration. On the one hand, the pyramidal neurons that define the dorsal cortex are formed through processes that reflect pallial origins. On the other hand, the GABAergic neurons and layer 4 projections that are critical to the ventral cortex are found to emerge from the subpallial substrate.

New tools for characterizing gene expression (Rakic, 2009) have allowed insights into the biochemical gradients that have long been apparent in embryonic neural differentiation and that now can be understood to define these developmental origins. For example, Emx2 shows not only a high concentration in the caudodorsomedial (back, top, center) regions of the developing mammalian (and human) brain, but a decreasing concentration in the rostroventrolateral (front, bottom, side) direction. In contrast, Pax6 is another key trophic factor, and it shows the opposite (rostroventrolateral to caudodorsomedial) concentration gradient. These global trophic gradients not only anchor the opposite anatomical poles to guide neural differentiation; they provide clues to the organization of the mammalian cerebral hemispheres in relation to the externalizing functions of the caudal (posterior) sensory networks, and the internalizing functions of the rostral (anterior) motor networks. In the development of the mammalian cortex and the limbic circuits that control it, these *somatic* sensory and motor networks are themselves organized in a complementary pattern with the dorsal and ventral *visceral* control functions of the dual limbic systems (Figure 17.2; Tucker & Luu, 2012). The rostroventrolateral

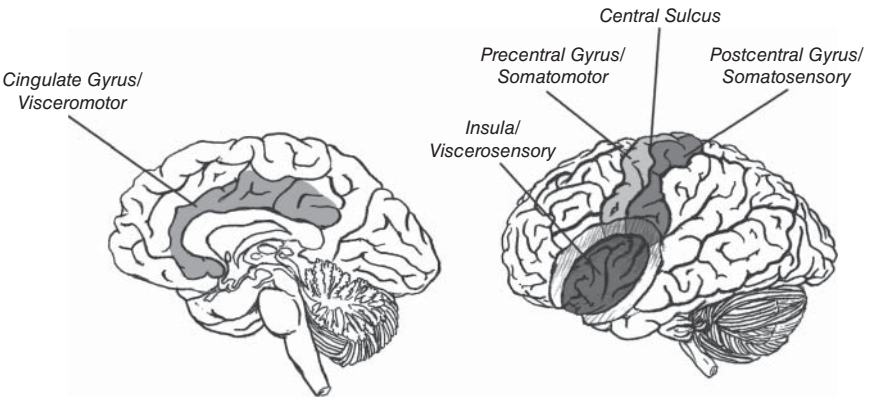


Figure 17.2 The visceromotor functions of the dorsal limbic networks appear to be balanced by the viscerosensory functions of the ventral limbic networks in motivating behavior. This balance complements a similar input–output balance between the somatic motor division of anterior cortex and the somatic sensory division of posterior neocortex.

to caudodorsomedial embryonic trophic gradient thus appears to combine and capture the complementarity of the somatic rostral-caudal dimension with the visceral ventral and dorsal dimension of cerebral organization.

Developmental defects of these major trophic factors provide clues to how these dimensions of the embryonic cerebral hemispheres emerged from their evolved roots in subcortical networks. For example, deficits in Pax6 are associated with impairment of rostroventrolateral structures of the hemisphere, specifically with the differentiation of the ventral corticolimbic anlagen, including the claustrum and piriform cortex (Rakic, 2009). Consistent with the ventral limbic distribution of these cortical structures, dopamine modulation is specifically impaired with disruption of Pax6 control. Consistent with the evolutionary-developmental reasoning outlined above, Butler and associates (Butler & Molnar, 2002) found that these Pax6 sensitive structures of the ventral cortex may have origins in unique striatal regions of the reptilian brain, specifically the anterior dorsal ventricular ridge, classically known as the external striatum (Nauta & Karten, 1970). Whereas the external striatum was the primary target of thalamic sensory and motor projections to the telencephalon in reptiles, the cerebral cortex (layer 4) became the target with the emergence of the 6-layered cortex in mammals. The obvious implication is that the incorporation of the external striatum into the neocortex was a key aspect of the transition to the mammalian 6-layered architecture. The fact that the granular layer 4 is highly developed in the ventral division of the mammalian cortex is additional evidence of the subpallial (striatal) origins of the ventral brain.

Thus both the trophic control of embryological differentiation and the evolutionary anlagen of the mammalian cortex provide clues that the internalizing mode of behavior control can be traced to the integral motive bias of subcortical (originally subpallial, striatal) control systems. In excessive internalizing, such as in obsessive-compulsive disorder, the routinized, stereotyped action and cognition appears to reflect the exaggerated operation of primitive basal ganglia (subpallial) habit and motor control circuits specifically.

Considering the opposite embryological trophic gradient, the high concentration of Emx2 in dorsal cortex is associated with the pyramidal architecture of the dorsal division of the hemisphere. The preferential projection of norepinephrine pathways to the dorsal brain may be integral to the expansive attention and feedforward motor control of dorsal limbic circuits (Tucker & Luu, 2012). In the morphogenetic process, norepinephrine modulation is critical to the formation of pyramidal neuronal connections (Marin-Padilla, 1998), suggesting that the role of norepinephrine in the regulation of attention and learning in psychological development is continuous with the more primitive regulation of neuronal differentiation and synaptic pruning in embryogenesis and critical periods.

Thus, even in the trophic stage of neural differentiation, before intrinsic activity-dependent neuronal function and connectivity can contribute to neural self-organization, there are primitive anlagen of internalizing and externalizing systems that can be recognized in the developmental process. Although we have only outlined these patterns briefly here, they provide clues to how the early ontogenetic self-organization of the brain proceeds along functional lines regulating the internalizing and externalizing modes of behavior that have been critical in guiding vertebrate evolution. For neurodevelopmental theory, evolution is thus as important an explanatory context as is the ontogenesis that recapitulates it.

At birth, the neurodevelopmental mechanisms shift from organizing the global architecture of the embryo and fetus to articulating fine synaptic structure in the child's learning and memory consolidation. At that point, the modes of internalizing and externalizing shift from their roles in anatomical differentiation to new roles in motivating the activity-dependent plasticity underlying the learning process. Based in primitive but fundamental patterns of motive arousal and experiential reactivity, the manifestations of variation in the neurodevelopmental control systems—with internalizing and externalizing as the primitive dimensions—can be seen to create individual characteristics of temperament and personality. These characteristics may be extreme, such as in autism, or more subtle, such as in the strong sense of engagement and agency seen in the extraverted toddler. In whatever form they take in the individual child, these outcomes of embryonic development can be seen to shape self-organization in postnatal life, where they must interact immediately with the requirements for effective social development.

Vertical Integration of Motivation and Learning

In classical neurophysiology, the visceral nervous system, organized around the limbic core of the cerebral hemispheres, was considered to be the motive basis for regulating both development and behavior (Yakovlev, 1948). Figure 17.2 illustrates that the posterior-anterior division between *somatic* sensory and motor systems in the neocortex is paralleled by the dorsal-ventral division between *visceral* sensory and motor systems in limbic circuits. For certain classical neuroanatomists (Coghill,

1929), the study of the origins of behavior was carried out through observing the first actions of the organism, revealed in synchrony with the progressive emergence of neuronal connections in embryogenesis. Following in this tradition, the dimensions of internalizing and externalizing can be seen as two integral modes of negotiating the self-world interchange, regulating both neural development and the organism's behavioral development through the interaction between the visceral limbic motives and the somatic neocortical sensory and motor representation of the interface with the world (Tucker & Luu, 2012). For humans, the core neurodevelopmental mechanisms continue to tune the vector of control between internal and external constraints, balancing the growth and maturation of the brain—and the self—within the complex demands of the social environment.

A key principle for understanding the control of activity-dependent plasticity—both in embryogenesis and in later learning—is the vertical integration of arousal control systems within multiple levels of the neuraxis (Figure 17.3). The motive control circuits of the limbic system regulate neural activity in support of memory consolidation through engaging the neuromodulator-specific arousal systems (norepinephrine, dopamine, serotonin,

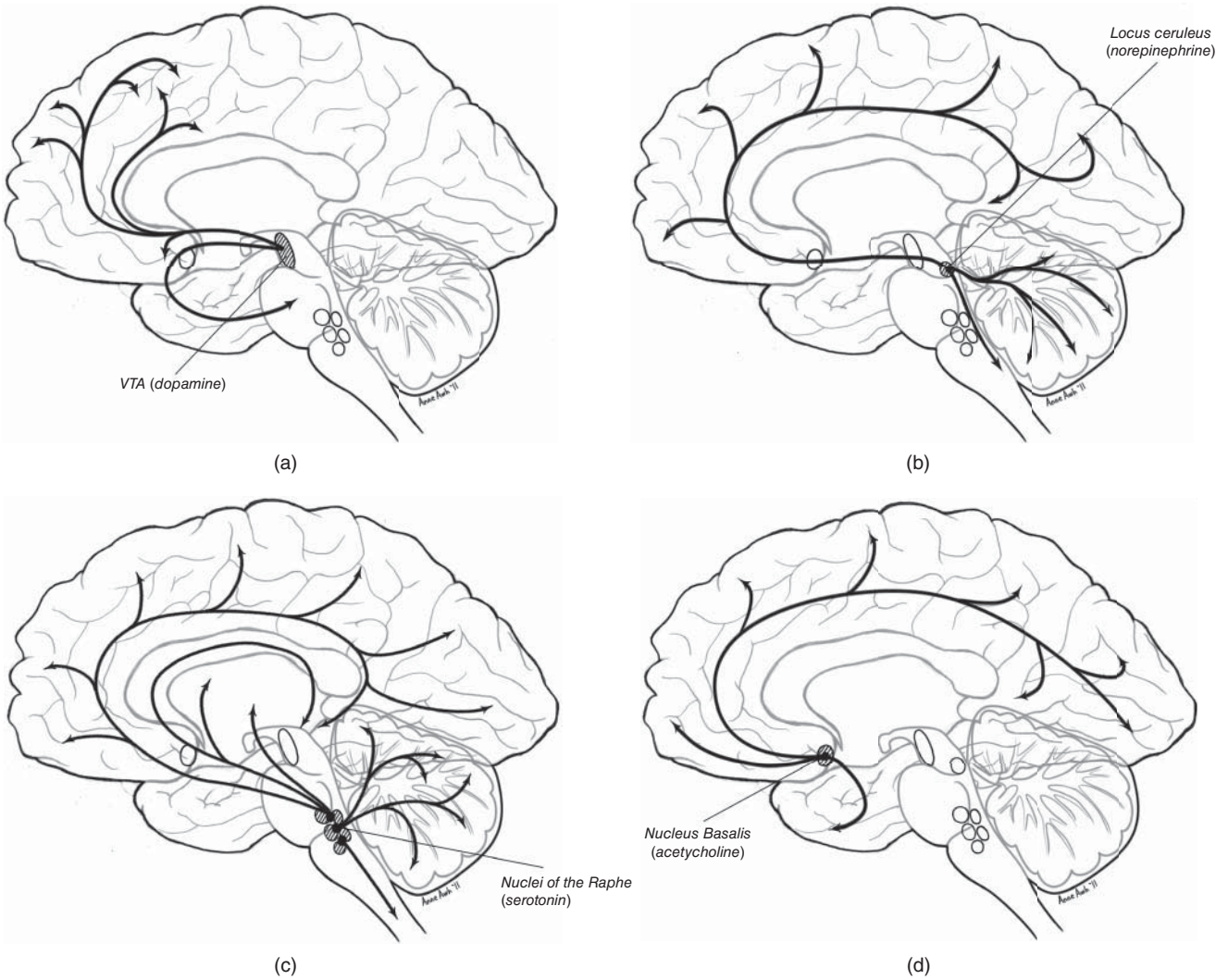


Figure 17.3 The regulation of arousal from brainstem neuromodulators is critical to neural self-regulation. The midbrain control of activation appears to be regulated by dopamine projections from the ventral tegmental area (upper left) and norepinephrine projections from the locus coeruleus in dorsal midbrain (upper right). The raphe nuclei in the lower brainstem (lower left) send widespread serotonin projections that appear to moderate the activating influences. The cholinergic projections are also critical to regulating neural activity, and include not only brainstem but forebrain control centers (lower right).

acetylcholine) of the brainstem (Cooper, Bloom, & Roth, 2002). In psychological terms, these arousal systems regulate both general alertness and more specific intensities of both emotional and cognitive processes (Tucker & Williamson, 1984). Beginning with the spontaneous neural oscillations of the embryo, the brainstem neuromodulator systems provide the initial basis for activity control, suggesting to developmental neuroscientists that these brainstem projection systems are critical to regulating not only the general substrate for neural growth and differentiation (Trevarthen, 1980), but the specific tuning of critical periods, such as in the formation of ocular dominance columns of the visual system (Bear & Singer, 1986b). It must be one of the key realizations in neuroscience that there is extensive if not complete overlap between the mechanisms of neural plasticity in brain growth and the mechanisms of neural plasticity in learning and memory (von de Malsburg & Singer, 1988).

Arousal is an important principle in psychological theory as well as neurodevelopmental theory. Although psychologists have often considered arousal as a unidimensional function that operates independently from the mechanisms determining the valence (good or bad) of affect or experience, the modern psychometric evidence suggests that there are two major dimensions of arousal that regulate psychological function. One is experienced as positive affect (PA) or *elation* and the other as negative affect (NA), including both *anxiety* and *hostility* (Watson & Tellegen, 1985). Considering the brainstem neuromodulator systems underlying these dimensions of affect/arousal (Tucker & Williamson, 1984), Tucker & Luu (2012) theorized that self-regulation of these affect/arousal dimensions is integral to maintaining not only motivational control, but the essential activity control that shapes synaptic differentiation in neural development. The PA system is integral to approach motivation; it facilitates the expansive attention and confident intention that motivate learning under conditions of success. The NA system is integral to avoidance motivation; it facilitates focusing attention on potential dangers and the tonic vigilance required under conditions of threat. Thus, the motive regulation of approach and avoidance in cognition and behavior is simultaneously the regulation of modes of neural activity that shape the connectional architecture of the developing brain.

The early notion of the reticular activating system of the brainstem (Moruzzi & Magoun, 1949) can now be differentiated into specific control systems, each of which plays a specific role in the self-regulation of affect, attention, intention, and cognition. It makes sense psychologically that avoidance motivation would be associated with symptoms of internalizing, and that approach motivation would be associated with symptoms of externalizing. But it is useful to examine the cerebral architecture for higher level control of motivation and arousal to understand exactly how these biases of the self-world orientation are regulated, and what this has to do with controlling neural development.

We have proposed that the primary differentiation between internalizing and externalizing is found in the functional differentiation between ventral and dorsal divisions of the limbic system (Tucker & Luu, 2012). Both these divisions regulate neural activity in part through their control over diencephalic (hypothalamic and thalamic), midbrain (ventral tegmental, collicular), and brainstem (pontine and lower brainstem) systems. The subcortical control of approach motivation in the mammalian brain has been outlined in Ikemoto's comprehensive integration of research on self-stimulation and local self-administration of drugs (Ikemoto, 2010). Many neuroscientists have accepted a fairly simple model of reward being controlled by the mesolimbic dopamine system. In turn, many cognitive neuroscientists have assumed this model explains the fMRI findings of ventral striatal (nucleus accumbens) hemodynamic activity under conditions of approach in human studies. However, Ikemoto points out that, although they are critical to motor readiness, learning, and habit formation, the dopamine circuits are *not* involved in the experience of pleasure, thus contradicting the typical notion of a dopamine reward system in drug use. Furthermore, in Ikemoto's review, the literature on the regions and circuits supporting self-stimulation and self-administration points to a complex subcortical network, involving not only the ventral striatum (including olfactory tubercle) but also the septal area of the limbic system, the supramamillary nucleus of the hypothalamus, and the ventral tegmental area of the midbrain. Ikemoto emphasizes that these are the linked subcortical controls of the limbic system. The integrated function of these limbic, striatal and midbrain networks, and not just mesolimbic dopamine, are critical to organizing approach behavior with reference to fundamental visceral regulatory functions (Figure 17.2).

At a higher level, the subcortical controls on approach motivation reviewed by Ikemoto (2010) may be aligned to what Tucker and Luu (2012) consider to be the dorsal limbic system. This dorsal limbic system was originally described by Papez as the circuit connecting the cingulate cortex to the anterior thalamus, septum, hippocampus,

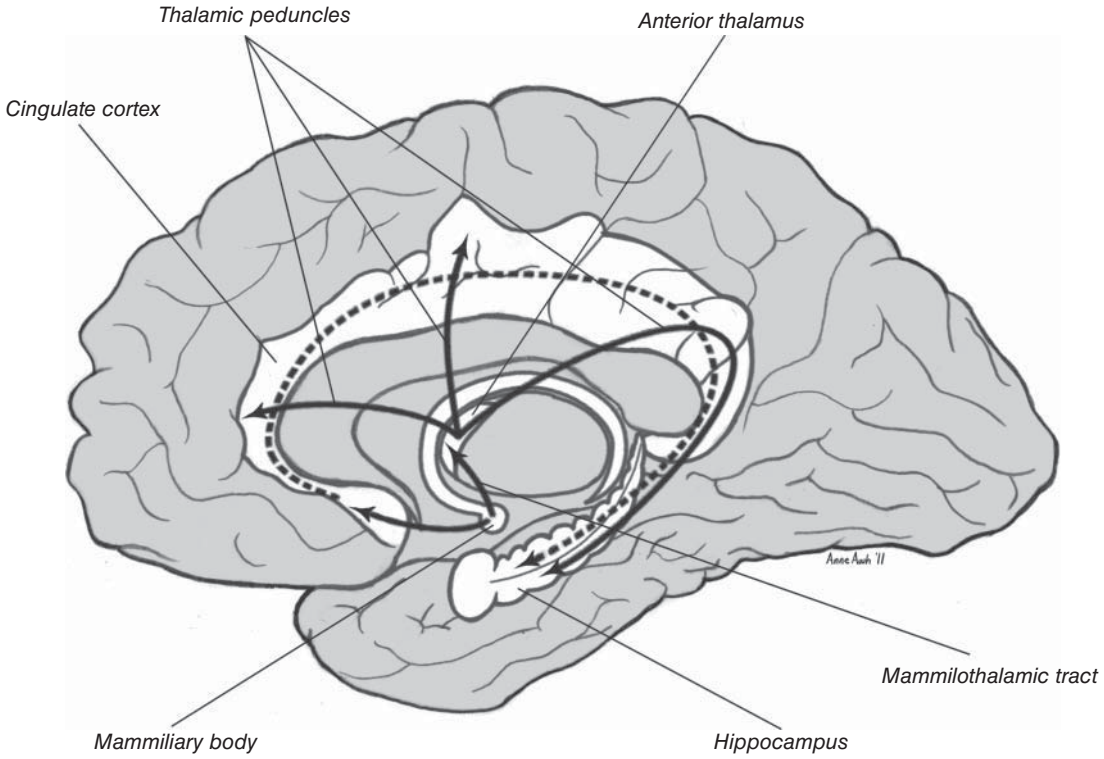


Figure 17.4 The dorsal limbic circuit, centered on the septum and hippocampus and their hypothalamic nuclei, engages the cingulate cortex as described by Papez.

and the mammillary bodies of the hypothalamus (Papez, 1937) (Figure 17.4). Although Ikemoto emphasizes the subcortical control of approach, Tucker and Luu emphasized that the control of learning and neural development requires the integration of the subcortical approach system (with its integral arousal control properties) with the limbic and cortical networks that regulate neural activity within the cerebral hemispheres. The important point is that activity-dependent organization of network function is as much a cognitive function as it is a motive-arousal function, and thus requires the corticolimbic mechanisms controlling memory consolidation. In this view, memory consolidation has not only a psychological outcome (learning) but also a neuroanatomical outcome (self-organizing the differentiation of connectional neuroanatomy).

The specific role of the dorsal limbic system can be seen to engage the subcortical approach system to support the unique form of learning and memory—rooted in the habituation bias of norepinephrine arousal control—that supports the feedforward cybernetics and the holistic conceptual structure of the dorsal brain (Tucker & Luu, 2012). These cybernetic and conceptual features can be understood as basic psychological properties of *extraversion*, and as neurophysiological properties of *externalizing* as a neurodevelopmental mechanism for exercising the growth of the dorsal brain.

The idea of feedforward control in the dorsal brain has come from both neuropsychological (Goldberg, 1985) and neurophysiological (Shima et al., 1991; Tanji & Shima, 1996) studies of action regulation. The control of motor processing by cingulate cortex and mediodorsal regions of the frontal lobe appears to involve a kind of *projectional* control, where the action is engaged in relation to a goal without ongoing guidance. For example, in turning on a light switch, you first reach toward the switch with the action launched by holistic and projectional feedforward control. The action is initially a vectoral impulse. This contrasts with the *constrained* form of action regulation from the ventrolateral frontal lobe (and ventral limbic regions), in which feedback guidance from sensory input becomes integral to fine-grained adjustments. As your hand nears the switch, feedback constraint from vision (or, in the dark, from touch) then becomes essential to assess the difference between the initial projectional trajectory and the precise location of the switch, such that error-correction mechanisms must then be effected through visual or haptic and tactile feedback guidance.

The cybernetics of action regulation from dorsal and ventral limbic and cortical systems can be aligned with the learning mechanisms that are uniquely directed by these brain systems. Drawing particularly on the neurophysiological studies of learning by Gabriel and associates (Gabriel et al., 1996), Tucker and Luu (2007) emphasized that the gradual or operant form of learning context-based associations is mediated by the dorsal limbic system, and is particularly important to engaging the context (externalizing) under conditions of approach.

In contrast, consistent with the neurophysiological evidence (Gabriel et al., 1996), the rapid, focused learning under conditions of discrepancy or threat is mediated by the ventral limbic system (Figure 17.5). These differential cybernetic effects can be seen as unique ways that learning is controlled by the approach (dorsal) and avoidance (ventral) learning systems, extending the function of the specific subcortical control systems into the more general task of regulating the cognitive function of the mammalian cerebral hemisphere (Tucker & Luu, 2007).

The unique cognitive capacities discovered for the dorsal brain, in spatial memory and contextual organization of action, can be seen as emergent from the more elementary motivational control linked with approach systems. The elementary cybernetic properties of dorsal limbic control help to explain basic features of extraversion, in normal personality, and externalizing disorders, in psychopathology. For example, the impulsive child, or one with attention deficit disorder, may operate excessively under feedforward control not only in specific actions but in behavior and self-regulation generally. Similarly, it may be the exclusive reliance on holistic thinking and the lack of constrained, analytic feedback control in cognition and behavior that characterize the impressionistic cognition of the person with histrionic personality disorder. In patients with lesions of the mediodorsal frontal networks, a syndrome of *pseudo-depression* is typically observed (Blumer & Benson, 1975), reflecting a loss of positive affect and the associated impulse toward hedonic engagement that is associated with the normal approach function of the dorsal limbic system.

In a similar fashion as with extraversion and externalizing, the elementary adaptive controls that are exaggerated in introversion and internalizing disorders can be seen to emerge from limbic constraints on affect, cognition, and behavior, specifically from the ventral limbic circuits of the

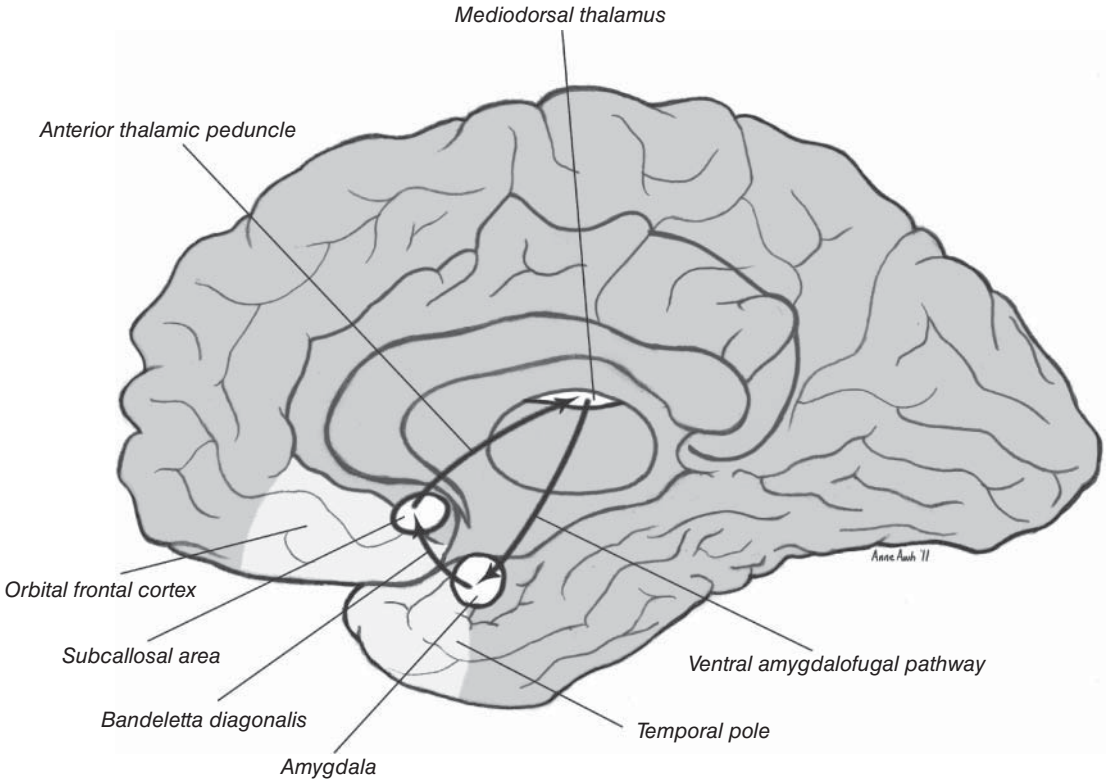


Figure 17.5 The ventral division of the limbic system involves the piriform cortex (paleocortex), the amygdala, and the orbital frontal lobe, coordinated by hypothalamic circuits through the stria terminalis (not shown) and the mediodorsal nucleus of the thalamus.

amygdala, anterior temporal lobe, mediodorsal thalamus, and orbital frontal lobe (Figure 17.5). The hypothalamic base for the ventral limbic network is the ventromedial nucleus, via the stria terminalis (not shown). The avoidance motivation emerging from the ventral division of the limbic system may become chronic in humans as symptoms of anxiety. The dopaminergic and cholinergic forms of neuromodulation that are integral to the basal ganglia support the sensitization or redundancy bias that is engaged by anxiety and hostility (Tucker & Williamson, 1984). Given the important links of amygdala and ventral limbic networks with striatal controls, when anxiety becomes a chronic organizing influence in personality, such as in anxiety disorders or obsessive-compulsive disorders, there is exaggeration not only of the object-oriented perception of the ventral corticolimbic networks, but exaggeration of the sequencing and routinization functions of striatal control over action (Tucker & Derryberry, 1992). These pathological features, consistent with exaggeration of internalizing, can be seen to reflect excessive feedback control and constraint in cognition and affect as well as in behavior. Conversely, the loss of adequate internalizing control with lesions of the orbital and ventrolateral frontal lobe is manifested in the *pseudopsychopathic* syndrome (Blumer & Benson, 1975) in which the person loses the constraint component of normal self-regulation. The result is that the impulsivity of the dorsal approach system is released, no longer modulated by normal ventral frontolimbic feedback constraint.

Thus the developmental mechanisms regulating the embryological differentiation of the major functional systems of the brain may continue to shape the internalizing and externalizing modes of self-regulation throughout psychological development. At birth, there is a key transition, in which the infant must engage the social world. In the embryo, self-organization is self-contained, such that canalization of trophic and activity-dependent mechanisms serves only to correct incipient developmental errors with system-level organismic feedback to create coherent neural systems. For the human infant, the transition from womb to culture creates fundamentally different challenges for the developmental mechanisms of internalizing and externalizing.

Canalization and Primitive Self-Organization in Autism

Autistic children cope in various ways with their challenged neurodevelopmental capacities. The core syndrome of autism might be seen as an effort in self-organization, attempting to create a more or less coherent self through maintaining boundaries against outside influences. The problem with this in autism, of course, is it causes a failure to engage the extensive interpersonal communion that embeds normal human intelligence within the social context. Nonetheless, it may be useful to appreciate that autistic symptoms are a kind of canalization of organismic coherence to form a primitive self. This organismic process may explain the appearance of the typical autistic symptoms as a common final path of canalization in the face of remarkably varied genetic defects.

Because twin and family studies showed high heritability of both autism and autism spectrum disorders, researchers over the last decade or so have applied the recent advances in genetic sequencing to characterize the genetics of autism (Chaste & Leboyer, 2012). Instead of revealing consistent abnormal genes, the results have shown that the genetic defects in autism are often uncommon *de novo* mutations that arise in different forms in different individuals. In addition, the increasing evidence that genetic deficits of autism interact with environmental insults, such as maternal viruses and immune responses during pregnancy, has led autism researchers to focus on gene–environmental interactions, rather than just inherited defects of genetic code (Chaste & Leboyer, 2012).

Genetic defects are more common in children with older parents, implying that they indeed reflect a risk from the reproductive process (Idring et al., 2014; McGrath et al., 2014). Yet this is a diffuse genetic risk, resulting from many inconsistent and varied mutations of the genome. Many of these mutations do have a common path of affecting synaptic regulation, and thus various aspects of neural development. Nonetheless, the fact that a common syndrome of autism results from a variety of neurodevelopmental abnormalities suggests that this syndrome reflects the organism's effort to adapt to a nonspecific developmental insult. We can speculate that the embryonic process is guided by the requirement to maintain the framework for organismic developmental coherence, what may be described as a primitive individual self. It is as if the normal, but intense, process of human interpersonal communion is too challenging for the infantile self that struggles to maintain a fragile organismic integrity. The result is a primitive mode of internalizing.

The autistic self thus seems to be developed at the expense of more challenging capacities in social cognition, such as shared intentionality and intersubjectivity. Unfortunately, these are the exactly capacities that allow the powerful interaction effects of social support for the normal child's mind. Instead, the autistic child manifests exaggerated anxiety and internality. Rather than isolated

symptoms, these responses can be seen as primitive organismic reactions reflecting a self-organizing adaptation. These are clearly maladaptive in that they threaten the essential developmental avenue of acquired intelligence and culture through social interaction. The effective interventions with autism have succeeded through redoubling the social support provided (Gulsrud, Hellemann, Freeman, & Kasari, 2014; Kasari, 2014). Even though the child is poorly prepared to engage this support, it appears to be essential to allow the socially competent self that is prepared to adapt to the ongoing social developmental process.

Progressive Neurodevelopmental Dysfunction in Adult-Onset Psychopathology

In forms of severe psychopathology with adolescent and adult onset, the disorders of the self can also be seen as fundamental, and they often preclude the normal adaptation and self-regulation that could allow correction of pathological patterns.

For example, in mania and depression the strong mood states themselves appear to be pathogenic, with later episodes predicted by the severity of earlier episodes (Lewinsohn, Hops, Roberts, Seeley, & Andrews, 1993; Lewinsohn et al., 1994). Given what we are learning about neuroepigenetics (Day & Sweatt, 2011; Sweatt, 2013), it is tempting to think that an epigenetic mechanism of kindling, activated by the extreme mood state itself, may be involved in mood-specific learning. This mechanism might be suspected to mediate the biological sensitization that causes mania or depression to predispose the person to augmenting mood responses in the future. Although it is thus likely that a specific biological mediation is responsible for the sensitization or kindling effect of repeated mood disturbance (Harkness & Tucker, 2000; Post, 1986), the pathological effect of the strong mood states may also have an organismic psychological basis, biasing the operation of the self in ways that are mood-congruent but highly maladaptive. In a manic state, the person is grandiose, impulsive, and optimistic to a fault. Transitioning to depression, the same person loses all confidence, cannot find hope, and may become intensely self-critical to the point of suicide. These mood shifts are fundamentally shifts in self-regulation, and they seem to be incorporated within the organization of the self as well as specific sensitizations of neurophysiology.

The mood shifts of mania and depression involve positive affect in greater or lesser degrees, and appear to reflect the operation of the dorsal limbic approach system and its externalizing function, ranging from strongly engaged to fully suppressed (Tucker & Luu, 2007). There is of course a fundamental continuity of the self through these mood states, but the normal mood-congruent self-regulation becomes exaggerated to the point that any perspective that could be provided by knowledge of the historical self is lost in the presence of strong affective modulation.

In a different example of severe psychopathology, the schizophrenic episode, the distortion of experience and behavior is associated with severe anxiety. Yet, unlike the nonpsychotic anxious person, the internalizing cognition of the schizophrenic person is not simply routinized, overly focused, and biased toward threat, but it becomes disorganized to the point of a breakdown in the capacity to maintain contact with reality. The disorganization of the neuropsychological process in the schizophrenic break seems to reflect a fundamental, and often irreversible, breakdown in the organization of the self. The fact that first schizophrenic episodes often occur toward the end of adolescence emphasizes the importance of neurodevelopmental mechanisms; this is a point in time when the completion of adolescent cortical thinning suggests a maturation process that is normally associated with the crystallization of the adult personality (Mutlu et al., 2013).

With its typical features of severe anxiety and autism, schizophrenia can be seen as an internalizing disorder, reflecting an exaggeration of the ventral limbic avoidance system and its strong dopaminergic and cholinergic modulation. However, the disorganization of the schizophrenic person reflects profound defects of the self that must also be seen as loss of the capacity for externalizing. There is typically a loss of the normal feeling of agency and intentionality, such that the schizophrenic person's own thoughts and actions are interpreted as controlled by an external agent (Blakemore & Frith, 2004).

That these effects are disorders of the normal externalizing function is shown by the parallel symptoms of loss of personal agency with lesions of the dorsal limbic and frontal networks. In the anarchic hand syndrome, for example, the patient experiences actions of a hand or a leg as caused by someone else (Goldberg & Bloom, 1990). In the person with mediodorsal frontal lesions, the loss of agency is a circumscribed defect, associated with a particular limb. In the schizophrenic person, the loss of agency is fundamental to the fragmentation of the self, such that ongoing self-regulation is then carried out with reference to delusional assumptions. As a result, self-regulation becomes ineffective in integrating the accurate interpersonal feedback that is essential to coping with society.

The Interpersonal Context for the Developing Self

The disorders of the self in psychopathology may appear in infancy, in the autistic child's failure to engage the sharing of perspectives in interpersonal communication, or they may become progressively more apparent, leading to the young adult's schizophrenic break. Although neural development is cumulative, with each stage of organization building the base for later growth, ontogenesis is remarkably protracted in humans, such that there is a long period of social support that provides even the genetically challenged child with time to find a way to adapt. When parental and societal support is effective, we might consider it as cultural canalization.

Human evolution has resulted in an extended neoteny, providing a long period of brain maturation that may be integral to the capacity for developing intelligence. Extending the juvenile stage of neural plasticity allows the child to self-organize through the motive cybernetics of learning and memory while incorporating the rich cultural information of human society. Human neuroembryology can be understood to create a complex neural substrate, yet one that is profoundly immature at birth, requiring major support by parental caregivers.

The primordial neural mechanisms for regulating neuroembryological development, organized around the internalizing and externalizing modes of self-regulation, must transition at birth to the complex tasks of intersubjectivity, engaging the available parenting that is critical to organizing a socially competent self. Even the most biologically robust child is unlikely to escape some degree of enduring psychopathology in the face of abusive and neglectful parenting. Conversely, the temperamentally vulnerable child may succeed with developmental challenges only through skillful social support from family, peers, and the community.

The major dimensions of internalizing and externalizing thus take on new roles as the self-regulatory tools for coping with the considerable developmental challenges of socialization. Forming effective dependency relationships is an essential function of externalizing. The specific cybernetics of the dorsal limbic system are relevant to this function, with a strong hedonic tone motivating the approach to social contact, and the extraversion of intentionality (habituation bias, feedforward control) supporting the learning process within the attachment relation.

For example, in acquiring language, the toddler learns the meaning of words through *social referencing*, interpreting the intention of the mother as she communicates (Baldwin, 1993; Baldwin et al., 1996). In this way, the child's developing capacity for extraversion supports incorporating the intentionality of the mother, a process described by philosophers and psychoanalysts as *intersubjectivity*. The interpersonal context is thus critical to the child's early experiences with cognitive and emotional development that are integral to the organization of the biological substrate. The neural mechanisms of self-regulation must support the development of the self, through the incorporation of interpersonal bonding with the caregiver. The capacity for externalizing is essential to this process of bonding and identification.

After the first year, the child's increasing autonomy will lead to struggles with the dependency relationship of infancy, and the capacity for internalizing will become an essential counterpoint for individuating a more autonomous self from the family context (Mahler, 1968; Tucker & Moller, 2007). In embryogenesis, the ventral limbic networks organize the substrate for avoidance (internalizing) in the ventral division of the hemispheres. Operating through the fundamental mechanisms of anxiety and hostility, these networks are now challenged by the complex task of establishing the autonomy of the toddler self. This task requires both separation from parental control and effective individuation of the capacity for effortful agency.

In these familiar interpersonal dynamics of the family, recapitulated in the struggles for individuation in adolescence, neurodevelopmental mechanisms optimally balance the modes of introversion and extraversion. Yet imbalance is common, with exaggeration of one mode creating not only the familiar personality types but the variety of personality disorders. We have emphasized the primitive controls provided by the motive mechanisms of internalizing and externalizing. Yet through their integration with complex cognitive capacities, these motive modes support more sophisticated self-regulatory processes that may be integral to what has been described in the temperament literature as *effortful control.* This capacity for executive self-regulation may arise through unique contributions from both internalizing and externalizing modes of control. The cognitive operations of internalizing, for example, draw on its motive basis of anxiety and hostility. In the effortful control of attention, anxiety allows the child to anticipate problems and dangers, but also to solve problems through analytic and sequential reasoning (Derryberry & Tucker, 1992). Hostility supports the individuation of a personal perspective, and when appropriately integrated with cognitive processes of effortful control, may be essential to the development of critical thinking (Tucker, 2007). In its pathological forms, internalizing provides the motive basis of debilitating anxiety, obsessions, and paranoia. But it may be integral

to adaptive cognitive control as well, providing the focused attention and motivated engagement required for analytic reasoning (Derryberry & Tucker, 1992).

Similarly, externalizing may be an essential component motive process in effortful control, with important implications for the successful child's ability to develop interpersonal skills. Emerging from the dorsal corticolimbic networks, externalizing may develop from primitive impulsiveness to support more complex processes of intentional effort. Closely linked to the interpersonal engagement of extraversion, externalizing supports identification with significant others, and the capacity for mentalizing that is required for socialization and education. The holistic thought supported by the dorsal corticolimbic pathways is specifically engaged by the positive affect of extraversion, and it provides the child with the optimism that is often necessary to persist in effortful self control under adverse challenges.

Motives are thus integral to more complex operations of the personality that become engaged in effortful control. For each child, the self is an important construct for understanding both primitive and sophisticated processes of self-regulation. Psychologically, the self is the coherent system of concepts, memories, and regulatory capacities for attention and intention that operate to maintain internal consistency, as well as consistency in interpersonal relations. For the embryo and fetus, the self is the biological process of organizing internal consistency, through the cybernetic capacity for canalization. Through many specific biological mechanisms of functional feedback control, canalization in embryogenesis achieves a coordinated, viable phenotype through the capacity for developmental self-regulation that normalizes the variations of the genotype (Waddington, 1942). In neurogenesis, this must be achieved by the multiple developmental mechanisms for trophic and activity-dependent neuronal self-organization. For the child and adolescent, the same neurodevelopmental process of maintaining internal consistency continues, but now achieved within the social context to create the integrated psychological patterns of a coherent self. When self-organization fails, the result may be the fragmented self of psychopathology.

CONCLUSION AND FUTURE PERSPECTIVES: CONTINUITY AND DIVERSITY IN THE HUMAN ONTOGENETIC PROCESS

In this chapter, we have proposed that it now may be feasible to explain the developmental processes leading to both normal personality and psychopathology in common biological terms. We think that a better integration of biological and psychological theory will be important to translating from the remarkable advances in modern biology to improve assessment and treatment of mental illness. Students of human development can draw from new insights into genetic mechanisms and the specific workings of neural plasticity. Yet these mechanisms cannot be interpreted in isolation but must be understood within an organismic theory of psychological development. In such a theory, epigenetic mechanisms broadly conceived serve to maintain the coherence of systems within the whole organism, even in light of extensive human genetic variability.

Organismic mechanisms of self-regulation maintain the continuity of the self. These biological cybernetics begin as the control systems that coordinate embryonic morphogenesis at molecular and neurophysiological levels. They continue to operate throughout ontogenesis, forming the substrate of psychological self-organization, where the process of learning through neural plasticity must not only maintain homeostatic internal coherence of the self, but must achieve effective interchange with the social environment.

We have outlined a theoretical approach to basic dimensions of internalizing and externalizing that guide the process of self-organization. This process begins with the differentiation of sensory and motor systems in the embryo, regulated by the evolutionary mechanisms for controlling not only somatic sensorimotor systems, but also the visceral sensorimotor systems that provide the homeostatic regulation of neural activity. Internalizing appears to reflect the viscerosensory bias of the ventral limbic system, externalizing the visceromotor bias of the dorsal limbic system. With these specific motive bases, the process of neural differentiation and plasticity continues after birth to support the child's learning and memory consolidation, as internalizing and externalizing provide adaptive control of intelligence in the child's cultural context.

Even though we have emphasized the adaptive continuity of human ontogenesis—from embryogenesis through adolescence—it is also clear that human development involves remarkable individual diversity. The evolution of the human brain has resulted in extensive phenotypical variability at the same time that neural maturation has been prolonged to extend the period of juvenile plasticity and parental instruction. It may be that these aspects of human uniqueness have evolved together. In the context of two decades of parental support, diversity in the genome, and thus developmental process, may have evolved in modern populations because of the availability of increasingly effective human cultures.

Human intelligence cannot be traced to a single mutation, with some novel developmental capacity, but is associated with a genome that includes a mosaic of diverse ontogenetic factors. This diversity of the genome—perhaps amplified further by epigenetic diversity—may have only become possible with the expanding cultural capacity for tolerating individual differences.

For simpler mammals, the instructions of the genome must code for adaptive behavior, within the narrow limits of adjustments provided by elementary capacities for learning and memory consolidation. For humans who are sheltered by family and community over a juvenile period spanning decades, greater diversity may have been tolerated within the genome. Individual variations, including not only biases toward internalizing and externalizing, but highly unique mutations, may have been protected by the presence of social support such that they propagated to succeeding generations. We can even speculate that, within the few millennia that have seen the explosive process of human cultural evolution, the protection of genetic diversity may in turn have conferred adaptive ability to the reproductive group under more widely varying conditions, such as unusual environmental threats or creative opportunities.

Although it is often said that the human brain has not changed since the Stone Age, this is almost certainly not true. First of all, if cultural success really has fostered reproductive success of diverse ontogenetic variations, it may not even be true for the genome, which now may span considerably greater variety than existed in the small populations of our Stone Age ancestors. Furthermore, once we appreciate how neural plasticity allows self-organization of the neural architecture through engagement with the culture, it becomes clear that the functional architecture of the brain itself is a kind of cultural artifact. Although there are, of course, important capacities of intelligence achieved by a child in a Stone Age culture, it is a very different brain that emerges through literacy, an effective education, and a rich set of cultural experiences.

In current times, the multiplicity of individual outcomes can thus be reinterpreted in light of the diversity of the human genome, as highly unique children encounter the wide range of social support in existing cultures, from devastating insults and pernicious trauma to the fortunate cases of skilled and highly invested parenting. Considering this perspective, the high degree of both genetic and cultural heterogeneity in current human populations may have created a range of developmental psychopathology that is itself uniquely human.

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CHAPTER 18

Adolescent Brain Development

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NEUROCONSTRUCTIVE PROCESSES

The construction of the human brain requires a long and protracted process. In fact, it has been argued that a defining characteristic of the human species is its long developmental time scale, including not only infancy but also childhood and adolescence (Thompson & Nelson, 2011). In some respects, adolescence may be our species' adaption that provides prolonged opportunity dedicated to learning and refinement of brain circuitry via extended exposure to environmental input. No other species dedicates as high a percentage of its lifetime to development (Thompson & Nelson, 2011). The goal of this chapter is to review and consider the functional significance of adolescent brain development with the aim of characterizing some primary aspects of the construction of the human brain.

General Principles

Unlike understanding the mechanics of a simple machine, it is not possible to understand the construction of the human brain through deconstruction of its component parts. This commonly used analogy rests on the principle of hierarchical construction (Quartz & Sejnowski, 1997). Brain development occurs hierarchically, where the phenotype of one circuit depends heavily on the phenotype of previously developed circuits. For example, expert face processing abilities observed in the majority of adults rests critically on the proper formation of several earlier developing processes, including the development of basic visual, attentional, and social motivation processes. If one of these processes develops in an atypical way, the odds of face processing skills developing in a typical manner are greatly diminished (Le Grand, Mondloch, Maurer, & Brent, 2001).

Central to a hierarchical organization is the factor of development timing. Evolutionary developmental (evo-devo) theorists have posited that time itself, that is, the mere duration of developmental processes, is a critical factor in the ultimate phenotype of brain systems (Charvet & Finlay, 2012). Both phylogenetically and ontogenetically, humans experience a prolonged immature state,

which if temporally modified, significantly impacts neural phenotypes. On an ontogenetic scale, maturational timing of systems has been considered to give rise to developmentally unique phenotypes in behaviors (Casey, Galvan, & Hare, 2005; Somerville & Casey, 2010; Steinberg, 2010). For example, subcortical systems, including regions such as the nucleus accumbens that mediate reward-related processing, show evidence of developmental timeline that is distinct from cortical regions, like the prefrontal cortex that can regulate arousal of the nucleus accumbens (Galvan et al., 2006; Somerville, Hare, & Casey, 2011). Therefore, adolescence is a period when there is a temporal imbalance of subcortical arousal without the regulatory influence of top-down prefrontal input. Another way of saying this is that adolescence marks a time of differential timing between subcortical and cortical maturation.

Another aspect of timing involves the age-related timing of environmental exposures. Each stage of development presents new niches and changing needs to be satisfied by environmental input. A priming or readiness of a particular neural system may be referred to as either a sensitive period or a critical period. A sensitive period is a period in development during which certain capacities are readily shaped or altered by experience (Knudsen, 2004). Critical periods are a special class of sensitive periods that result in irreversible changes in brain function. In other words, these special periods allow for developmentally unique moments for learning, which will shape later brain function and behavioral output. It is this learning aspect of sensitive periods that we wish to emphasize because there are other important periods that are distinct from sensitive or critical periods. For example, there are other periods of development when large individual differences in behavior emerge or are finally observed. We would argue that these other developmental moments are distinct from sensitive or critical periods because they encompass the expression of the phenotype, not the learning of the system. This point will become important in this chapter as we discuss behavioral domains for which adolescence is a sensitive period.

The notion of sensitive periods relies on the principle of brain plasticity, a concept referring to the likelihood that brain structure and function change as a result of environmental influence. This concept, although common in modern scientific literature, replaced the long-held belief that the brain is a static tissue that results from genetic unfolding. The shift in thinking about plasticity dates back to the Nobel Prize–winning work of Hubel and Wiesel in the 1960–1970s (Hubel & Wiesel, 1970) showing that environmental light input shaped cellular organization in the visual cortex. Although genotype sets large architectural constraints on brain development, the state of the science recognizes the ubiquity of gene–environment (GxE) correlations (Caspi & Moffitt, 2006; Gottlieb, 2007), which emphasizes the interdependence of environmental input on gene activity to influence phenotypic outcome. More recently, this perspective has been amended to incorporate developmental timing, with the appreciation that gene expression varies across different ages resulting in the concept of gene–environment–development (GxExD) interactions (Casey, Glatt, et al., 2009).

On one hand, plasticity is beneficial to brain development in that it allows for learning from environmental input. However, life-long plasticity is likely to be detrimental to the organism. At some point in development, it benefits the organism to sacrifice plasticity for efficiency. Thus, some have argued for a plasticity–efficiency trade-off in development (Lebel et al., 2012; Lu et al., 2009). This perspective argues that plasticity is adaptive early in life when a system is undergoing massive learning and developing optimal strategies. However, a plastic system lacks efficiency, much in the way that a town full of several dirt roads (high degree of options) does not allow for the fast travel that one with paved super highways does (high degree of efficiency). Once information is learned and strategies are optimized, the system should shift to an efficient one at the sake of plasticity. According to this perspective, early life is designed for learning and practicing skills, whereas later life (e.g., adulthood) represents a period of performance, where those learned skills are now put into use. This perspective harkens back to the concept of a protracted childhood mentioned earlier. The long period of immaturity afforded to humans allows for a long period for learning (or establishing of systems via mechanisms of plasticity) that enables the complex behavioral repertoires humans are able to express in adulthood.

The Importance of Animal Models

Although the focus of this chapter is on human brain development, central to the arguments that will be presented is the large body of work produced by animal models. There are several important and large differences between humans and animals of other species, such as rodents or even nonhuman primates. However, the state of human neuroscience is much newer relative to what has been learned in these other species, and as will become clear in this chapter, many of the hypotheses and theories about brain development upon which we currently rely have been

generated by animal models. In addition to the shorter life spans, and thus the facility with which nonhuman animal brain development can be studied, animal models allow for investigations that are either ethically or practically impossible in human samples. Of course, animals can provide only a model of a system, as a rodent is the product of a very different dynamic system from a human. However, great insights into mechanisms of brain development can be gleaned from these models. Another concern raised regarding the use of animal models to study human brain development pertains to the appropriate age comparisons. For example, a reasonable question is whether neural substrates that mediate mother–pup relationships during infancy correspond to the same mechanisms in a human infant (who at the cellular level may be at a very different age from a rodent pup). However, another perspective to take when regarding these comparisons is to consider the developmental niche or needs of the organism at that time. So, while the infant pup may be at a very different age than a human infant, both species are altricial (or at least semi-altricial) and require maternal input for survival. The needs of the infant are analogous, although not always identical (good maternal care in the rat would include high levels of licking and grooming—not so in the human). However, both species require analogous input, for example, contingent and reliable care from a primary caregiver. Similarly, adolescent rodents, monkeys, and humans have similar goals in transitioning toward adulthood and mature sexually. Thus, we, as many others have (Casey, Ruberry, et al., 2009; Cohen, Tottenham, & Casey, 2013), argue that animal models are highly valuable to the field of human brain development.

Connectivity

Animal models have been very important in heightening awareness of connectivity of systems. Although much of the research presented in this chapter focuses on one or possibly a few brain regions, these regions are highly interconnected with each other and several other regions, which the field of developmental systems neuroscience works toward understanding and characterizing. This idea is consistent with the notion of the development of dynamic systems in the behavioral domain (Smith & Thelen, 2003). The central tenet of these system approaches is that the function of brain activity is an emergent property of the connectivity of the system. We will provide a more in depth description of recent advances in adolescent brain development that have been revealed through analysis of connectivity patterns across development.

WHAT IS ADOLESCENCE? A HISTORICAL PERSPECTIVE

Prior to the 1900s, there was no formal recognition of the developmental period of adolescence. However, the behavioral phenotypes that typically emerge during adolescence had been noted throughout history. Aristotle observed, "The young . . . are naturally as hot-blooded as those who are drunken with wine . . . Their life is guided by their character rather than by calculation" (Aristotle [460 BC]. The Art of Rhetoric. p. 249). Socrates characterized youth as inclined to "contradict their parents" and "tyrannize their teachers" (Arnett, 2011.p. 277). In a landmark two-volume series, Granville Stanley Hall is credited with being the first to formalize the study of youth in the second decade of life and coined the phrase "storm and stress" with reference to adolescence (1904). This phrase was taken from the German Sturm und Drang movement, which was composed of three key aspects: conflict with parents, mood disruptions, and risky behavior. Hall argued that this is characteristic of most adolescents, biologically based and influenced by culture (Arnett, 2011). Psychoanalytic theorists, especially Anna Freud (1946, 1958, 1968), strongly endorsed Hall's proposed model of adolescence. They viewed adolescent storm and stress as the manifestation of Oedipal conflicts from early childhood (Blos, 1962), which, in their view, provoked emotional volatility (as the adolescent ego attempted to conquer resurgent instinctual drives), depressed mood (as the adolescent mourned the abandonment from the Oedipal parent), and conflict with parents (Blos, 1962). In contrast, Margaret Mead led fellow anthropologists in countering the universality of storm and stress in adolescence by drawing on multiple examples in non-Western cultures in which the characteristic adolescent behavior was not observed (Mead, 1928). Although most contemporary adolescent theorists do not accept the claim of storm and stress as universal, they do acknowledge its relevance to understanding behavioral changes during adolescence and that although not all adolescents experience storm and stress, adolescence is a period highly characterized by these behaviors.

Despite all the discussion, proposed theories and plausible predictors and biological explanations regarding adolescence, the field has, remarkably, failed to agree on an operational definition of this important developmental period. The number of studies and public interest in adolescents has sharply increased in the last decade (Galván, 2014) and many consider adolescence as a transitional period in life between childhood and adulthood (Dahl, 2004; Spear, 2000; Steinberg, 2010), but there is no general

consensus about when adolescence begins and when it ends. Generally speaking, the onset of puberty marks the beginning of adolescence and the full independence from caregivers signifies the end of adolescence. However, both of these biological and psychosocially defined constructs are complex and multi-faceted.

Sexual maturation in girls involves three events that typically proceed in the following manner: breast development, pubic hair growth and first menses. It would therefore be most precise for adolescent researchers interested in puberty as an adolescent milestone to report age of first breast growth. Instead, most reports that include puberty use the age of first menses as an adolescent-onset marker (Blakemore, Burnett, & Dahl, 2010). The reason for this convention is a methodological one: obtaining accurate pubertal measures is laborious, expensive, and challenging (Dorn, Dahl, Woodward, & Biro, 2006). Therefore, many researchers simply dichotomize the measure by asking girls if they have or have not begun menstruating and then classify the sample as either prepubertal (pre-menses) or post-pubertal (menses begun). This approach precludes differentiation of pubertal status along the fine-grained spectrum that includes various stages of breast and pubic hair growth. It is therefore plausible that a prepubertal group in a study includes girls who are truly prepubertal (typically under age 8) and those who are on the cusp of sexual maturation. Similarly, a postpubertal group might include girls who menstruated early (as is more common in underrepresented minorities or girls with stressful family contexts (Herman-Giddens, 2007) as well as those who are both biologically and psychosocially more mature.

Perhaps more challenging than defining when puberty begins is defining when adolescence ends. It has been argued that one function of adolescence is to establish independence from the family unit and caregiver (Casey, Getz, & Galván, 2008). In nonhuman animals, this autonomy typically involves leaving the natal troop to seek out new sexual mates, food resources, and sleeping burrows or trees (Spear, 2000). In humans, the split is not as discernible. The very definition of independence varies across generations, adolescents, parents, and societies. Most countries define the end of adolescence when an individual is mature enough to be trusted with certain responsibilities, including driving a vehicle, having legal sexual relations, serving in the armed forces or on a jury, purchasing, selling, and drinking alcohol, voting, finishing certain levels of education, marriage, and renting a car. But even the age at which these rights and privileges are granted varies within a single nation or culture. Even more perplexing is that the set legal age limits seem arbitrary relative to the legal age for comparable or more significant activities. For instance, youth can hold employment in many U.S. states at the age of 14 but are not legally allowed to drive, vote, and buy alcohol until the ages of 16, 18, and 21 years, respectively. They can fight in wars and serve in the armed forces at age 18 but cannot rent a car until age 25.

By some standards, individuals transition from adolescence into adulthood when they are either married or financially independent, or both. In previous generations, these events typically coincided with the graduation from high school (age 18). However, since approximately the late 1980s, youth have remained more financially dependent on their parents for longer and are marrying later. One obvious reason for this trend is that there has been an increase in the number of people (particularly women) who are attending college or university. In fall 2012, a record 21.6 million students enrolled in American colleges and universities, an increase of about 6.2 million only since fall 2000 (NCES, 2012). In 1970, 42.3% of the college-attending population was women; today, women make up 56.8% of the college population (NCES, 2012). This increase makes individuals more dependent on parents or government loans for financial support, particularly as the costs of college continue to rise steadily. Adjusting for inflation and represented in current dollars, the average total cost of college in 1976–77 including tuition, fees, room, and board was $7,146 for a public university and $14,686 for private institutions; for the 2010–2011 academic year the costs were $15,605 and $31,975 for public and private institutions, respectively (NCES, 2012). College-attending youth also marry later in modern times compared with previous generations: in 1976, the average age of first marriage was 23.8 for men and 21.3 for women. In 2012, the age of first marriage was 28.7 and 26.5 for men and women, respectively. The economic downfall in 2008 further contributed to continued financial dependence on parents, as college graduates struggled to find jobs and moved back home with parents in record numbers. A 2011 Pew Research Center analysis of U.S. Census data found that 39% of adults ages 18 to 34 say they either live with their parents or moved back in at some point in recent years. Among 18- to 24-year-olds, 53% said they live at home or moved in temporarily, compared with 41% among adults ages 25 to 29, and 17% among those ages 30 to 34, and 60% reported being financially linked to their parents (Pew Research Center, 2012).

Although attaining maturation in terms of physical, biological, and neurobiological milestones occurs in the majority of individuals by the late teens, the delayed emotional and financial dependence undoubtedly contributes

to the protracted transition from adolescence into young adulthood. Given the seemingly endless possible definitions of adolescence, adolescent researchers face a daunting task in deciding how to define the adolescent group in their research studies. Some scientists have identified adolescence as "the gradual period of transition from childhood to adulthood" (Spear, 2000. p. 417). While this broad definition is useful when describing heterogeneous bodies of work, as in literature reviews, it is not the most suitable way to define participant samples to be included in developmental studies (Galván, 2010). In general, neuroscience studies on human adolescents have defined adolescence in one of the following ways: age (van Leijenhorst, Zanolie, et al., 2010); grade level (Galván et al., 2006; Geier & Luna, 2009); or pubertal status (Goddings, Burnett Heyes, Bird, Viner, & Blakemore, 2012).

Trajectories of Human Brain Development

Compared with other species, human brain development is a protracted process. In particular, early childhood and adolescence seems to be lengthened in the human species compared with most other species (Thompson & Nelson, 2011). The elongation of these periods may serve the purpose of extending opportunities during which learning can occur, particularly with regard to complex social learning. Large longitudinal MRI studies have shown that in the human, developmental changes are observed in cortical development throughout young adulthood (Caviness, Kennedy, Richelme, Rademacher, & Filipek, 1996; Giedd et al., 2008; Giedd & Rapoport, 2010; Lenroot et al., 2007; Reiss, Abrams, Singer, Ross, & Denckla, 1996; Sowell et al., 2004; Sowell, Thompson, Tessner, & Toga, 2001).

By the time an individual reaches adolescence, the majority of basic anatomical structural development has occurred. However, late occurring organizational development can have significant impacts on behavioral refinement that occurs during adolescence. Development occurring during adolescence and early adulthood involves a process of cortical thinning, which may reflect changes at the cellular level, such as synaptic pruning. This hypothesis is drawn from post mortem findings, which have shown an overproduction of neural synapses in the early stages of a system's development followed by a period of synapse pruning, or selective activity-based elimination (Bourgeois, 1997; Huttenlocher & Dabholkar, 1997; Petanjek et al., 2011). Synapse overproduction and subsequent pruning occurs in sequential waves following a general pattern of caudal to rostral, or back to front, of the brain, such that an area like the visual cortex, which is in the back of the brain, reaches maturity (i.e., a pattern of synapse pruning that most likely reflects a history of activation) earlier than areas like the prefrontal cortex. This pattern of development characterized by post mortem studies has been recapitulated in structural MRI studies such that by charting the relative thickening and thinning of cortex, investigators have been able to establish an index of regional variations in brain age (Houston, Herting, & Sowell, 2014). From these types of studies, it has been shown that the prefrontal cortex is the latest to develop relative to other cortical regions.

It has been hypothesized that synapse overproduction supports moments of increased learning from the environment. Based on activity, or frequency of use, certain circuits are maintained, while others are pruned through programmed cell death and synapse elimination (Greenough, Black, & Wallace, 1987). Taken together, these findings would support the argument that adolescence may be a time of enhanced plasticity of the prefrontal cortex; that is, adolescence may be an optimal developmental moment for prefrontal cortex mediated learning about the environment because adolescence is a time when the prefrontal cortex is undergoing large developmental change.

In addition to a gradual reduction or thinning of grey matter, adolescence is also marked by a gradual increase in white matter (Giedd, 2004; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999). The timing of white matter maturation in the life span of a human is critical when considering plasticity. Myelination is the final stage of neural development and once it occurs, neural efficiency is significantly increased. However, there is a trade-off for efficiency, in that neural plasticity is lost (Lu et al., 2009). Indeed, animal models have shown that genetic knock-out animals who were designed to have degraded white matter retain their neural plasticity throughout life (Yang, Lin, & Hensch, 2012). Thus, the increases in white matter during adolescence and early adulthood, particularly in the frontal cortex, may signal that the period of plasticity is ending to replaced by a period of efficiency.

Functional MRI studies have provided additional insights into adolescent brain development. Resting state methods measure functional brain activity from participants without the presence of a task. The primary measure of interest is the stability of connectivity, or correlations, in spontaneously recorded brain activity. This measure is fairly robust to momentary fluctuations in cognition and whether eyes are open or closed. Using this method, researchers have identified the existence of stable brain networks across individuals (Dosenbach et al., 2007). Using a sample of over 200 participants between the ages

of 7 and 30 years old (a sizeable sample for an fMRI study), researchers have shown that stable networks exist in young children, but that developmental change across this span is largely characterized by the weakening of short-range functional connections between adult brains' major functional networks (Dosenbach et al., 2010). In other words, brain development during childhood and adolescence may generally be described as transitioning from shorter range connections to longer range ones. These findings seem consistent with the findings that layer II in cortical regions develop earlier than layer III, with the former responsible for local connections and the latter for establishing longer distance connections (Landing, Shankle, Hara, Brannock, & Fallon, 2002). Taken together, such changes may facilitate the increasing integral capabilities that emerge over development and allow for more efficient and cooperative neural processing that characterizes mature human cognition. In the following sections, we focus on how such neural changes operate across adolescence in several key behavioral domains.

NEUROPERCEPTUAL CHANGES DURING ADOLESCENCE (FACE PROCESSING)

Although the majority of sensory and perceptual development occurs very early in life, there is evidence of continued change that extends through adulthood (Cohen Kadosh, Johnson, Dick, Cohen Kadosh, & Blakemore, 2013; Germine, Duchaine, & Nakayama, 2011). The domains that exhibit refinement tend to be those skills with which humans exhibit behavioral expertise. A prime example is visual processing of human faces. Humans demonstrate profound expertise in face memory and recognition. Faces can be discriminated from other objects in less than 200 ms (Allison et al., 1994), perhaps even as early as 125 ms (Schendan, Ganis, & Kutas, 1998) or 100 ms (Liu, Harris, & Kanwisher, 2002) in adulthood. Because humans seem to process faces in a special manner, this has been considered a special type of cognitive process (Diamond & Carey, 1986) (Farah, Wilson, Drain, & Tanaka, 1998a; Turati, Valenza, Leo, & Simion, 2005). As a consequence, a debate about the etiology of face perception has ensued (Scott & Nelson, 2004).

By adulthood, most of us are face experts, although we usually take this skill for granted. Face perception is a skill that requires an extensive developmental period and continues to develop through adolescence (Carey, Diamond, & Woods, 1980; Cohen Kadosh & Johnson, 2007; Itier & Taylor, 2004). Faces are objects for which we have representational expertise, and face representations become more robust than nonface objects at a much faster rate from childhood to young adulthood (Tottenham, Leon, & Casey, 2006), arguably because of the massive amount of experience acquired with faces throughout development. The large literature on face processing in infants, children, and adolescents suggests that faces became special as a consequence of a *developmental process*.

Within the first 30 minutes of life, neonates will track a moving face farther than they will other patterns of equal contrast, complexity, and spatial frequency (Johnson, Dziurawiec, Ellis, & Morton, 1991), suggesting dedicated circuitry that creates a preference for faces at birth. Despite the initial preference for faces during infancy, such a preference does not signify expertise with faces per se (Cassia, Turati, & Simion, 2004). Face processing improvements during childhood and adolescence seem to be the result of adopting expert strategies for visual representation.

Adult Strategies

Adults excel at face processing as a result of their expert strategies used with faces, strategies that have been classified as configural, holistic, or second order relational strategies (Diamond & Carey, 1986; Farah, Wilson, Drain, & Tanaka, 1998; Rhodes, 1988). Adults' use of configural strategies interferes with their ability to identify the constituent parts of a composite face (top and bottom are different individuals (Young, Hellawell, & Hay, 1987), as evidenced by slower reaction times for identification of the top half of, for example, Richard Nixon's face when it is aligned with the bottom half of Prince Charles's face because alignment with Prince Charles's face changes the configuration of the entire face.

Configural processing refers to visually processing the object in its entirety, rather than focusing on its constituent parts. One thing that separates experts from novices is the experts' relative reliance on configural processing. For example, car, dog, greeble (i.e., computer generated artificial objects), and face experts (i.e., normal adults) all use configural information when discriminating their respective objects of expertise from each other (Gauthier & Tarr, 1997; Tanaka & Farah, 1993; Yin, 1969; Young et al., 1987). These visual strategies are orientation-specific (Carey, 1992), and adults perform worse on face identification tasks when the face stimulus is turned upside down relative to when it is right side up (Yin, 1969). This inversion effect is exaggerated for faces relative to other nonface objects and is often used as evidence that faces are

a special category of object processing. Although it is still debated when face processing reaches maturity (Freire & Lee, 2001; Itier & Taylor, 2004; Pellicano & Rhodes, 2003), most studies find that children under 10 years old are less sensitive to the configural properties of faces than those over the age of 10 years old are (Baenninger, 1994; Diamond & Carey, 1977; Flin, 1985; Tanaka, Kay, Grinnell, Stansfield, & Szechter, 1998). This ability improves until late adolescence (although it temporarily declines around 12 years old; Carey, 1992; Carey & Diamond, 1977).

It has been argued that children do not use configural strategies when processing faces (Carey et al., 1980; Diamond & Carey, 1977) because when asked to identify faces containing salient features, children under 10 are easily distracted from correct identification by any strong physical features. The argument is that since children do not appreciate the configural properties of an upright face, their performance is not facilitated when right side up relative to the inverted condition. Instead, children rely on featural processing in that they tended to use isolated features to make their decisions. Similarly, Pedalty and colleagues (1985) found that children under the age of 10 years use fewer features at one time when processing faces than adults do. The N170, an ERP component that is potentiated by whole faces, continues to develop until adulthood, whereas a mature N170 to eyes was present at 4 years old (Taylor, Edmonds, McCarthy, & Allison, 2001), suggesting that processing of constituent face parts develops first.

Puberty

Although age-related increases in face processing skills have been observed across a number of behavioral studies (Carey et al., 1980; Flin, 1985; Golarai et al., 2007; Goldstein, 1975; Lawrence et al., 2008), so has a performance dip in skills during the transition between childhood and adolescence. Some studies have found this shift in performance has been tied to pubertal changes (Carey et al., 1980), and yet others have not (Lawrence et al., 2008). Using a face-encoding task, prior work has suggested a role of puberty in face processing in that regardless of age, girls in the midst of puberty (summed score of 5–7 on breast and pubic hair development) encoded faces less efficiently than other girls (Diamond, Carey, & Back, 1983). It has been speculated that this dip was a result of pubertal changes that spur reorganization in the face processing system. Diamond et al. (1983) suggested that these data are evidence for genetic control of face processing skills and that this dip is necessary for adult processing (via a switch to mature configural processing) to develop. Alternative possibilities remain, however; puberty may be a period of life when attention to faces increases because of increased interest in faces (one's own or others'). Thus, the increased amount of time (and experience) looking at faces may contribute significantly to the reorganization of face-processing skills.

Neurobiological Correlates

Taken together, the behavioral findings suggest that the transition from childhood into adolescence is marked by an increased reliance on adult-like configural strategies for face processing. Face perception is supported by a distributed neural network (Haxby, Hoffman, & Gobbini, 2000). However, distinguishing faces from other object categories and from each other distinctively activates the fusiform gyrus (FG) (Haxby et al., 1991; Kanwisher, McDermott, & Chun, 1997; Puce, Allison, Asgari, Gore, & McCarthy, 1996; Sergent, Ohta, & MacDonald, 1992). Expert strategy use has been associated with recruitment of the FG, a functional region within the ventral occipitotemporal cortex portion of the ventral visual processing stream, which is especially sensitive to faces. It has a response that is greatest to whole faces (Tong, Nakayama, Moscovitch, Weinrib, & Kanwisher, 2000) and upright faces (i.e., is sensitive to inversion) (Kanwisher, Tong, & Nakayama, 1998) relative to partial or inverted faces. The response is slightly right lateralized, although the left fusiform gyrus also responds to faces. The fusiform gyrus response to faces is a reflection of high-level shape processing, not low-level feature extraction or an indication of increased visual attention (Kourtzi & Kanwisher, 2001).

The identification of a face-selective neural region has contributed to a long-standing debate in neuroscience, which is whether the brain represents information in modular form or in a distributed manner (Cohen & Tong, 2001). The modular view claims that the brain is organized into subcomponents that are dedicated to processing and representing a particular type of information in a domain-specific way (Kanwisher, 2000). The distributed view maintains that information is represented in a distributed manner such that regions of cortex process information in a domain-general way (Gauthier, Curran, Curby, & Collins, 2003; Haxby et al., 2001; Haxby et al., 2000). These responses overlap with each other, but are unique in their pattern of maximal and submaximal responses, such that the object category being viewed by the subjects could be discerned by other naïve subjects simply on the basis of the pattern of activity seen within the ventral occipito-parietal cortex. These patterns are

established, presumably, through experience, such that objects tune the cells in the ventral occipito-parietal cortex to respond with characteristic maxima as well characteristic minima. These minima are not captured by the typical image subtraction techniques (e.g., faces minus objects) that have been presented thus far. We will return to this issue of subtractive methodology in the next section on fusiform development.

Fusiform Development

Developmental fMRI studies have shown that responses of the fusiform gyrus in response to faces change across childhood and adolescence. When comparing responses to faces and houses (an example of subtractive methodology, a standard approach in fMRI data analysis), adolescents, but not younger children, showed significantly more activation in bilateral fusiform gyri for faces than for houses (Aylward et al., 2005). These types of contrasts are useful for obtaining an index of face selectivity (that is those voxels that show a stronger response for faces relative to another object). Using wide age ranges, researchers have identified large age-related change in FG responses to faces between 7 and 37 years old (Cohen Kadosh et al., 2013). Unlike many behavioral studies that had identified a shift in face processing skills, fMRI studies tend to show a linear increase in FG face selectivity with age.

Passarotti and colleagues (2003) investigated the development of response to faces relative to a location-processing task. Although no between-group statistics were performed on the imaging data, the authors suggest that the FG response to faces is more diffuse in children and becomes more focal with increasing age. These results are consistent with the notion that the representations of object categories are more overlapping at younger ages, comparison of the response to faces with response to another object category, like houses, would solidify those conclusions.

Other studies that have provided statistical age comparisons have confirmed an age-related increase in the spatial extent of face-selective suprathreshold activation within right FFA (Peelen, Glaser, Vuilleumier, & Eliez, 2009). Specifically, linear age-related increases were observed in the FFA selectivity to faces, and the age-related change was associated with an increasing perimeter of face-selectivity as age increased. The expansion of FFA into surrounding cortex was correlated with a behavioral improvement in recognition memory for facial identity (Golarai et al., 2007). A more focal, intense response in the FG to faces with increasing age is consistent with experiential tuning and refinement of the representation across adolescence. With development and experience, representations of face information (and other objects) should become more focal (or even appear modular if only their respective maxima are examined (reviewed in Burnett, Sebastian, Cohen Kadosh, & Blakemore, 2011).

Multivoxel pattern analyses (MPVA), which do not face the problem described earlier of subtractive methodology, detect differences between conditions with higher sensitivity than conventional univariate analysis by examining distributed patterns of activity across a swath of voxels. This approach has shown that the degree of FG distinctness for faces (over neural representations of other objects) is significantly lower in adolescents compared with adults (Golarai et al., 2007). The use of dynamic displays of faces has also been associated with an age-related increase in size of face-selective FFA between childhood and adolescence (Scherf, Behrmann, Humphreys, & Luna, 2007). In this study, no further changes in functional specificity for face processing were noted between adolescence and adulthood, although activity became more bilateral with age.

Thus, the neuroimaging evidence suggests that large changes occur in the neural representations of faces in the FG across childhood, adolescence, and adulthood. The changes appear to be linear, which is in contrast to many behavioral studies of face encoding and representation. It is possible that the resolution of the neural methods do not allow for the observation of shift-like changes in neural activity that are observed in behavioral data. Alternatively, it is possible that linear age-related changes in neural activity can nonetheless give rise to nonlinear changes in behavior. Another important change is that of changing connectivity between cortical and subcortical regions with the FG. Inputs into the FG may show large change from childhood into adolescence. For example, age-related changes in top-down modulation of FG connections have been observed from childhood through adulthood (Cohen Kadosh, Henson, Cohen Kadosh, Johnson, & Dick, 2010). Changes in connectivity will change the behavior of FG and hold promise in explaining much of the age-related variance for such a highly refined perceptual process that requires at least three decades to reach peak performance levels. The face processing literature has provided not only important information about how high-level visual perception develops across adolescence, but also more broadly provides a useful framework for considering how environmental factors and biological readiness interact to shape the social brain during adolescence. In the following section, we continue with this theme to consider the affective domain during adolescence.

NEGATIVE AFFECT-RELATED NEUROBIOLOGY DURING ADOLESCENCE

Large changes occur in processes related to negative affect across development, beginning in infancy and extending to adulthood. The common observation of adolescent moodiness warrants examination of changing negative affect neural circuitry during this time (Somerville, Jones, & Casey, 2010). Moreover, the increased incidence of mental illness, in particular clinical anxiety and depression (Kessler et al., 2005) with the onset of adolescence has led many neuroaffective researchers to target this developmental period.

The neurobiology of negative affect is complex, and typically involves interactions between subcortical and cortical regions. In adults, negative affect has been associated with differential activity in several cortical regions, most notably the prefrontal cortex and anterior cingulate cortex, and several subcortical areas, including the amygdala, hippocampus, periaqueductal grey, septal area, and ventral striatum. Among all of these regions, the amygdala's role in mediating negative affect has been most well characterized (particularly developmentally) and will be the focus of this section on negative affect.

The amygdala is a phylogenetically old structure (reviewed in Laberge, Muhlenbrock-Lenter, Grunwald, & Roth, 2006), present in all vertebrates in some form. The amygdala is in fact not one structure, but is composed of at least nine different nuclei; however, the ability to examine individual nuclei in humans is either extremely challenging or impossible, and therefore, most of the existing data in humans does not distinguish between nuclei. The amygdala rests subcortically and mediates emotional learning. One of the most well-characterized behaviors associated with amygdala function is Pavlovian fear conditioning, a basic form of learning by associating two events, one emotional and one neutral. However, the amygdala's role in affective behaviors may be broader and may include directing attention to emotionally relevant stimuli for the purposes of learning and maintaining arousal (Davis & Whalen, 2001).

The amygdala is also an ontogenetically old structure (reviewed in Tottenham & Sheridan, 2010). The basic architecture of the human amygdala is present at birth (Humphrey, 1968; Ulfig, Setzer, & Bohl, 2003), undergoes massive structural growth during early infancy (Gilmore et al., 2012; Uematsu et al., 2012), and then exhibits much more volumetric stability after this period. The same pattern has been identified in nonhuman primate models using longitudinal MRI methods (Payne, Machado, Bliwise, & Bachevalier, 2010). Despite these early structural developments, additional volumetric growth is also observed later around the transition into adolescence (Ostby et al., 2009). Boys who experience puberty at younger ages show greater amygdala volumetric growth than late maturers (Bramen et al., 2011), suggesting puberty might be one last period of additional growth. In fact, in this study, amygdala growth in boys was associated with circulating testosterone. There was no effect on pubertal timing in the girls, which may be a sign that the girls had already experienced their maturational amygdala growth by the ages examined in this study. This assertion is supported by the finding that amygdala volumes may reach a volumetric peak between 9 and 11 years old (with girls showing their peak 1.5 years earlier than boys) and may start to show normative decreases in volume after this age. Thus, maturation after puberty may be associated with declines in amygdala volume (Blanton et al., 2012).

Rodent Studies of Amygdala Development

Despite early structural development, rodent models have provided evidence that the amygdala remains functionally dormant for some time before exhibiting adult-like plasticity. For example, during the infant period, the amygdala is typically not recruited either by arousing stimuli (e.g., a male intruder; Moriceau, Roth, Okotoghaide, & Sullivan, 2004) or during odor-shock cued conditioning (Moriceau, Wilson, Levine, & Sullivan, 2006). This inactive functional period of the amygdala is due in part to the presence of the mother and in part to the developmentally normative low levels of glucocorticoid production, a neurohormone that is necessary for amygdala function onset (Moriceau et al., 2004). Glucocorticoids are the one of the primary products of the hypothalamic pituitary adrenocortical (HPA) axis, and seem to play a large role in the initial onset of amygdala functional engagement by environmental stimuli. This protracted developmental period in amygdala dormancy is striking considering the early structural development that occurs during the post-natal period.

Changes in amygdala reactivity have been observed beyond the infant period in rodent models. In rodent models, significant changes in amygdala-based function have also been identified in the juvenile (post-weaning, prepuberty) and adolescent (pubertal, preadulthood) period. As mentioned above, fear conditioning is a common paradigm used to test amygdala function. Cued fear conditioning pairs an unconditioned stimulus, for example a foot or tail shock, with a conditioned cue, for example a tone or an odor. This association relies heavily on amygdala-based learning. Freezing behavior is typically

used as an index of learned fear when conditioned stimuli are presented. During cued fear conditioning, freezing behavior (a threat-related behavior) is at its highest at early ages (during the juvenile period) and then attenuates to adult levels during adolescence (P35; Pattwell et al., 2012). This finding, although a behavioral index, may suggest a linear decrease in amygdala reactivity from the early juvenile period through adulthood during cued fear conditioning.

Contextual fear conditioning paradigms are designed to examine learning to express fear to a particular context that has been paired with an unconditioned stimulus. It is well understood that context conditioning relies on both intact amygdala and hippocampal-based learning (Zelikowsky, Hersman, Chawla, Barnes, & Fanselow, 2014). Using contextual fear conditioning paradigms, researchers have shown that unlike juvenile and adult mice, adolescent mice suppress expression of the learned fear response (Pattwell, Bath, Casey, Ninan, & Lee, 2011). The fear is clearly learned because retesting the adolescent mice in adulthood shows the emergence of the fear that was learned in adolescence. That is, the evidence seems to suggest that although adolescent mice learned the fear association with a particular context, the animals do not express the fear behaviorally during adolescence (i.e., via freezing measures). The source of fear learning expression suppression during adolescence was blunted synaptic activity in the basal amygdala and decreased intracellular signaling in the hippocampus. Thus, the fear conditioning literature taken together would suggest that, at least in the rodent, the amygdala exhibits very little reactivity during infancy, after which is exhibits a robust developmental switch to very high levels during the juvenile period, and attenuates across development, showing adult-like levels during cued fear conditioning, and may exhibit a suppression during adolescence (during contextual fear conditioning).

Human Studies of Amygdala Development

Fear conditioning studies have been used to study amygdala function in human adolescents. Relative to adults, adolescents showed greater amygdala recruitment during fear learning, although behaviorally, they reported less discrimination between threat and safety cues (Lau et al., 2011). In another study with only adolescent participants, those who reported increased fear showed amygdala increases during both the threat condition (aversive puffs of air to the eye) as well as the safe condition (Monk et al., 2003). These responses were lateralized, with the right amygdala being recruited for the threat condition and the left for the safety condition. This study showed that for adolescents, learning that certain cues are *not* associated with aversive puffs of air to the eye (i.e., safe conditions) is paralleled by recruitment of the amygdala in adolescents.

Although in many ways, using conditioning paradigms to examine amygdala learning in adolescence is ideal, the overwhelming majority of information about amygdala function in adolescence comes from using facial expression stimuli. In part, the challenge of using fear conditioning with developmental samples may limit their use. Facial stimuli, in contrast, provide a child-friendly means of obtaining reliable amygdala increases. As pointed out by Whalen et al., (2013), facial expressions are naturally conditioned stimuli that allow researchers to investigate normative variations in amygdala function. However, caution must be used when interpreting developmental amygdala findings in response to emotional stimuli because the nature of the neural response may interact with developmental experiences with those stimuli.

The use of facial expressions as stimuli has led to large advances in our understanding of human amygdala development. For example, several studies have shown increased amygdala response to facial expressions in adolescents relative to adults (Gee, Humphreys, et al., 2013; Guyer et al., 2008; Hare et al., 2008; Monk et al., 2003; Swartz, Carrasco, Wiggins, Thomason, & Monk, 2014; Vink, Derks, Hoogendam, Hillegers, & Kahn, 2014), with some studies showing higher and some showing lower reactivity in adolescence than childhood. This age related difference has been observed for facial expressions that have been masked and therefore not consciously perceived (Killgore & Yurgelun-Todd, 2007), suggesting that the amygdala during adolescence is highly sensitive to emotional cues even when presented below awareness thresholds. There is some evidence that pubertal development may drive some of these changes, although the findings are mixed, with some evidence for increased amygdala response with increasing pubertal change (Moore et al., 2012) and some for decreased amygdala response with increasing pubertal development (Forbes, Phillips, Silk, Ryan, & Dahl, 2011).

Some of the differences across studies may be attributed to differences in facial stimuli used. For example, longitudinal changes in amygdala reactivity were not observed from 10 years old to 13 years old when averaged across emotional expressions, but were observed in response to sad faces (Pfeifer et al., 2011). Similarly, a linear decrease with age was observed in response to fear faces (Gee, Humphreys, et al., 2013; Swartz et al., 2014; Vink et al., 2014), whereas adolescent-limited hyperactivity of the

amygdala has been observed in response to facial emotions when averaged across fear, happy, and calm faces (Hare et al., 2008).

The nature of the task may matter when considering amygdala reactivity during adolescence. For example, when the identifying emotional expressions in the context of a behavioral regulation task (Hare et al., 2008), inhibitory control processes may interact in important ways with amygdala signal. Indeed, the prefrontal cortex, a primary mediator of regulatory behaviors, undergoes significant change across development (Alahyane, Brien, Coe, Stroman, & Munoz, 2014; Casey, Giedd, & Thomas, 2000; Raznahan et al., 2011; Somerville et al., 2011). These changes are often reflected in changes in connectivity between PFC and the amygdala (discussed next).

Developmental Change in Amygdala–PFC Connectivity

Connections between the prefrontal cortex, in particular the medial prefrontal cortex (mPFC) support regulation of amygdala activity. Human neuroimaging studies in adults have revealed both structural (Kim & Whalen, 2009) (Johansen-Berg et al., 2008; Swartz et al., 2014) and functional (Gabard-Durnam et al., 2014; Hare et al., 2008; Roy et al., 2009) connections between the amygdala and mPFC similar to those identified in animal models (Amaral et al., 1992; Croxson et al., 2005; Ghashghaei, Hilgetag, & Barbas, 2007). The identification of inverse coupling between amygdala and mPFC activity in many fMRI studies may indicate top-down connections with a theorized regulatory role of the mPFC in controlling amygdala reactivity (Hare et al., 2008; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Kim, Somerville, Johnstone, Alexander, & Whalen, 2003; Pezawas et al., 2005). Interactions between the amygdala and mPFC are fundamental to emotion regulation (Delgado, Nearing, Ledoux, & Phelps, 2008; Goldin, McRae, Ramel, & Gross, 2008; Lieberman et al., 2007; Ochsner et al., 2004; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008) and extinction (Delgado et al., 2008; Hartley, Fischl, & Phelps, 2011; Milad et al., 2007; Phelps, Delgado, Nearing, & LeDoux, 2004) in adults. Moreover, individual differences in the strength of amygdala–mPFC functional connectivity have predicted greater amygdala habituation to affective stimuli (Hare et al., 2008), more effective emotion regulation (Banks, Eddy, Angstadt, Nathan, & Phan, 2007), and lower temperamental anxiety (Pezawas et al., 2005; Monk, 2008).

Evidence from nonhuman animal studies has confirmed the presence of top-down connections from the mPFC to the amygdala (Aggleton, Burton, & Passingham, 1980; Amaral & Insausti, 1992; Carmichael & Price, 1995; Ghashghaei & Barbas, 2002; Ghashghaei et al., 2007). The mPFC likely regulates through input to the basolateral nuclei of the amygdala and the intercalated cells, which inhibit amygdala activity by regulating inputs from the basolateral nuclei to the central nucleus (Akirav, Raizel, & Maroun, 2006; Milad & Quirk, 2002).

In humans, the prefrontal cortex exhibits protracted development and connections between the amygdala and the prefrontal cortex undergo large developmental change across middle childhood and adolescence (Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013; Perlman & Pelphrey, 2011; Swartz et al., 2014). In these studies, the nature of connectivity differs between children and adolescents, suggesting reorganization in the circuitry between these two time points. Correspondingly, regulation of emotion improves across this period and is mediated by the switch in connectivity (Gee et al., 2013). Adult-like connections between amygdala and mPFC are present during adolescence and are correlated with regulatory ability (Hare et al., 2008), a finding suggesting that the circuitry is functional, although the strength of the connections increases from adolescence to adulthood. Illustrating the immaturity of these connections during adolescence, Monk et al., (2003) showed that external constraints on affective processing (task demands) moderated the difference between adults' and adolescents' amygdala reactivity to emotional faces. That is, age-related differences were not observed when the task focused attention to a nonemotional feature (e.g., nose width of the stimulus), but adolescents' amygdala reactivity increased above adults when attention was not constrained by the task, suggesting that regulatory ability during adolescence is yet immature when compared with adults.

This interpretation of the functional MRI data has been supported by rodent data examining the development of the prefrontal cortex in emotional tasks. Extinction learning refers to a decrease in a behavioral response to a learned fear association, and is believed to be a new memory that is learned, which actively suppresses the original learned fear. In this way, extinction learning is a form of emotion regulation in that the animal learns to regulate its emotional response. In adult animals, this new learning is dependent on inputs from the medial prefrontal cortex, specifically the infralimbic cortex (IL; Milad & Quirk, 2002). In young rats, it has been shown that extinction learning is independent of the IL, and once the animal enters the juvenile period (prepubertal), extinction learning begins to be mediated by the IL as in the adult. Inactivation of IL in infant rats does not

impair extinction learning as it does in the adult and the juvenile animal (Kim, Hamlin, & Richardson, 2009; Kim & Richardson, 2009). This qualitative difference in the neural mechanics involved in extinction training in very young rats mirrors the qualitatively different patterns of amygdala–mPFC connectivity observed in young children (Gee et al., 2013), suggesting that the period before adolescence (i.e., childhood/juvenile period) is a developmentally unique period for amygdala–mPFC connectivity.

During adolescence, the circuitry beings to resemble to adult, although adolescent rats do not show complete maturation of amygdala–mPFC circuitry. The circuitry is more mature than the infant and juvenile, but it is not used as effectively as in the adult. Using extinction learning paradigms, it has been shown that adolescents exhibit decreased learning compared with adults, and notably compared with juveniles (Kim, Li, & Richardson, 2011; Pattwell et al., 2011; Pattwell et al., 2012). Pattwell et al., (2012) also showed that this decrease is present in adolescent humans, who did not show the typical decrease in galvanic skin conductance following extinction training. This decrease in extinction learning seems to be a suppression during adolescence, as extinction that is learned during adolescence (and is not expressed in adolescence) will be expressed later in life (Pattwell et al., 2012). In the IL, adolescent rats show decreased levels of phosphorylated mitogen-activated protein kinase (pMAPK), part of an intracellular cascade that is involved in producing long-lasting changes in synaptic efficacy. However, with increased training pMAPK increased in the IL in adolescents and extinction learning was achievable (Kim, Li, et al., 2011) . These findings are highly consistent with those from human adolescents who exhibit amygdala–mPFC connectivity that is adult-like, but still less robust than the adult (Gee et al., 2013).

Early-Life Adversity and Amygdala–PFC Development During Adolescence

Adversity early in life, particularly when it involves caregiving, is a potent stressor for the developing human (Fisher, Van Ryzin, & Gunnar, 2011; Gunnar & Fisher, 2006; Lewis, Dozier, Ackerman, & Sepulveda-Kozakowski, 2007; Tottenham, 2012). Stress can be defined as exposure to events that negatively impact emotional or physical well-being to an extent that exceeds an individual's ability to cope (Gunnar & Quevedo, 2007). A large clinical literature has established a strong link between early-life adversity and subsequent deficits in emotion regulation processes (e.g., anxiety and depression; Cicchetti, Rogosch, & Oshri, 2011; Dackis, Rogosch, Oshri, & Cicchetti, 2012; Valentino, Cicchetti, Rogosch, & Toth, 2008) that in adults and older adolescents have been associated with alterations in amygdala–PFC neurobiology (Burghy et al., 2012; Herringa et al., 2013; Kim, Loucks, et al., 2011). These deficits often emerge during the transition from childhood into adolescence, with a sharp increase in clinical anxiety and depression emerging after age 10 years (Angold & Rutter, 1992; Kessler et al., 2005; Kessler & Magee, 1993).

Although biological responses to acute stressors are adaptive for the organism in that they allow for management of potential challenges and increase the tone of stress systems that facilitate future stress regulation (Gunnar & Quevedo, 2007; McEwen, 2000), chronic exposures can overwhelm regulatory systems and ultimately result in mental health difficulties. These processes have been examined extensively in nonhuman animal studies of early-life adversity, which have frequently demonstrated that the amygdala is targeted by early caregiving adversity. For example, as reviewed in Tottenham & Sheridan (2010), the amygdala is particularly sensitive to early-life adversity perhaps because of its early development (Calabrese, Badea, Watson, & Johnson, 2013; Gilmore et al., 2012; Payne, Machado, Bliwise, & Bachevalier, 2010; Ulfig et al., 2003), thus being functionally available as a substrate for stress effects. At the molecular level, the amygdala is rich with stress hormone receptors starting at an early age (e.g., post-natal day 2 in the rat (Avishai-Eliner, Yi, & Baram, 1996; Fenoglio, Brunson, Avishai-Eliner, Chen, & Baram, 2004; Vazquez et al., 2006) and may even be more susceptible stress at early ages compared with adulthood. This position is supported by the findings that the amount of corticotropin releasing hormone (CRH; a stress hormone present in the central nervous system) needed to induce amygdala-mediated seizures in the developing rat is 200 times smaller than in the adult animal (reviewed in Baram & Hatalski, 1998).

CRH is a major hormone produced within the hypothalamic-pituitary-adrenocortical axis (HPA), a major stress regulatory axis of mammals. Psychosocial stress can adversely impact brain development largely through dysregulated activity of the HPA axis (reviewed in Loman, Gunnar, Early Experience, & Neurobehavioral Development, 2010). The activity of the HPA axis leads to peripheral (systemic) glucocorticoid increases via hypothalamus, pituitary, and adrenal gland activity and increases in central CRH (Makino, Gold, & Schulkin, 1994). Eventually peripheral glucocorticoids make their way to the brain by readily passing through the blood–brain barrier (Pardridge, Eisenberg, Fierer, & Kuhn, 1986) and binding

to receptors in numerous brain regions, including the amygdala. In the rodent (Moriceau, Roth, & Sullivan, 2010; Sapolsky & Meaney, 1986), and possibly in the human as well (Gunnar & Donzella, 2002), early life may represent a stress hyporesponsive period, during which time it is unlikely that a young animal will mount a full glucocorticoid response to a stressor. Because the developmental onset of amygdala function relies on increases in glucocorticoid production, the amygdala remains functionally dormant during this period under typical caregiving circumstances (Moriceau, Shionoya, Jakubs, & Sullivan, 2009; Shionoya, Moriceau, Bradstock, & Sullivan, 2007; Shionoya et al., 2006).

When caregiving conditions are suboptimal, as in the cases of abuse and neglect, the activity of the HPA axis changes, such that in the rodent infant, the stress hyporesponsive period comes to a premature end (and the infant exhibits glucocorticoid increases in response to environmental threats (Shionoya et al., 2006). As a result of increased glucocorticoid production under stressful conditions, the amygdala's functional dormancy ends prematurely (Moriceau & Sullivan, 2006; Moriceau et al., 2006). In other words, caregiving adversity (either abuse or maternal deprivation) has been shown to accelerate amygdala development as well as extinction learning in the rat (Callaghan & Richardson, 2011, 2012; Moriceau et al., 2006; Ono et al., 2008). There are remarkable parallels across species such that in humans too, there is evidence of accelerated amygdala–mPFC development following early caregiving adversity (Gee et al., 2013). This acceleration may be an adaptive response of the limbic-cortical circuitry to environmental cues that early maturation of defensive systems is warranted and might increase short-term survival. Although speculative, this acceleration may be seen as a short-term resilience factor (although it may have long-term costs).

The interpretation of this atypical behavioral and neural development as evidencing an ontogenetic adaptation (such that development is accelerated to meet the short-term needs of the young animal or human) has been described in the literature on resilience following early adversity (e.g., Cicchetti & Blender, 2006). The resilience literature is founded on the observations that not all individuals exhibit maladaptive developmental outcomes following exposure to adversity, and some even show great strength and gains in the face of adverse environments. One important question for future research to address is whether the stress-induced phenotypes described in this section are the neurobiological sources of resilience observed at the level of behavior. These types of interpretations are distinct from traditional views of early adversity influences in that they highlight the organism's adaptive response to environmental cues to develop in ways to maximize its performance in that context (even if the context is adverse).

In slightly older rats that have been exposed to maternal deprivation (post-natal day 17; prepubertal juveniles), similar accelerating effects of caregiving adversity have been observed for amygdala development. Typically, young rats exhibit infantile amnesia for learned fear memories; that is, typical juvenile rats exhibit forgetting of fear associations learned 10 days earlier. However, juvenile rates with a history of maternal separation exhibited near perfect retention of the memories, and it was suggested that early-life adversity removes the brakes on infant fear memories (Callaghan & Richardson, 2012). This effect was replicated by testing rats whose mothers drank the glucocorticoid cortiscosterone, who retained fear memories for up to a month—a finding that suggests premature fear learning is mediated by HPA axis activity.

Adversity that occurs in infancy can have long-term effects that are observable into adolescence, although the behavioral phenotypes in adolescence may differ compared with earlier ages. For instance, in rodents, exposure to either maternal abuse (induced by providing mothers with insufficient bedding) or exposure to olfactory classical conditioning in infancy is followed by depressive behaviors in adolescence (that were not observable at earlier ages) (Raineki, Cortes, Belnoue, & Sullivan, 2012; Sevelinges et al., 2011). Depressive behaviors were measured as willingness to continue swimming in a forced swim test, and animals with a history of early adversity gave up swimming earlier than controls. This giving up behavior was shown to be amygdala mediated such that temporary deactivation of amygdala rescued the depressive behaviors. These findings suggest that adolescence may be a period when emotional behaviors that result from early-life adversity manifest differentially than at younger ages.

Adolescence in humans is also a period that has been shown to reveal new emotional phenotypes following early adversity. Unlike anxiety, which tends to be elevated in both young children and adolescents following early-life neglect (postinstitutionalized [PI] children), depression symptoms are elevated in adolescents relative to children (Goff et al., 2013), mirroring epidemiological reports showing mood disorders exhibit a sharp rise after age 10 years. In a separate group of PI children adopted from Romania, parents reported that emotional problems exacerbated once children transitioned into adolescence (Colvert et al., 2008).

Given that rats and humans are both (semi-)altricial species that depend critically on species-typical caregiving for optimal development (reviewed in Cicchetti & Valentino, 2006; Tottenham, 2012), it is likely that early-life caregiving adversity operates through similar neurobiological pathways in both species. Children who have been exposed to maltreatment have exhibited alterations in HPA axis activity as measured by the glucocorticoid cortisol (Hart, Gunnar, & Cicchetti, 2008), particularly when the maltreatment occurred early in life (compared with later life maltreatment; Cicchetti, Rogosch, Gunnar, & Toth, 2010). The nature of HPA axis dysregulation seems to differ by the nature of adversity, as it has been found that children with a history of severe physical neglect tend to show very low levels of morning cortisol, whereas children with a history of severe emotional maltreatment tend to show elevated levels of morning cortisol (Bruce, Fisher, Pears, & Levine, 2009). Children with a history of extreme neglect in the form of institutional care (e.g., orphanages) have also been shown to exhibit very low levels of morning cortisol (Koss, Hostinar, Donzella, & Gunnar, 2014). These findings suggest that although patterns may differ as a function of type of adversity and timing, the HPA axis in developing humans is sensitive to adverse caregiving during development.

PI youth have also exhibited altered amygdala development, as has been demonstrated in the developing rodent. Using structural MRI, researchers have shown that youth who had experienced institutional care through their first birthday (and then been subsequently been adopted into stable families) exhibited enlarged amygdala volumes relative to peers (Mehta et al., 2009; Tottenham et al., 2010) (although see Hanson et al., 2015; Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012)). Enlarged amygdala volume in PI youth was associated with greater internalizing problems and trait anxiety by parent report as well as poorer behavioral regulation in the context of negative emotional information (Tottenham et al., 2010). Amygdala enlargement was observed in a separate study examining children (10-year-olds) who had been exposed to maternal depression, suggesting that low maternal interaction had served as a stressor for the developing infant even within a more normative range (Lupien, McEwen, Gunnar, & Heim, 2009). Functional MRI showed that amygdala reactivity was also elevated in PI youth (Gee, Gabard-Durnam, et al., 2013; Tottenham et al., 2011), and amygdala hyperactivity mediated group differences in eye contact (Tottenham et al., 2011). That is, youth with greater elevations in amygdala reactivity tended to exhibit decreased eye contact, which may serve as a short-term emotion regulation strategy to combat emotional overarousal that accompanies direct face-to-face contact. Although speculative, hyperactivity in the amygdala observed in this study may reflect an earlier development of amygdala function that has been observed in rodent studies of early adverse care.

More normative variations in care have also been shown to impact amygdala-PFC development. In a longitudinal study, early-life maternal stress measured when the child was 4 years old was associated with altered functional connectivity between the amygdala and prefrontal cortex at 18 years old. This association was fully mediated by salivary cortisol obtained during childhood (Burghy et al., 2012). Importantly, these associations were only observed in female participants suggesting that the circuitry between amygdala and PFC may be more sensitive to early-life stress in females and may explain increased rates of internalizing problems commonly found in females.

Developmental changes in the neurocircuitry supporting negative affect can be observed well into childhood and adolescence. Some changes are quantitative in nature and some exhibit qualitative shifts across this age span. These changes appear to define sensitive periods of development, or at the very least, developmental moments of increased plasticity. Adverse experiences that occur in infancy or childhood have significant effects on negative affect and associated neurobiology that can be observed in adolescence. Important directions for future research will include continued examination and identification of human sensitive periods that inform outcomes in adolescence.

MODELS OF ADOLESCENT RISK TAKING AND REWARD-SEEKING BEHAVIOR

Many experts in the field of adolescent development have written about the adolescent paradox (e.g., Chick & Reyna, 2011; Dahl, 2004): the notion that while adolescents are old enough to know better (Chick & Reyna, 2011) and are stronger, bigger, and faster and smarter than children (Dahl, 2004), they are at their lifetime peak of engaging in emotionally driven, impulsive, and potentially harmful behaviors. This paradoxical phenomenon is often explained by dual process models (Galván, 2012). There are many variations of the standard dual process model, but most distinguish between a fast, automatic, unconscious way of processing information and a slow, deliberative, conscious and advanced way of processing (Chick & Reyna, 2011; Evans, 2008). These systems or

processing methods have also been called impulsive versus reflective (Strack & Deutsch, 2004), holistic versus analytic (Nisbett, Peng, Choi, & Norenzayan, 2001), heuristic versus analytic (Evans, 2006) and experiential versus rational (Epstein, 1994).

From a neurobiological standpoint, analogous categories have been made in the form of β (which reflects weight placed on outcomes that are immediate) and δ (which represents delayed outcomes) systems, mediated by limbic structures and lateral prefrontal cortex, respectively (McClure, Laibson, Loewenstein, & Cohen, 2004), and an impulsive amgydala-based system and reflective prefrontal system (Bechara, 2005). Specific to neurobiological development in adolescence, overlapping theories have been described: a subcortical versus cortical system (Casey et al., 2008), an early emerging bottom-up system that expresses exaggerated reactivity to motivational stimuli and later maturing top-down cognitive control system (Casey & Jones, 2010) and a socio-emotional versus regulatory system (Steinberg, 2008). While these models have incorporated emotion synonymously with the bottom-up, automatic system, it is worth noting two models that have taken a more nuanced view of the role that emotion can play in behavior. Reyna and colleagues have proposed and put forth empirical evidence in support of the fuzzy trace model, which does not assume that the "influence of emotion on decision making is always primitive and usually maladaptive" and instead aims to integrate aspects of emotion that may lead to more mature choices (Chick & Reyna, 2011. p. 407). For instance, they posit that in mature decision makers quick, valenced choices (good–bad, approach–avoid) are not simple-minded but rather are the product of experience and insight. They also argue that mood can influence choices (e.g., negative feeling states encourage detailed representations of options and longer time to make a choice while positive feeling states tend to yield quicker, reactive processing; Storbeck & Clore, 2005). Finally, they note that arousal, or physiological reactivity, interacts with neural systems to influence decision making (Reyna & Rivers, 2008). The triadic model is another well-known model of adolescent motivated behavior (Ernst & Fudge, 2009). The model comprises three neural nodes that each holds functional control over distinct cognitive constructs: approach (striatum); avoidance (amygdala); and behavioral regulation (prefrontal cortex). Involvement of these systems depends on the context in which the motivated behavior occurs. For instance, in appetitive contexts, the model predicts that amygdala signal will be weak and does not elicit a withdrawal response while the striatal response is robust, eliciting an approach response with minimal input from the relatively immature regulatory system (Ernst, Romeo, & Andersen, 2009).

The models discussed in this section are beginning to help us explain and predict adolescent behavior but they are under constant refinement. New empirical evidence and reassessment of the interpretations and implications of the models help fine-tune how the field conceptualizes adolescent behavior and the role that changing neural systems play in normative development. For instance, recent calls have asked the field revisit the notion that cognitive control capacity in adolescents can be enhanced or impaired based on contextual factors (Somerville & Casey, 2010), note the need to place greater emphasis on how increased behavioral and neural sensitivity to affect may help confer adaptive advantages (Crone & Dahl, 2012) during this transitional developmental window and encourage network-based approaches that will help disentangle the complexity of adolescence behavior (Pfeifer & Allen, 2012). It is clear that no one model will completely explain adolescence but collectively, these models may set the stage for understanding the role that changing neurobiological systems play in development.

Changes in Reward Sensitivity Across Adolescence

Adolescence is characterized by heightened reward sensitivity. Relative to children or adults, converging evidence suggests that adolescents exhibit increased behavioral motivation to obtain rewards and greater arousal in response to rewards (Galván, 2013). In almost every measurable domain, adolescents exhibit greater interest and sensitivity to rewards than children or adults. For instance, there is a peak in reward and sensation-seeking behaviors (Steinberg et al., 2009), sensitivity to monetary incentives (Smith, Xiao, & Bechara, 2011) and social rewards (Chein, Albert, O'Brien, Uckert, & Steinberg, 2011), and even greater reactivity to sweet substances in mid-adolescence (Galván & McGlennen, 2013; Post & Kemper, 1993). These findings led to an explosion of interest in characterizing the neurobiological correlates that underlie these striking behavioral changes across adolescence, particularly as they relate to increased risk for psychopathology and addiction.

Dramatic increases in the onset of psychiatric disorders occur during the adolescent period. A United States population-based study of over 9,000 adults revealed that the median age of onset for any psychiatric disorder was 14 years (Kessler et al., 2005). Notably, prevalence of onset is greatest in disorders in which dysfunctional motivation or reward-related processes are implicated (Fairchild,

2011), including depression and substance use disorders. A recent survey of 10,123 adolescents (aged 13–18 years) by the National Institutes of Mental Health (Merikangas et al., 2010) reported that the prevalence of major depressive disorder increased two-fold over the adolescent period, while the rate of substance use disorders were six times higher in 17–18 year olds relative to 13–14 year olds (Fairchild, 2011). As will be discussed, emerging evidence suggests that, indeed, adolescents afflicted with psychiatric disorders exhibit aberrant recruitment of reward circuitry.

Neurochemical Changes

Reward sensitivity appears to be conserved across evolution, as many mammalian species, including rodents and nonhuman primates, show similar patterns of reward-related behavior as humans (Spear, 2011). Studies in juvenile rats show an inverted U-shaped developmental trajectory in the realms of reward and novelty seeking (Douglas, Varlinskaya, & Spear, 2003), risk-taking social interactions (Douglas, Varlinskaya, & Spear, 2004), and consummatory behavior (Friemel, Spanagel, & Schneider, 2010; Spear, 2011). For instance, adolescent rats are more sensitive than adult rats to the hedonic properties of sucrose (Wilmouth & Spear, 2009). They also demonstrate enhanced behavioral responses to novelty (Douglas et al., 2003) and social peers (Varlinskaya & Spear, 2008) compared with adult rats. The increased proclivity toward drugs in human adolescents versus adults is also observed in rats (Brenhouse & Andersen, 2008; Torres, Tejeda, Natividad, & O'Dell, 2008) and nonhuman primates (Nelson et al., 2009). This conservation of reward sensitivity has facilitated our understanding of the neurochemical and neurobiological correlates of this characteristic adolescent behavior. As described below, most studies are driven by the hypothesis that changes in dopamine circuitry account for reward-seeking behavior in adolescence.

Dopamine is the neurotransmitter most commonly linked to reward, as it is essential for detecting, responding to, and learning from rewarding events (Schultz, Dayan, & Montague, 1997). Burst firing of dopamine neurons occur in dopamine target regions in response to rewards (Roitman, Wheeler, Wightman, & Carelli, 2008), social interactions (Robinson, Heien, & Wightman, 2002) and unexpected events or stimuli (Takahashi et al., 2009). Importantly, this neurochemical reactivity to reward leads to increased approach behavior (Robinson, Zitzman, Smith, & Spear, 2011).

Much of the neurochemical development of the dopamine systems has been performed in rodent models. These models have shown that the mesocorticolimbic dopamine system undergoes significant changes during adolescence. In the striatum, dopamine levels increase during adolescence (Andersen, Dumont, & Teicher, 1997; Teicher, Andersen, & Hostetter, 1995) and dopamine D1 and D2 receptor expression in ventral striatum (VS) increases from pre-adolescence to adolescence, with some studies suggesting that binding in adolescence is higher than in adulthood (Doremus-Fitzwater, Varlinskaya, & Spear, 2010). Several reports have also noted that there is dopamine receptor over-production followed by pruning during adolescence (Teicher et al., 1995). Striatal dopamine receptor binding of D1 and D2 receptors peaks in adolescence at levels that are about 30–45% greater than those seen in adulthood (Tarazi, Tomasini, & Baldessarini, 1998, 1999; Teicher et al., 1995). Using autoradiography in male and female rats, Andersen et al. (1997) showed a sexual dimorphism of this effect, such that adolescent males had greater overproduction (approximately 4.6-fold) and elimination of striatal D1 and D2 striatal receptors than adolescent females (Andersen et al., 1997). Bolanos et al. (1998) showed that striatal slices from adolescent rat brain were more sensitive to the dopamine uptake inhibitors cocaine and nomifensine than adults (Bolanos, Glatt, & Jackson, 1998). These neurochemical and structural changes seem to have functional significance; functional studies show that compared with adults, the adolescent rat brain releases more dopamine if stimulated by environmental or pharmacological challenges (Laviola, Pasucci, & Pieretti, 2001), despite reduced dopamine release in basal conditions (Andersen & Gazzara, 1993; Stamford, 1989), and exhibit longer sustained dopamine release following a social interaction (Robinson et al., 2011).

A similar pattern of dopaminergic reorganization during adolescence is observed in prefrontal cortex, albeit with a more protracted elimination period (Andersen, Thompson, Rutstein, Hostetter, & Teicher, 2000). Confocal microscopy has revealed that retrogradely traced cortical output neurons in the prefrontal cortex express higher levels of D1 receptors during adolescence than older or younger rodents (Brenhouse, Sonntag, & Andersen, 2008). Similar U-shaped trajectories are observed in the firing rates of dopamine neurons (McCutcheon & Marinelli, 2009) and the number of dopamine neurons that are activated in anticipation of reward (Sturman & Moghaddam, 2012), peaking in adolescence. Together, these data suggest that during adolescence rewarding events may result in larger dopamine release, when compared with adults (Laviola, Macri, Morley-Fletcher, & Adriani, 2003).

Neurobiological Correlates

To investigate the neural phenotype of heightened reward sensitivity in humans, researchers typically pair fMRI with computer tasks that have a rewarding component. From these studies, we have learned that during adolescence there is an exaggerated neural activation in the VS to reward (Ernst et al., 2005; Galván et al., 2006; Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010; van Leijenhorst, Zanolie, et al., 2010). However, it is important to note that some reports have reported diminished activation to reward (Bjork, Smith, Chen, & Hommer, 2010) and either hyperresponding or hyporesponding during different stages of reward processing (e.g., anticipation of reward versus reward receipt) (Geier & Luna, 2009). Plausible explanations for differences across studies as well as implications for adolescent behavior are reviewed elsewhere (Galván, 2010).

Our own work suggests nonlinear patterns of striatal development. In an fMRI study, children, adolescents, and adults performed a youth-friendly computerized reward task in which they were presented with three cues that were each associated with increasing monetary values (small, medium, and large) (Galván et al., 2006). The task was similar to a reward learning task previously used in monkeys to show that dopamine firing patterns temporally shift to track the most meaningful information in the task (Fiorillo, Tobler, & Schultz, 2003). In brief, the monkey work showed that in the beginning of the task, the dopamine response is greatest when reward is received; however, as the animal learns that a particular cue predicts the reward outcome, the dopamine neurons become increasingly more responsive to the reward-predicting cue. By the end of the experiment the dopamine neurons are minimally responsive to the actual reward delivery and most responsive to the cue (Fiorillo et al., 2003). In our study, all age groups showed strong VS activation to the reward outcome. However, interesting developmental differences emerged when we examined how the temporal dynamics of the task influenced VS activation. By the end of the experiment, adolescents showed the overall greatest activation to the large monetary reward, while adults showed the least. However, within the adult group, the greatest activation was to the cue and not to the actual reward outcome, which paralleled the monkey data. Particularly interesting is that these neural patterns of activation mapped onto the behavioral differences between groups. In the beginning of the experiment, none of the groups showed differences in reaction time (RT) to the three reward types. However, by the end of the experiment, adults had learned to discriminate between them, as evidenced by faster RT to the large reward and slowest RT to the small reward. Adolescents became significantly slower to the small reward and children continued to show no differences in reaction between the three reward types. From this study, we concluded that neural discrimination of reward value is paralleled by changes in behavior and that adolescents show heightened VS sensitivity to reward compared with children and adults (Galván et al., 2006).

Other work supports this hyperresponsive view as well. For example, a probabilistic monetary reward task was used to show that adolescents demonstrated significantly more VS activation than adults when they earned money (Ernst et al., 2005). It has also been shown that adolescents exhibit heightened VS activity both in anticipation of reward (Geier et al., 2010; Jarcho et al., 2012) and to expected (van Leijenhorst, Moor, et al., 2010) and unexpected (J. R. Cohen et al., 2010) reward outcomes. Even in response to liquid rewards (e.g., sugar water), the adolescent brain shows greater striatal activation than adults (Galván & McGlennen, 2013). Together, these findings demonstrate that across different labs, methodological techniques, participant samples, and reward tasks, the adolescent brain is hyperresponsive to one or more aspects of reward processing, compared with other age groups. This unique sensitivity to reward is behaviorally meaningful, as it has been tied to task performance as well as real-world reward sensitivity (e.g., drug use, thrill-seeking behavior).

Individual Differences in Reward Sensitivity

It is important to note that not all adolescents exhibit heightened reward sensitivity. In fact, the likelihood of reward seeking behavior is largely influenced by individual differences, including reward availability, gender, and personality traits. For instance, reward-seeking and risk-taking behaviors are more frequent in individuals with elevated novelty and sensation seeking (Rao et al., 2011) and in those who report greater risk taking among their peers. More recently, studies using fMRI have suggested that neural variability may also help explain individual differences in reward sensitivity.

Neuroimaging data in adults shows that individual differences in activation of the VS predict reward-related risks (Kuhnen & Knutson, 2005). For example, individuals who exhibit greater VS activation in response to appetitive cues are subsequently more likely to make risky choices to obtain monetary reward (Kuhnen & Knutson, 2005), to consume unhealthy snacks (Lawrence, Hinton, Parkinson, & Lawerence, 2012), to gain weight and report

greater sexual desires (Demos, Heatherton, & Kelley, 2012). Recent work using positron emission tomography, a technique used to examine dopamine function in adult humans (Tatsch & Poepperi, 2012), found that individual differences in dopamine function in the VS and ventromedial prefrontal cortex were correlated with a willingness to expend greater effort for larger rewards (Treadway et al., 2012), further implicating dopamine in reward sensitivity.

These associations between VS activation and reward have also been observed in developmental populations. By examining individual neural responses to reward and correlating them with self-reported risk-taking behavior, we found a positive association between VS activation in response to monetary reward and the likelihood of engaging in risky behavior across development; that is, individuals more likely to report higher frequency of risky behavior in real-life showed greater VS recruitment (Galván, Hare, Voss, Glover, & Casey, 2007). A more recent study found similar results in adolescents, with a positive association between individual differences in reactivity of the VS during anticipation of reward and externalizing behaviors such as drug use (Bjork, Smith, Chen, & Hommer, 2011).

Psychopathology, Addiction, and Reward Circuitry

Research over the past decade has yielded new insights into neural alterations in psychopathology. A number of studies have implicated reward circuitry in underlying internalizing and externalizing disorders, albeit with opposite effects. While internalizing disorders such as depression are typically associated with blunted striatal responses to upcoming rewards, externalizing disorders are usually characterized by enhanced activation of striatal regions (Fairchild, 2011).

Anhedonia, the inability to experience pleasure, is a leading symptom in major depressive disorder. Neuroimaging studies have found that depressed children and adolescents exhibit reduced neural sensitivity to rewards (Forbes et al., 2009) and to happy faces (Monk et al., 2008) in striatal and orbitofrontal cortex. Interestingly, girls who have a high familial risk for depression but who themselves have not been diagnosed with depression also show disruptions in reward-related brain activity (Gotlib et al., 2010). These developmental findings are consistent with studies in adult depressives, which show reduced activation in the ventral striatum (McCabe, Cowen, & Harmer, 2009; Steele, Kumar, & Ebmeier, 2007), caudate (Pizzagalli et al., 2009), cingulate, and ventromedial prefrontal cortex (McCabe et al., 2009).

Numerous studies have suggested that individuals with substance use disorders exhibit impairments in reward processing. For instance, adolescent and adult substance abusers are more likely to take risks to gain large rewards than nonstimulant users (Leland, Arce, Feinstein, & Paulus, 2006), discount delayed rewards more steeply than control subjects (Kollins, 2003; Petry & Casarella, 1999), and to be more influenced by potential rewards available on a simulated gambling task than controls (Stout, Rock, Campbell, Busemeyer, & Finn, 2005). However, neuroimaging findings across different labs are not as consistent as the behavioral findings. While some fMRI studies report blunted striatal activation in substance-dependent adults (Buhler et al., 2010; Goldstein et al., 2007), there is also evidence showing increased activation in dependent adults (Bjork, Smith, & Hommer, 2008). Surprisingly, many fewer studies have examined reward processing in adolescent substance users. One study in adolescent smokers found decreased striatal activation during reward processing relative to nonusers (Peters et al., 2011). Another study examined children of alcoholics and found that ventral striatal activation was positively correlated with precursive externalizing risk, as well as current and lifetime alcohol consumption (Yau et al., 2012). In a large sample of 14-year-old adolescents ($N = 324$), the IMAGEN Consortium found that personality traits (impulsivity, sensation seeking, extraversion) were more predictive of early onset drinking than reward-related brain activation (Nees et al., 2012).

In sum, the growing literature on adolescent reward circuitry suggests that characteristic increases in reward sensitivity during adolescence are due to neurobiological changes. These changes appear to be nonlinear in nature, such that there is a study increase in both reward behaviors and reward-related brain activation as children become adolescents, followed by a gradual decrease from adolescence into adulthood. Numerous theories about the role of reward circuitry in psychiatric disorders and substance use have been put forth (Ernst, Pine, & Hardin, 2006), but much more empirical work is necessary to delineate the exact mechanisms by which aberrant reward sensitivity contributes to the onset and maintenance of these disorders.

RISK TAKING IN THE DEVELOPING BRAIN

Adolescence and young adulthood are characterized by increased risk-taking behavior. Typically, the occurrence of these risk-taking behaviors follows an inverted U-shape

pattern across development, being relatively low in childhood, increasing and peaking in adolescence and young adulthood, and declining again thereafter (for overviews, see, e.g., Reyna & Farley, 2006). This behavioral pattern is intricately tied to neurodevelopmental changes in brain regions critical for decision making and risky behavior, namely, frontostriatal circuitry, and has significant implications for both positive and negative outcomes. On one hand, increased drive, motivation and willingness to take risks help adolescents become fervid activists, leaders, and explorers. It is no coincidence that young people are often at the forefront of new ideas, impassioned defenders of ideals, and the ones having the most fun. The risk-seeking nature of the teenage brain undoubtedly contributes to the energy and passion we as adults admire and envy in youth. From an ecological perspective, this increased proclivity toward exploration and willingness to take risks, regardless of the potentially harmful consequences facilitates important developmental milestones. Seeking out potential mates, self-reliance, and new adventures is at the very core of transitioning from a state of dependence on caregivers to one of relative independence. In fact, risk taking around the time of sexual maturation is not unique to humans; like their human counterparts, rats undergoing the developmental transition of adolescence show a significant increase in the amount of time spent in social interactions with peers (Varlinskaya & Spear, 2008) and at play. They also are more likely to engage in risk-taking behavior, and they seek out new situations and explore unknown areas more avidly than they do at either a younger age or in adulthood (Spear, 2000). In humans, Shedler and Block (1990) proposed that modest amounts of risk taking may be constructive. According to their findings, adolescents who engaged in moderate amounts or risk taking were found to be more socially competent both in childhood and adolescence than were those who abstained or who were more frequent risk takers (Shedler & Block, 1990).

However, excessive or high-stakes risk taking may lead adolescents to stumble into harmful behaviors. Risk taking that takes the form of drug experimentation, thrilling but dangerous behaviors (e.g., speeding or car racing), or recklessness can lead to irreparable negative outcomes. As such, the public health concerns of teenage risk taking, along with the potential for positive exploration and growth, have led to a vigorous interest in understanding risk taking and decision making in the adolescent brain (Casey & Jones, 2010; Ernst & Fudge, 2009; Reyna et al., 2011).

As reviewed in the previous section, there is significant neurobiological change in frontostriatal circuitry during adolescence. Neural regions in this system are also those that exhibit robust sensitivity to risk. Early neuroimaging studies of risk in adults used task paradigms that manipulate variance in the probability distribution of reward, enabling the identification of neural responses associated with objective risk defined in economic terms (Schonberg, Fox, & Poldrack, 2011). This work identified risk-related responses in several regions, mainly the striatum (e.g., (Preuschoff, Bossaerts, & Quartz, 2006) anterior cingulate cortex (ACC), lateral orbitofrontal cortex (OFC) and insula, all of which are also responsive to monetary gains or losses (Critchley, Mathias, & Dolan, 2001). The posterior parietal cortex, dorsolateral prefrontal cortex (DLPFC) and anterior insula were found to be more active during a choice of risky versus safe options (Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003); in addition, fMRI activation levels in the right insula following a negative outcome were negatively correlated with subsequent risky choices. Similarly, in a study using a financial decision-making paradigm risky (as opposed to safe) choices were predicted by increased activation in the ventral striatum immediately preceding the risky choice (Kuhnen & Knutson, 2005).

Developmental fMRI studies of risk taking report similar circuitry, albeit at varying degrees of activation. Using a child-friendly gambling task, van Leijenhorst and colleagues (2010) examined brain activation during risk taking in a sample of children, adolescents, and adults. Behaviorally, there were no age-related differences in risk-taking behavior for gambles associated with high rewards; all participants were more likely to take risks as the potential reward increased. However, developmental differences emerged at the neurobiological level: activation in dorsal ACC showed a linear decrease with age, whereas activation in VMPFC and VS showed an inverted U-shaped developmental pattern, with a peak in adolescence (van Leijenhorst, Zanolie, et al., 2010). Similar findings were reported using a different risky decision-making task in high-risk behavior induced greater activation in dorsal ACC, ventrolateral OFC and mPFC than the control condition (Shad et al., 2011).

These activation patterns during risk taking are predictive of individual differences in actual risk-taking behavior. Neuroimaging data in adults shows that individual differences in activation of the VS predict reward-related risks (Kuhnen & Knutson, 2005). For example, individuals who exhibit greater VS activation in response to appetitive cues are subsequently more likely to make risky choices to obtain monetary reward (Kuhnen & Knutson, 2005), to consume unhealthy snacks (Lawrence et al.,

2012), to gain weight and report greater sexual desires (Demos et al., 2012).

These associations between VS activation and reward have also been observed in developmental populations. By examining individual neural responses to reward and correlating them with self-reported risk-taking behavior, we found a positive association between VS activation in response to monetary reward and the likelihood of engaging in risky behavior across development; that is, individuals more likely to report higher frequency of risky behavior in real life showed greater VS recruitment (Galván et al., 2007). A more recent study found similar results in adolescents, with a positive association between individual differences in reactivity of the VS during anticipation of reward and externalizing behaviors such as drug use (Bjork et al., 2011).

Risk Taking in Context

As converging evidence provides the empirical link between reward circuitry and risk taking, attention has started to shift toward understanding the contextual factors that interact with risk taking and associated brain function. Broadly speaking, researchers are empirically testing the notion that risky choices differ based on whether the decision to engage in risk is made under hot or cold contexts, with the former referring to choices made under emotionally arousing circumstances and the latter referring to choices made in more deliberate, nonemotional or cognitive contexts. Studies using the hot and cold versions of the Columbia Card Task (CCT). Figner, Mackinlay, Wilkening, & Weber (2009) have shown that heightened involvement of affective processes in risky decision making (in the hot CCT) leads to increased risk taking in adolescents compared with children and adults (Burnett, Bault, Coricelli, & Blakemore, 2010; Figner et al., 2009). In contrast, when risky decisions are made involving mainly deliberative processes and no or little affect (cold CCT), adolescents show the same levels of risk taking as children and adults (Figner et al., 2009). (See also van Duijvenvoorde & Crone, 2013 for similar hot/cold differences in adolescents). These findings show similarities to findings from research using a simulated driving game in which the presence of peers leads to increased risk taking in adolescents (but not adults) when making choices between driving through versus stopping at traffic intersections with a yellow light (Chein et al., 2011; Gardner & Steinberg, 2005). This socioemotional influence of peers on adolescents is not surprising given that much risk taking in adolescents occurs in the presence of peers (Gardner & Steinberg, 2005), and more broadly, given the changes in social motivations during this period, with adolescents achieving greater independence from their parents and, in turn, peers growing in importance (Blakemore, 2008).

Peers

Why do peers influence risk taking? Mounting evidence suggests that social interactions and the presence of peers elicit emotions that subsequently engage affective neural systems. Given the lower threshold with which rewards yield exaggerated neural signals in adolescents compared with adults or children, peers are conditioned stimuli that engage the reward-sensitive striatum. Research suggests that changes in brain development during adolescence orients teens toward the social world (Blakemore, 2010) and heightens neural sensitivity to peers (Guyer, McClure-Tone, Shiffrin, Pine, & Nelson, 2009). Further, recent work suggests that there is a relationship between resistance to peer influence, risky behavior and ventral striatal activity (Pfeifer et al., 2011). As such, peers induce significant contextual changes at both the behavioral and neurobiological levels. Chein and colleagues (2011) provided convincing fMRI evidence in support of this hypothesis (Chein et al., 2011). Building on work by the same group showing that adolescents took more risks on a computer-simulated driving game than adults (Gardner & Steinberg, 2005), they demonstrate that the presence of peers increases teen risk taking by enhancing activity in the brain striatal (reward) circuitry (Chein et al., 2011). These compelling findings lend further support for the notion that context (in this case, peers) can alter the relative contribution of neural mechanisms underlying reward seeking and risk taking.

Stress

Due to the significant changes in social landscape, expectations and identity development, adolescence is marked by increased stress and heightened reactivity to acute stress, compared with children and adults (Dahl & Gunnar, 2009; Dorn et al., 2006). Adolescence bears many types of stressors (Persike & Seiffge-Krenke, 2012) including family, academic (Arnett, 2002; Bynner, 2000), and peer (Eccles et al., 1993; Smetana, Campione-Barr, & Metzger, 2006) pressures. For example, demanding coursework and preparation for college placement often lead to stressful increases in schoolwork (McAndrew, Akande, Turner, & Sharma, 1998). Socially, adolescents frequently experience stressors in the domain of romantic relationships and peer networks

(Hand & Furman, 2009; Kuttler & LaGreca, 2004). Also common is elevated stress associated with developing more intimate friendships while maintaining family relationships and establishing autonomy (Laursen & Collins, 1994; Nieder & Seiffge-Krenke, 2001). Ethnographic data demonstrates that these effects are observed globally, as adolescents from over 140 cultures report high feelings of stress in these domains (Schlegel, 2001). These normative life stressors are paralleled by higher basal cortisol levels in older adolescents or more pubertally mature adolescents (Adam, 2006; Netherton, Goodyer, Tamplin, & Herbert, 2004). Stroud and colleagues used laboratory-based manipulations to demonstrate a heightened stress response to psychological stressors in adolescents relative to children (Stroud et al., 2009). In response to typical laboratory stressors (e.g., public speaking) and to a novel social stressor (e.g., peer rejection), adolescents showed a greater response in salivary cortisol and other physiological measures compared with children (Stroud et al., 2009). These results parallel more traditional investigations that utilized performance and/or academic stressors (Adam, 2006; Klimes-Dougan, Hastings, Granger, Usher, & Zahn-Waxler, 2001). In addition, Gunnar and colleagues (2009) show nonlinear patterns of heightened basal HPA activity and greater stress reactivity to a stressor across development, with adolescents showing the most robust effects compared with children and young adults (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009). This increase in actual and perceived stress has consequential implications for risky behavior and decision making because the neural systems most sensitive to stress.

A recent survey by the National Center on Addiction and Substance Abuse (CASA) in a large sample of adolescents (n=1987; aged 12–17) reported an alarmingly strong association between high rates of poor health choices and high levels of stress. The survey found that high-stress teens (those who report high levels of perceived stress with ratings of 7–10 on stress scale) are twice as likely as low-stress teens (those who report low levels of perceived stress with ratings of 0–3 on stress scale) to smoke, drink, and use illegal drugs. A separate, longitudinal study in a sample of younger youth (4th–8th graders) found that higher perceived acute stress is associated with increased risk for alcohol use and higher likelihood of driving in a car with a drunk driver (Rew, Horner, & Brown, 2011). The results are also consistent with findings that greater perceived acute stress levels are significantly associated with greater risk taking among older adolescents (Fields, Leraas, Collins, & Reynolds, 2009; Schepis, McFetridge, Chaplin, Sinha, & Krishnan-Sarin, 2011). These results are intriguing in that they beg a causal question: does stress cause adolescents to engage in risky decisions, or does risky decision making in adolescents lead to greater feelings of stress?

In a large sample of 89 late adolescents, Johnson and colleagues (2012) found that participants who experienced a cognitive or social laboratory stressor exhibited greater risk taking behavior on a computerized risk-taking task than those in a control no-stress condition (Johnson, Dariotis, & Wang, 2012). A separate study examined whether perceived stress influences delay discounting (i.e., the preference for a smaller, immediate reward over a larger, delayed reward). Adolescents with higher perceived daily-life stress were more likely to have difficulties delaying rewards (Fields et al., 2009), which is consistent with a similar study in adults (Diller, Patros, & Prentice, 2011).

Work from our own group suggests that acute stress perturbs decision making in adolescents and young adults (ages 14–21) (Galván & McGlennen, 2012). In this study, participants' daily, self-perceived stress was monitored via text messaging for 2 weeks. Each participant visited our lab twice during the study—once when he or she endorsed a high level of stress and once when he or she endorsed a low level of stress. At the lab, they each performed a risky decision-making task and a response inhibition task. By administering these different cognitive challenges, we were able to determine whether any observed stress effects were bestowed upon cognition in general or decision making in particular. Participants made riskier decisions under conditions of high versus low stress (Galván & McGlennen, 2012). In a follow-up fMRI study in adolescents and adults using the same design, all participants exhibited worse response inhibition under high, versus low, stress states, an effect that was significantly stronger in adolescents. At the neural level, there was a significant age by stress interaction, such that adolescents exhibited less recruitment of the dorsolateral prefrontal cortex (DLPFC) during inhibition under high-stress versus low-stress; adults evinced the opposite activation pattern in DLPFC (Rahdar & Galvan, 2014). These data suggest that the developing brain may be a more vulnerable target to the cognitive and neurobiological effects of daily stress.

Family

More recently, work has extended the study of how social relationships influence risk taking by examining the role of the family unit on this behavior. The changing nature of family relationships during the adolescent years can have significant implications for risk taking and associated

health consequences, such as substance use and externalizing problems (Gfroerer & de la Rosa, 1993; Warner et al., 2006). Family obligation—the importance of spending time with the family, high family unity, family social support, and interdependence for daily activities (Cuellar, Arnold, & Gonzalez, 1995; Fuligni, 2001)—is a key aspect of family relationships that may have significant consequences for adolescents' health. Family obligation and family pride have been associated with reduced likelihood and delayed onset of drug use and lower rates of externalizing problems (German, Gonzales, & Dumka, 2009; Gil, Wagner, & Vega, 2000; Kaplan, Napolos-Springer, Stewart, & Perez-Stable, 2001; McAndrew et al., 1998; Romero & Ruiz, 2007; Vega, Zimmerman, Warheit, Apospori, & Gil, 1993). Moreover, neuroimaging research shows that family assistance is associated with activation in neural regions responsive to reward (Telzer, Masten, Berkman, Lieberman, & Fuligni, 2010). Together, these studies suggest that family obligation is associated with feelings of value, meaningfulness, and intrinsic reward, which may deter adolescents from engaging in health compromising risky behavior.

Family obligation may reduce risk taking because it is a meaningful activity that increases adolescents' motivation to control their own impulses and desires for the sake of their family as well as provides opportunities to practice engaging in self-control. For example, adolescents who value family obligation report greater negative consequences for engaging in risky behavior because risk taking reflects poorly upon their family (German et al., 2009). Therefore, the negative consequences of risk taking may be more consequential for these youth, and so risk taking becomes comparatively less rewarding. Risk taking is amplified during states of affective arousal among adolescents, such as in the presence of peers (Chein et al., 2011; Figner et al., 2009; Gardner & Steinberg, 2005). In contrast, during cold deliberative states of decision making, heightened risk taking is not always found among adolescents (Figner et al., 2009). Therefore, family obligation values may decrease the affective nature of risk taking, reducing reward sensitivity during risk. In the absence of heightened arousal, cognitive control capacities may come online and reduce risky decision making. Likewise, adolescents who value family obligation may be more motivated to engage in self-control to avoid risky behaviors. Indeed, scholars refining the dual systems model suggest that cognitive control capacities are not necessarily immature during adolescence, but, rather, there is a great deal of flexibility, and the degree to which adolescents engage in cognitive control is strongly influenced by the motivational salience of the context (Crone & Dahl, 2012). Thus, reward sensitivity and self-control may be altered by adolescents' motivation to avoid risk taking. To test this hypothesis, Telzer and colleagues (2013) examined whether family obligation related to neural markers of risk taking. Participants performed the Balloon Analogue Risk Task (BART), a computerized assessment of risk taking, while undergoing fMRI. They also provided measures of family obligation values and self-reported risk-taking behavior. Results suggest that adolescents with greater family obligation values show decreased activation in the ventral striatum (VS) when receiving monetary rewards and increased dorsolateral prefrontal cortex (DLPFC) activation during behavioral inhibition. Reduced VS activation correlated with less real-life risk taking behavior and enhanced DLPFC activation correlated with better decision-making skills. Thus, family obligation may decrease reward sensitivity and enhance cognitive control, thereby reducing risk-taking behaviors (Telzer, Fuligni, Lieberman, & Galván, 2013).

SOCIAL COGNITIVE DEVELOPMENT

Similar to other primates, humans are social creatures. We are highly interested, responsive to, and dependent on social interactions. It is thus unsurprising that cognitive neuroscientists have mapped out neural regions that are particularly attuned to social information. This system is commonly referred to as the social brain and is composed of the medial prefrontal cortex (mPFC), the temporoparietal junction (TPJ), the posterior superior temporal sulcus (pSTS), the amygdala, the anterior insula, and the anterior insula. Together, these brain regions work in concert to facilitate different aspects of social cognition that are critical for forming and maintaining social bonds, including thinking about the mental states of others (often called mentalizing), observing and interpreting faces, recognizing conspecifics, and making decisions that consider social information.

During adolescence, there is an increased interest in social information, a phenomenon that has been termed *social reorientiation* (Nelson, Leibenluft, McClure, & Pine, 2005). During this period, there is refinement of social processes and cognition, such as the understanding of others' emotions, intentions and beliefs, increased motivation for social change and heightened self-consciousness and intensification of peer relationship (Steinberg & Morris, 2001). Perhaps not coincidentally, there are marked structural and functional neurodevelopmental changes in regions of

the social network. In a recent study of almost 300 youth and 900 scans, Mills and colleagues examined changes in the structural developmental trajectories of social brain regions in the longest ongoing longitudinal neuroimaging study of human brain maturation (Mills et al., 2012). Structural trajectories of grey matter volume, cortical thickness, and surface area were analyzed using surface-based cortical reconstruction software and mixed modeling in a longitudinal sample of 288 participants (ages 7–30 years, 857 total scans). Grey matter volume and cortical thickness in medial prefrontal cortex, TPJ, and pSTS decreased from childhood into the early 20s. The anterior temporal cortex increased in grey matter volume until adolescence and in cortical thickness until early adulthood. Surface area for each region followed a cubic trajectory, peaking in early or preadolescence before decreasing into the early 20s (Mills et al., 2012).

These structural changes appear to have functional consequence, as the myriad studies that have addressed questions of social cognition have found significant changes in these same regions. Mentalizing has been studied a variety of ways, including through the use of tasks that asked participants to decide whether a speaker was being sincere or ironic (Wang, Lee, Sigman, & Dapretto, 2006), to think about one's own intentions (Blakemore, den Ouden, Choudhury, & Frith, 2007), to engage self-reflective processing (Pfeifer, Lieberman, & Dapretto, 2007), and to consider intent in animation-based characters (Moriguchi, Ohnish, Mori, Matsuda, & Komaki, 2007). Despite the diversity of tasks, there was a consistent neurodevelopmental pattern of decreasing mPFC activation with age, with adolescents showing heightened engagement of this region relative to adults. In addition, there is evidence for differential functional connectivity between mPFC and other parts of the mentalizing network across age (Burnett, Bird, Moll, Frith, & Blakemore, 2009). During scanning, adults and adolescents asked to think about scenarios in which a social (e.g., embarrassment and guilt) or a basic (e.g., disgust and fear) emotion would be experienced. Compared with adults, the adolescent group showed stronger connectivity between the mPFC and pSTS/TPJ during social relative to basic emotion, suggesting that there are developmental changes in functional integration within the mentalizing system (Burnett et al., 2009). Using dynamic casual modeling and a task that requires participants to take into account another person's perspective to guide the selection of an action, Hillebrandt and collegues examined effective connectivity between prefrontal and posterior brain regions (Hillebrandt, Dumontheil, Blakemore, & Roiser, 2013). They found that social demands modulate the backward connection from the mPFC more strongly than the forward connections from the superior occipital gyrus and medial temporal gyurs to the mPFC (Hillebrandt et al., 2013).,

A number of functional neuroimaging studies have investigated the neural correlates of facial-expression recognition from childhood to adulthood (Goddings et al., 2012). An fMRI study reported increased activity in a number of lateral and superior prefrontal regions (bilaterally for girls, right sided for boys) in response to fearful faces in individuals between the ages of 8 and 15 years (Yurgelun-Todd & Kilgore, 2006). In a different study, adolescents (aged 9–17 years) showed activation of the ACC and left OFC during passive viewing of fearful faces (relative to neutral faces), whereas adults (aged 25–36) did not (C. Monk et al., 2003). When attention was directed to a nonemotional aspect of fearful faces, activity in the ACC was higher in adolescents than in adults. Therefore, in this study, frontal activity tended to decrease between adolescence and adulthood (C. Monk et al., 2003). In addition the findings indicate that, whereas adults modulate brain activity based on attention demands, adolescents modulate activity based on the emotional nature of a stimulus. This suggests that the neural basis of the ability to pay attention to a nonsalient stimulus (in this case, the nose of a fearful face) in the presence of emotionally evocative, attention-grabbing stimuli (the eyes of a fearful face) is still undergoing maturation between adolescence and adulthood (Blakemore, 2008).

In sum, converging evidence from numerous, laboratories around the world have independently found that during social cognitive tasks, the mPFC shows decreasing activation as adolescents become adults. This phenomenon is not yet understood but two nonmutually exclusive explanations have been put forward. One possibility is that the cognitive strategy for mentalizing changes between adolescence and adulthood (Blakemore, 2008). A second possibility is that the functional change with age is due to neuroanatomical changes that occur during this period, an argument that has received greater support with the recent paper described above.

TRANSLATIONAL IMPLICATIONS

Changes in behavior across the transitions into and out of adolescence have significant implications for both positive and negative outcomes. These changes facilitate the important developmental milestone of transitioning from a state of dependence on caregivers to one of relative independence. However, in the quest for autonomy, individuals may encounter challenges that are rooted in the changing brain.

Neurodevelopmental changes in limbic regions and auxiliary brain networks are implicated in psychiatric disorders, addiction, and impulse control problems. Dramatic increases in the onset of psychiatric disorders occur during the adolescent period. A United States population-based study of over 9,000 adults revealed that the median age of onset for any psychiatric disorder was 14 years (Kessler et al., 2005). Notably, prevalence of onset is greatest in disorders in which dysfunctional motivation or reward-related processes are implicated (Fairchild, 2011), including depression and substance use disorders. A recent survey of 10,123 adolescents (aged 13–18 years) by the National Institutes of Mental Health (Angst et al., 2010; Swendsen et al., 2010) reported that the prevalence of major depressive disorder increased two-fold over the adolescent period, while the rate of substance use disorders were six times higher in 17–18 year olds relative to 13–14 year olds (Fairchild, 2011). As new research on the neural correlates of symptomology is conducted, emerging evidence suggests that, indeed, adolescents afflicted with psychiatric disorders exhibit aberrant recruitment of reward circuitry.

In both internalizing and externalizing disorders, a number of studies have implicated reward circuitry, albeit with opposite effects. Whereas internalizing disorders such as depression are typically associated with blunted striatal responses to upcoming rewards (Forbes & Dahl, 2010) compared with healthy controls, externalizing disorders are usually characterized by enhanced activation of striatal regions (Fairchild, 2011). Anhedonia, the inability to experience pleasure, is a leading symptom in major depressive disorder. Neuroimaging studies on anhedonia report that depressed and anxious children and adolescents exhibit reduced neural sensitivity to rewards (Forbes et al., 2009) and to happy faces (Monk et al., 2008) in frontostriatal circuitry. Interestingly, girls who have a high familial risk for depression (Gotlib et al., 2010), or who endorse depressive symptoms (Goff et al., 2012), but who themselves have not been diagnosed with depression also show disruptions in reward-related brain activity. These developmental findings are consistent with studies in adults who suffer from depression, which show reduced activation in the ventral striatum (McCabe et al., 2009; Steele et al., 2007), caudate (Pizzagalli et al., 2009), cingulate (McCabe et al., 2009), and ventromedial prefrontal cortex (McCabe et al., 2009).

Limbic regions are also at the core of neural impairments in individuals with substance use disorders but the exact mechanism of influence is unclear. While some fMRI studies report blunted striatal activation in substance-dependent adults (Buhler et al., 2010; Goldstein et al., 2007), there is also evidence showing increased activation in dependent adults (Bjork et al., 2008). Surprisingly, very few studies have examined reward processing in adolescent substance users, despite the tight link between measures of reward hypersensitivity and substance use (Bava & Tapert, 2010; O'Conner, Stewart, & Watt, 2009). One study in adolescent smokers found decreased striatal activation during reward processing relative to nonusers (Peters et al., 2011). Another study examined children of alcoholics and found that ventral striatal activation was positively correlated with precursive externalizing risk, as well as current and lifetime alcohol consumption (Yau et al., 2012). In a large sample of 14-year old adolescents (N=324), the IMAGEN Consortium found that personality traits (impulsivity, sensation seeking, extraversion) were more predictive of early onset drinking than reward-related brain activation (Nees et al., 2012). These heterogeneous findings highlight how little is known in this important area of research. Without a mechanistic understanding of what leads some individuals to simply be experimenters in the teenage years versus those who come to abuse substances throughout life, it will be challenging to implement preventative approaches or effective treatment.

So how can research on brain development help ameliorate symptoms or negative outcomes? A long-standing goal of developmental psychopathology has been to do just that: bridge fields of study in ways that leverage basic research into real-world contexts (Cicchetti & Toth, 2009). Principles from developmental psychopathology provide guidance as to how best to marry these disparate fields: investigations at multiple levels of analysis, including clinical, biological, psychological, and social-contextual, are necessary to translate basic research information into application (Cicchetti & Toth, 2009). To this end, developmental psychopathology practice engages research in both typical and atypical population, and in maladaptive and adaptive processes, in an effort to understand development from a multi-faceted perspective. With the advent of more sophisticated tools, such as fMRI and ERP, the time is ripe to include additional levels of analyses to holistically address symptoms. This type of knowledge has led to improved efforts in assessing, diagnosing, and treating psychopathology but the field still has much to gain and the application of this perspective will only facilitate further insight into how to bridge basic and applied research.

SUMMARY AND FUTURE DIRECTIONS

The field has made great strides in characterizing the neurobiological changes that underlie social, emotional, and cognitive changes during adolescence. However, as new methods, questions, and ideas emerge, probing more

deeply into how the developing brain processes influences behavior will become possible. In particular, the field would benefit greatly from addressing a few questions that have direct relevance to translational applicability (Cicchetti & Toth, 2009).

First, a greater focus on developmental timing is warranted. If one goal of clinical application is to ameliorate symptomology, then knowing *when* the introduction of prevention or intervention strategies will be most effective is critically important. Currently, most researchers categorize individuals into age groups with rather large age ranges due to funding and resource-related constraints but moving forward will require meticulous attention to variations in behavioral and neural response based on age. Identifying the basic mechanisms and timing of change allows us to identify moments when the system is in its most dynamic state. Identification of these sensitive periods is crucial to identifying moments when interventions would have their greatest impact on mental health outcomes. For instance, recent translational research suggests that there are significant individual and developmental differences in the efficiency of fear-regulatory circuitry (Hartley & Casey, 2013). These data have significant implications for the treatment of disorders such as anxiety, which typically involves exposure therapy based on extinction-learning principles. One might imagine that if there normative changes in fear learning across development that there are, similarly, points in development when this type of therapy will be more or less effective. Although empirical support for this notion has yet to be garnered, a future clinical study examining exposure therapy efficacy across development is necessary.

Second, once optimal points of intervention have been identified, it will be important to determine how to manipulate sensitive periods. In other words, knowing how to reopen early-life sensitive periods in adolescence or reopening adolescent sensitive periods later in life to redirect a problem phenotype will significantly impact clinical intervention.

Third, it is important to underscore the strengths of adolescence. Although extensive statistics and literature serve as important reminders of the vulnerabilities associated with this period of development, only recently have the possibilities associated with adolescence been highlighted (Casey & Caudle, 2013; Crone & Dahl, 2012; Galván, 2014). At no other time in life are individuals faced with as much novelty, opportunity, excitement, and thrill than during adolescence. Youth are intrinsically motivated to learn about the world, to change policies and ideas they oppose and to make as many social links as possible. These normative characteristics are important for our species, as they ensure that we challenge existing principles, create new inventions, and stay connected to one another. Although previous media portrayals of adolescent brain research focused on the negative aspects of adolescence, researchers have used empirical research to show that ontogenetic changes in the adolescent brain are adaptive for the individual. Future research should focus on better determining how society can leverage normative adolescent phenotypes to enact healthy outlets for adolescent tendencies and appropriate responses to adolescent behavior.

Finally, with the inclusion of research from nonadolescent humans in this chapter, our goal was to illustrate the importance of considering transitions in and out of adolescence. As BJ Casey noted in a recent special issue, "we cannot know which behavioral and brain changes are specific to adolescence if we don't know what they looked like before and after this period of development" (Casey & Caudle, 2013. p. 80). This transitional approach will help the field differentiate adolescent-specific from adolescent-emergent from adolescent-nonspecific changes. Importantly, it will allow us to move beyond using age as an independent variable and instead focus on understanding the process by which change occurs, the agents of change that are highly correlated with age such as puberty and changes in social structure, and the vast individual differences that contribute to observable behavior.

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CHAPTER 19

Integration of Developmental Neuroscience and Contextual Approaches to the Study of Adolescent Psychopathology

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INTRODUCTION

The transitional, formative, and malleable nature of adolescence makes it arguably the most important period of development for the study of developmental psychopathology. As a transitional period, adolescence is marked by rapid and dramatic intraindividual change in the realms of biology, cognition, emotion, and interpersonal relationships and by equally impressive transformations in the major contexts in which children spend time: the family, the peer group, and school. These transformations present both opportunities and challenges that require adaptation on the part of the developing adolescent.

For a significant proportion of adolescents, the interaction between changes in intraindividual functioning and changes in context can result in the emergence of emotional and behavioral problems. Adolescence is often accompanied by the onset of behavioral and emotional problems that are rarely seen prior to adolescence, such as substance use, disordered eating and body image, and major depression. Beyond these disorders, adolescence is a period of experimentation with a broad range of risk-taking behaviors and, for some youth, the escalation of conduct problems into illegal activity. Although not considered a diagnosed psychopathology, risk-taking and criminal behavior during adolescence

nevertheless increase morbidity and mortality during this developmental period.

As a formative period, adolescence is important to the study of developmental psychopathology because after this age, some patterns of emotional and behavioral problems may be more difficult to alter. For reasons not yet understood, there appears to be relatively more consolidation of psychopathology in adolescence than in earlier developmental periods. Prospective longitudinal studies suggest that the majority of chronic and recurrent psychiatric problems that afflict adults are rooted in adolescence. Indeed, the initial manifestations of affective disturbance, antisocial behavior, and substance abuse emerge less frequently during the adult years compared with earlier developmental periods, and typically, these behavioral and emotional disorders emerge during the adolescent years (Paus, Keshavan, & Giedd, 2008). This applies both to problems with behavior, as in the disruptive behavior disorders, as well as to problems with emotion regulation, as in the mood and anxiety disorders (Moffitt, Caspi, Harrington, & Milne, 2002; Pine, Cohen, Gurley, Brook, & Ma, 1998).

In addition to being a heightened period of risk for the emergence of psychopathology, it is notable that adolescence is also critical in setting lifestyle trajectories with enormous long-term implications for adult health. These trajectories include early patterns of behavior in the realms of exercise; nutrition; the use of tobacco, caffeine, alcohol, and other mood-altering substances; and sleep and other health habits. Furthermore, adolescence is the period for establishing the foundation for advanced education, major life roles, relationships, and working toward long-term productive goals. As such, adolescence is an important developmental period for intervention efforts that aim to promote successful adaptation and prevent the development of more serious psychopathology in adolescence and adulthood.

Despite its formative nature, evidence increasingly suggests that adolescence is a period of malleability or developmental plasticity. Patterns of neural connections among and between systems of emotion, motivation, and cognitive processes undergo a natural reorganization during adolescence (Dahl, 2004; Spear, 2010). These neurological changes affect, and are likely affected by, experience. For example, the onset of puberty is associated with biologically based changes in motivational and emotional brain systems linked to reproductive behavior in ways that contribute to the development of sexual and romantic interests. A second example is how the developing concept of *self,* the cognitive abilities to imagine future versions of this self, and affective experiences of fears or excitement linked to tragic or heroic versions of the future self, emerge during adolescence. Early experiences not only influence youth in psychological and emotional domains but also have an impact through brain–behavior interactions on the patterns of connections among neural systems. The impact of this continued brain maturation on emotional, cognitive, social, and behavioral development has yet to be thoroughly studied, particularly within individuals, but the evidence for ongoing developmental processes and apparent plasticity of brain development in adolescence suggests that this period may present unique opportunities for prevention and intervention (including cognitive-behavioral, contextual, psychopharmacological, or other psychotherapeutic treatments).

Our goal in this chapter is to stimulate a research agenda that integrates neurobiological and contextual influences on the development of psychopathology, with the goal of pinpointing the developmental processes that underlie specific types of psychopathology in ways that can be used to leverage prevention and intervention efforts. For example, a better understanding of the processes underlying changes in affect regulation during pubertal maturation, and how context may affect that vulnerability, may ultimately inform interventions targeted toward children at high risk for developing a depressive disorder (such as individuals with symptoms of anxiety or those with a strong family history of depression) *before* the development of a more serious disorder. Similarly, a deeper understanding of the developmental processes and unique opportunities in this maturational interval can eventually inform a range of policies and programs designed to decrease vulnerability and risk, and promote healthier adolescent development, which hopefully will ultimately increase resilience.

The organization of this chapter begins with several general observations about development during adolescence and a conceptualization of adolescence as a unique period of both risk and opportunity. We then turn to a description of brain-based frameworks for understanding adolescent psychopathology, normative changes in brain development, and the developmental processes that are critical for the emergence of adolescent psychopathology. Following our overview of brain-based frameworks for understanding adolescent psychopathology, we examine several aspects of developmental and contextual change that occur in adolescence. In particular, we focus on the primary changes of adolescent development, how these changes are linked with psychopathology, and identifying individuals who change in the most vulnerable ways. The

chapter concludes with a call for new, interdisciplinary research that examines the interplay among neurobiological, psychological, and contextual influences on psychopathology in adolescence.

ADOLESCENCE AS A DEVELOPMENTAL PERIOD: GENERAL OBSERVATIONS

Adolescence as a Time of Transition

Adolescence as a developmental period is characterized by major transitions that can be organized broadly into biological, cognitive, and contextual domains. Change occurs universally in each of these domains and with virtually no exceptions, as adolescents undergo these transformations in every society. While the fundamental changes of adolescence can be sorted into one of these three domains, it is important to note that these categories are not mutually exclusive, and that transformations in one domain likely influence ongoing processes in the other domains. As such, interactions between and among biology, cognition, and context are noted throughout this chapter.

The past decade of scientific study on adolescence has yielded rapid increases in our understanding of the adolescent brain, its protracted development across the adolescent years, and the associated motivational and affective outcomes of this process. Much work has been focused on how the putative immaturity of the adolescent brain and associated developmental changes in affective and motivational processes might increase risk for psychopathology. Furthermore, research has begun to focus on a much broader array of contextual influences on adolescent development and how they might affect psychopathology. Given the salience of changes in adolescence across biological, cognitive, and contextual domains, we discuss in depth each of these major developmental transitions throughout this chapter.

The most formative biological change of adolescence is puberty, which culminates in reproductive capability. Across adolescence, individuals undergo rapid changes in physical appearance (the secondary sex characteristics, including breast development in females and the development of facial hair in males) and the development of reproductive capability (the primary sex characteristics directly affecting the sex organs). A second formative biological change of adolescence is continued maturation of the brain. In the past, the majority of research on brain development focused on the periods of infancy and early childhood, with the notion that the period from birth to age three was the most critical stage for neural development. Data revealing that the brain continues to mature well into the second decade of life, and perhaps beyond, have shifted research attention to the neurodevelopment of the adolescent period. Undoubtedly, rapid and fundamental changes in biology affect not only how the adolescent functions, but also how an adolescent is treated within his or her interpersonal relationships and by society as a whole, as well as the adolescent's self-perceptions. These major biological changes of adolescence are described in detail later in this chapter.

Concurrent with biological transformations such as puberty and brain maturation, adolescents undergo major changes in cognition and cognitive ability across adolescence. Continued development of brain structure and function occur throughout this developmental period, with these changes likely underlying the developmental gains in sophisticated thinking abilities that characterize adolescence. Compared with earlier developmental periods, adolescents are better able to think about hypothetical situations, abstract concepts, and what the future holds. The implications of these cognitive abilities are pervasive, enabling adolescents to think more hypothetically and abstractly about themselves, their relationships, and society. Moreover, the changes of puberty alter various brain-based affective and motivational processes, including reward orientation and cognitive control. The continued development of brain structure and function underlie the gains in cognitive control and regulatory competence that are observed across the adolescent period. Despite these cognitive gains, adolescence still represents a time of maturation and refinement of cognitive ability, and, as we discuss in a later section, this continued development is linked to risk for psychopathology.

The third domain of transitional change of adolescence is social or contextual in nature. First, behavioral autonomy increases across adolescence, as parents give their children increasing control over their activities and actions (Gutman & Eccles, 2007). Moreover, as adolescents transition into the teen years, time spent with parents declines and time spent within the peer group context increases (Larson, Richards, Moneta, Holmbeck, & Duckett, 1996). Although parents still hold influence over their adolescents (see subsequent section on the family context), it is certainly the case that adolescents spend more time with peers, either in structured (school, sports) or unstructured activities (hanging out), than with any other socialization agent (Brown & Larson, 2009). Notably, individuals also begin dating during the adolescent years, and thus navigation of romantic relationships, sex, and sexuality all occur – at varying times – throughout the second decade of life. More so than in earlier eras, modern adolescents are

exposed to a broad range of media and typically engage in high levels of media use (i.e., TV, music, gaming, and social networking). Finally, all of these contextual changes are nested within the adolescent's neighborhood and society, each of which may have direct, indirect, and interactive effects on the development of psychopathology.

Any discussion of developmental psychopathology in adolescence must also consider the broader historical context. Recent biological and social changes, together, have greatly expanded the length of this maturational stage. Most contemporary writers, including the present authors, define adolescence as the interval between the onset of puberty (ordinarily seen as the most important marker of the beginning of the period) and the transition into adult roles (ordinarily seen as the most important marker of the period's conclusion). Both historical data and anthropological studies indicate that the mean age of sexual maturation in premodern societies was around 16 or 17 years—very close to the age at which young people began assuming the adult responsibilities of work and family formation. Thus, throughout most of human history, adolescence—the interval between the onset of sexual maturity and the assumption of adult responsibilities—was often only a few years in length.

More recently, however, the physical manifestations of puberty have been occurring at earlier ages. A number of studies have documented this secular trend among females (Euling et al., 2008) and researchers have begun to document the trend among males as well (Herman-Giddens et al., 2012). At the same time, and especially in the most recent decades, the end of adolescence (taking on full adult roles and responsibilities) has been occurring at a relatively later time, with the prolongation of formal schooling and the extension of the adolescent's economic dependency on his or her family of origin. In the United States, for example, the *average* age of menarche (one of the final steps in pubertal maturation in girls) occurs at 12 years (Steinberg, 2011), but full entry into adult roles is delayed for the majority of the population until at least 20 years of age, and often well beyond (Arnett & Tanner, 2005). Thus, in most contemporary industrialized societies, many youth spend close to a decade with sexually mature bodies and reproductively activated brains, prior to taking on adult roles or status.

This general expansion of the adolescent interval makes early- and mid-adolescence in contemporary industrialized society a period of particular vulnerability for maturational disjunctions across biological, cognitive, and contextual domains. More specifically, this confluence of historical and individual changes in patterns of biological maturity, contextual demands, and contextual supports appears to have opened a window of risk for behavioral and emotional health problems for many young members of modern societies as they negotiate the transition from childhood to adolescence and from adolescence to adulthood.

Taken cumulatively, then, the adolescent years are characterized by dramatic changes in biology, cognition, and context from the start of puberty to the acquisition of adult roles. As we discuss in the subsequent sections of this chapter, these transitions of adolescence make the developmental period a time of risk for psychopathology, but also a malleable part of the life span, where prevention and intervention efforts may be powerful.

Adolescence as a Time of Risk

Although many adolescents navigate the important transitions of the period effectively, changes in the function of any one domain—or the interaction of multiple domains—introduce vulnerability to the onset of psychopathology. Adolescence is therefore a period of heightened risk in general because change occurs in more domains concurrently than in other developmental periods, with some individuals at greater risk than others. A portion of children clearly begin to struggle with various forms of psychopathology as they move into adolescence. Children at greatest risk include those who enter this demanding transition already vulnerable, as well as those whose prior vulnerability becomes expressed during this time (due to genetic predispositions and/or earlier adverse experiences); those for whom the disjunctions between developmental domains are greatest; individuals that encounter the greatest challenges during the transition; children with the least contextual support; and those with both few resources and heightened genetic vulnerability, developmentally acquired vulnerability, or some combination of these factors. The application of a developmental psychopathology approach to the study of adolescence can aid in identifying when these problems emerge, under what conditions, how they are maintained or integrated into these domains, as well as how they change with development. Thus, one of the most important goals of research on psychopathology in adolescence is to achieve a better understanding of the processes and mechanisms by which biology, cognition, and context interact during this transition, culminating in increased vulnerability and risk which, for some individuals, can spiral into significant long-term impairments and psychopathology.

On the other hand, risk does not inevitably lead to poor outcomes. Risk is defined as the probability of a

specific outcome within a group or population. During adolescence, teenagers can manifest considerable resilience despite their status as a member of a group at risk for negative outcomes. It is equally important to understand why certain individuals navigate this interval of development successfully, despite vulnerability, so that patterns and processes of protection and resilience can be better understood. An informative research agenda will thus need to focus both on mechanisms and on the trajectories of development during the adolescent transition, as well as preceding transitions. The adolescent transition may activate preexisting risk conditions—conditions that may reflect a cumulative chain of risk, divergence into a pathway of vulnerability, biological embedding of experiences over time, or the expression of a latent problem from an earlier critical period—or introduce new risks that are specific to this developmental period. Increasing our knowledge of these developmental processes is crucial to inform policies and programs aimed at improving the health and well-being of adolescents and the adults they will become. The very fact that multiple transformations are occurring in adolescence may provide not only heightened risk, but windows of opportunity for positive influence (Cicchetti & Blender, 2006).

One of the goals of the study of adolescent psychopathology is to identify and understand features of adolescence that increase vulnerability to psychological disorders and maladjustment. Examination of biological and contextual factors that are specific to adolescence has provided important perspectives on *why* adolescence is a period of vulnerability to psychopathology. Fundamental biological changes occur during adolescence in the domains of brain development, pubertal maturation, and sleep, in combination with key contextual changes occurring in relationships with parents, peers, and the community. These fundamental biological and contextual factors tend to follow an established ordering of events and are evident across cultures, but the wide individual variability seen in the characterization of these factors such as their timing, rate of change, or their interaction with each other has provided important explanations for why the period of adolescence renders some individuals vulnerable to psychopathology.

Adolescent Brain

Relative to childhood and adulthood, the adolescent brain shows remarkable change in both structure and function. For example, even relatively simple structural measures, such as the ratio of white to gray matter in the brain, demonstrate large-scale changes into the late teenage years (Giedd, 2004; Giedd & Rapoport, 2010; Sowell, Trauner, Gamst, & Jernigan, 2002). The continued maturation of neural systems and structures during adolescence may make individuals more vulnerable to the development of disorders. Given this developmental pattern, the last decade has seen an increase in brain-based frameworks for understanding the emergence of psychopathology during this period. Although we discuss these perspectives in detail later in the chapter, generally these frameworks suggest that changes in the connections within and between core neural circuits that play a role in generating and regulating emotion, motivation, and cognition place adolescents at risk for psychopathology. For example, continued elimination of unused synaptic connections, decreases in cortical grey matter volume and thickness, and the degree of myelination are all neural processes occurring during the adolescent transition which could impact development of psychopathologies. Neural connectivity and neurotransmission properties are another explanation for the age-related and psychopathology-related differences found involving adolescent brain function. Other brain-based explanations for increased vulnerability to psychopathology include exposure to stress and perturbations in stress hormone production and regulation during adolescence that would be expected to impact neural systems still undergoing refinement (Eiland & Romeo, 2013). Still other adolescent-specific risk mechanisms that operate through the brain may be related to when pubertal hormones are generated, particularly if a mismatch is created between changes in levels of pubertal hormones and development of brain circuits that are needed to support adaptation to the physical and social changes instantiated by the onset of puberty.

The mechanisms that contribute to psychopathology are likely diverse and complex. Through three illustrative examples, puberty, sleep, and changes in the parent-child relationship, we illustrate how a variety of changes in biology, cognition, and context may contribute to the underlying risk for psychopathology that emerges during adolescence.

Puberty

Because puberty brings a constellation of intraindividual changes that impact a child's physical appearance, motivations and drives, social interactions and relationships, and risk taking, puberty inherently casts the period of adolescence as a time of risk for psychopathology. Pubertal processes introduce vulnerability in a variety of ways during adolescence. With regard to puberty itself, the timing/age of pubertal onset and the tempo/rate of

pubertal change can increase risk for psychopathology, with these factors having differential effects for boys and girls in terms of well-being and adjustment. For example, early onset of puberty in girls is linked to a wide range of problems in multiple domains including psychological, academic, and health (Graber, Lewinsohn, Seeley, & Brooks-Gunn, 1997; Stice, Presnell, & Bearman, 2001; Wichstrom, 1999). In addition, the rate of change in pubertal status has been associated with change in depressive symptoms particularly in boys but not girls (Mendle, Harden, Brooks-Gunn, & Graber, 2010). Other work has shown that both pubertal timing and tempo are especially important for predicting psychological outcomes in girls, while showing a weaker association with outcomes among boys (Marceau, Ram, Houts, Grimm, & Susman, 2011). Vulnerability to psychopathology is also heightened in adolescence because pubertal changes coincide and interact with social-contextual changes, including increased salience of peers, burgeoning romantic relationships and exploration of one's sexuality, and more advanced cognitive abilities that permit rumination and social comparison about one's changing body and physical attractiveness (Mendle, Harden, Brooks-Gunn, & Graber, 2012). The hormonal changes of puberty may also heighten an adolescent's stress reactivity (Sontag, Graber, Brooks-Gunn, & Warren, 2008; Stroud et al., 2009; E. Walker, Sabuwalla, & Huot, 2004), while also augmenting his/her orientation toward and motivation for thrill seeking, exploration outside the home, and rewarding stimuli. Finally, the link between early maturation and girls' problem behavior may be partly due to common genetic influences (i.e., genes that influence both the timing of puberty and involvement in delinquency; Harden & Mendle, 2012).

Sleep

Notable changes occur in the regulation of sleep patterns during adolescence, which appear to be intricately linked to pubertal development (Carskadon, 2011). Dahl, Trubnick, al-Shabbout, and Ryan's (1997) longitudinal study of normal sleep found that changes in REM sleep showed a strong link to pubertal increases in reproductive hormones, whereas changes in stages 3 and 4 non-REM sleep appeared to be more strongly linked to the rapid physical growth at puberty (as measured by body mass index). There is also a circadian shift (delay of sleep) resulting in a biologically based tendency to stay up later (and sleep in later) that occurs in early to midpuberty and an increase in objectively measured daytime sleepiness, which may represent an increased biologic need for sleep during pubertal maturation (Carskadon, 2011). There are further maturational changes in the effects of sleep loss in adolescence. By midpuberty, adolescents show much greater objectively measured sleepiness, as well as complex changes in mood and affect regulation, in response to sleep loss (Gregory & Sadeh, 2012).

The impact of pubertal change on sleep and arousal may have important implications for the development of psychopathology, with, for example, adolescent depression directly associated with disturbed sleep (Gregory & Sadeh, 2012) and, particularly, difficulties falling asleep (Gangwisch et al., 2010). Furthermore, compromised sleep in early adolescence is associated with poor performance when processing emotional information (Soffer-Dudek, Sadeh, Dahl, & Rosenblat-Stein, 2011). In addition to the direct effects of sleep loss on outcomes such as mood, attention, and motivation, sleep loss in adolescents can also increase stimulant use during the day (e.g., caffeine, nicotine, methylphenidate, and illicit stimulants), which may in turn increase risk for psychopathology. Accumulated sleep loss results in a variety of behavioral adaptations such as extensive catch-up sleep on the weekends (by sleeping in very late). These types of adjustments ultimately can have negative effects on the circadian system, as it is slow to adapt to alterations in sleep schedules. Neuroimaging work suggests that sleep-deprived individuals have difficulty moderating emotional responses, as evident by an altered amygdala response to negative emotional stimuli and less co-activation between the amygdala and associated prefrontal cortex regulatory regions (Walker & van der Helm, 2009). Poor sleep quality in adolescence may also be related to negative mood and risk taking as well as how the brain processes rewarding stimuli (Holm et al., 2009). In these ways, it appears that insufficient sleep can sometimes contribute to a spiral of problems associated with emotional dysregulation.

Contextual factors have also been found to negatively impact adolescent sleep-wake cycles. A consistent finding is that the timing of bedtime shifts to later hours in the night from middle to high school (Carskadon, 2011). While part of the bedtime delay stems from biologically driven changes in circadian timing, adolescents also engage in high levels of media use (e.g., television, computer games, internet, mobile phones) at night, often resulting in increased arousal levels that keep teenagers up very late (Cain & Gradisar, 2010). Despite the later bedtime, the high school transition often introduces the need for adolescents to wake sooner due to an earlier start of their school day, thereby creating a shorter sleep period and increased vulnerability to emotional dysregulation. To ameliorate such risks, interventions could be used to help parents

and adolescents to set appropriate sleep schedules and to encourage schools to delay start times for adolescents and provide information about sleep to families.

Parent-Child Relationships

As individuals transition into adolescence, there are many changes in the parent-child relationship. For example, during adolescence parents and children must negotiate increasing need for autonomy during adolescence. Parents who are able to balance encouraging adolescent independence and maintain a supportive bond facilitate self-esteem and social functioning (Van Petegem, Beyers, Vansteenkiste, & Soenens, 2012), which in turn protect against psychopathology. With respect to other dimensions of the parent-child relationship, conflict tends to decline across the adolescence years, although when conflicts arise they frequently pertain to matters of adolescents' personal choice (Laursen, Coy, & Collins, 1998; Smetana & Villalobos, 2009). Warmth between adolescents and parents remains relatively consistent across this age period (Trentacosta et al., 2011), although harsher, aloof parent–child interactions continue to place a youth at risk for development psychopathology.

It is likely that the changing nature of the parent-child relationship during adolescence is at least partially the result of the adolescent's biological and cognitive maturation. Increases in cognitive abilities during adolescence allow a child to begin the process of autonomy seeking, but also may place the adolescent at risk for increased conflict with parents (Smetana, 2011). Several studies have found that puberty, not age, is associated with increases in bickering between adolescence and their parents and diminished closeness between the parent and adolescent. (De Goede, Branje, & Meeus, 2009; McGue, Elkins, Walden, & Iacono, 2005). Relatively earlier maturation is linked with greater discrepancy between an adolescent's desired autonomy, and parent's age-based expectations about appropriate levels of autonomy (Weichold, Büttig, & Silbereisen, 2008), which may lead to greater conflict in the parent–child relationship. Consistent with this account, early maturing males and females report greater conflict and decreased closeness with parents compared with later maturing adolescents (Huddleston & Ge, 2003; Weichold et al., 2008).

Who Is More Vulnerable? What Are the Risk Factors?

During adolescence people vary in developmental processes that make them differentially vulnerable to psycho pathology, such as neural development, pubertal development, and changes in circadian rhythms. Some of the primary factors that increase individual vulnerability to psychopathology include being easily aroused emotionally, having poor self-regulation, seeking out opportunities that involve risk, being highly sensitive to interpersonal interactions, and experiencing contextual risks (e.g., poverty, extreme stress, abuse, or trauma). For example, we hypothesize that the increased intensity and duration of emotion, in combination with the increased strength of some appetitive drives, create new regulatory challenges, particularly with respect to self-regulation in the face of high-intensity emotions and motivations. During adolescence, there is a shift in regulatory capability away from regulation assisted by external agents, such as parents, toward regulation that is primarily internal, cognitive in nature, and involving higher order executive functioning. The type of executive function that is manifest during the adolescent transition is in fact an integration of a number of specific cognitive achievements, particularly in planning, monitoring, evaluating, and reflecting. Together, these can be thought of as an executive suite that comes increasingly, but gradually, under conscious control during adolescence (Keating, 2004). Because the maturation of regulatory systems (e.g., cognitive control) relevant to the modulation of emotion and motivation is not driven by pubertal development and is still taking place during late adolescence (Smith, Chein, & Steinberg, 2013a), adolescents may be relatively more vulnerable than children (whose levels of arousal and motivation are lower) or adults (whose regulatory capabilities may be stronger) to extremes in affective and drive states, which may leave adolescents more susceptible to psychopathology. These extremes in affective and drive states may be linked more strongly to social contextual change. As such, regulatory problems may result either from inadequate or incompletely developed regulatory capacities or both. Bringing the potent and novel affective and motivational systems into an integrated, functioning system is a lengthy and effortful process. Thus, emotional and behavioral disorders may result from underregulation (e.g., where the underregulation of anger may lead to conduct problems) or inappropriate regulation (e.g., where the overregulation of sadness by rumination may lead to the development of depressive disorder). As regulatory capacities mature, individuals become less susceptible to the development of psychopathology.

We also hypothesize that various forms of psychopathology in adolescence are directly related to the neurobehavioral changes of puberty, primarily through their association with changes in brain systems regulating arousal and appetite that subsequently influence the intensity and duration of emotion and motivation (not

the regulatory systems that undergo development across adolescence). Adolescents, we hypothesize, experience emotions and motivations that are qualitatively and subjectively stronger than those experienced by prepubertal children. Thus, for example, whereas children experience sadness, euphoria, anxiety, and anger, the biological changes of puberty result in the capacity of individuals to feel sadder, more euphoric, more anxious, and angrier and, furthermore, to experience these more intense affective states for longer periods of time. Similarly, the biological changes of puberty stimulate changes in the intensity and duration of various drives, not only the sex drive, which is presumed to intensify at puberty, but all drives relevant to reward, novelty, and stimulation seeking. In addition, motivational drives related to social status appear to increase during adolescence.

Adolescence as a Time of Plasticity

It is important to acknowledge that adolescence is also a period of plasticity. Plasticity is apparent through the reorganization that occurs among biological, cognitive, and emotion systems during adolescence. Given that these systems are reorganizing, it stands to reason that adolescence presents an opportunity for biological, cognitive, and emotional systems to be shaped in ways that may protect against psychopathology and other negative outcomes. The impact of continued brain maturation on emotional, cognitive, and behavioral development has yet to be thoroughly studied, but the evidence for continued development in these processes and for apparent plasticity of brain development in adolescence suggests that this period may present some unique opportunities for prevention and intervention (including cognitive-behavioral, psychopharmacological, or other psychotherapeutic treatments), particularly compared with the periods before and after adolescence.

We hypothesize that during the period of greatest disjunction between affect and appetitive motivations on the one hand, and regulatory competence on the other, individuals may be protected from extremes in emotion or drive by a context that provides adequate external regulation in the form of support, control, and predictability. Thus, although many individuals may experience emotions and drives whose intensity and duration exceeds their regulatory competence, those adolescents who enjoy supportive home, peer, school, and neighborhood contexts are buffered from the ill effects of the disconnection between high emotionality and still maturing cognitive control and self-regulation. In addition, their transition to an internal, consciously controlled regulatory system is more effectively scaffolded by contextual supports compared with individuals lacking in such support. Conversely, individuals whose environments do not provide sufficient support, control, and predictability are relatively more vulnerable to the development of psychopathology, perhaps because they lack the external regulatory control that supplements still maturing self-control.

The adolescent is not merely the passive recipient of contextual support, however. We view context as a resource that is both provided by outside agents (such as parents or teachers) and also actively recruited by adolescents. An important, yet remarkably understudied, question is how individuals develop the capacity to identify, enlist, and employ sources of contextual support during times of extreme emotions, drives, and stress as a means of protection against the development of emotional and behavioral difficulty. In this regard, resilience in the face of adversity may reflect in part the ability to engage contextual resources in the service of self-protection.

CURRENT BRAIN-BASED FRAMEWORKS FOR UNDERSTANDING ADOLESCENT PSYCHOPATHOLOGY

In the last decade, our knowledge of the protracted brain development that occurs during adolescence has increased exponentially. Driving this research and because of this research, major brain-based explanations of adolescent psychopathology have emerged. The brain can be conceived as a central arbiter of our behavior. That is not to say that biology is destiny, but rather that behavior is instantiated via the brain within the context of individual differences and environmental influences. To advance our understanding of the emergence of psychopathology in adolescence from a brain-based perspective, several explanatory models have been proposed over the last decade. One common theme across several of these models is an emphasis on the weighting of input from various neural systems and how alterations in the balance among these systems changes with maturation or psychopathology. In addition, these models have been put forth to explain specific behavioral changes during adolescence (e.g., risk taking, depression) as well as to provide a framework for understanding vulnerability to psychopathology more generally in adolescence. We highlight here three main approaches that have been foundational for generating several research agendas aimed at understanding adolescent psychopathology: Dual Systems approaches,

the Triadic Model, and the Social Re-Orientation model. While other approaches have been offered (Crone & Dahl, 2012; Luciana & Collins, 2012; Pfeifer & Allen, 2012), we highlight these three approaches as the most researched.

Increased risky behavior in adolescence is a normative and common occurrence relative to childhood and adulthood. One explanation from the field of developmental neuroscience suggests that this increase in risky behavior is the result of a temporal dissociation in the developmental course of two neurobiological systems across adolescence (Steinberg et al., 2008). These two distinct neurobiological systems center on a socioemotional system involving limbic and paralimbic regions of the brain, including the amygdala, ventral striatum, orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), and superior temporal sulcus, and a cognitive control system, which comprises the lateral prefrontal and parietal cortices and their interconnections with areas of the anterior cingulate cortex (ACC) (Steinberg, 2007). According to this dual systems model, adolescent risk taking is hypothesized to be sparked by a rapid and dramatic increase in dopaminergic activity within the socioemotional system around the start of puberty, a neurochemical change presumed to lead to increases in reward seeking behavior. However, this increase in reward seeking behavior precedes the full structural development of the cognitive control system and its connections to areas of the socioemotional system, a maturational process that more gradually unfolds over the course of adolescence, permitting more adult-like self-regulation and impulse control skills. The temporal gap between the arousal of the socioemotional system, which onsets in early adolescence, and the longer maturational course of the cognitive control system, creates a period of heightened vulnerability to risk taking during middle adolescence (Casey, Jones, & Somerville, 2011; Steinberg, 2008). That is, the temporal gap described by this model can account for normative increases in risky behavior during adolescence, but it also suggests that a wide gap between the development of these two neurobiological systems could explain why some adolescents may be more prone to risky behavior in general, engage in risky behaviors for a longer period of time, or take part in extreme forms of risky behavior. As one writer described, these processes are akin to starting a car engine without a skilled driver behind the wheel (Dahl, 2001). Similar perspectives have postulated that adolescent vulnerability to negative outcomes more generally is the result of an imbalance in input from socioemotional and cognitive control neural circuitry due to maturation.

Another important framework from the field of developmental neuroscience is the triadic model of motivated behavior (Ernst & Fudge, 2009). The triadic model differs from the dual systems model in that it emphasizes the interplay among distributed networks that drive behavior more generally and includes a second socioemotional neural system that underlies avoidance behavior. In the triadic model, motivated behavior is characterized as being dominated by input from either avoidance or approach neural systems (or equal contributions from both), and then regulated by a cognitive network. The triadic model also provides flexibility to account for all types of motivated behavior, such that both avoidance and approach systems are relevant to and influenced by social and non-social contexts. The key node of the avoidance systems is the amygdala, given its established association with fear and threat processing. For the approach system, the striatum more generally, and the ventral striatum more specifically, is the key node due to its well-documented role in reward processing. Functioning of the control network is relegated to the prefrontal cortex as the primary neural substrate of cognitive executive control (Miller & Cohen, 2001).

A third brain-based theoretical framework, the social re-orientation framework, is rooted in the dramatic social restructuring and continued brain refinement and maturation that accompany adolescence (Nelson, Leibenluft, McClure, & Pine, 2005). Given the changes in brain structure across adolescence, it is expected that social cognitive processes recruited for successful social interactions change during adolescence. These social and biological changes in adolescence have been interpreted based on the social information processing network (SIPN) model (Nelson et al., 2005). The SIPN model identifies three networks of nodes that process social stimuli in an interactive and integrated fashion. The detection node, including the superior temporal sulcus, intrapariental sulcus, fusiform face area, as well as inferior temporal and occipital cortical regions, is responsible for perceiving and categorizing basic social properties of stimuli. Following detection, the affective node further processes social stimuli in regions that include the amygdala, ventral striatum, hypothalamus, bed nucleus of the stria terminalis, and, in conditions involving emotion, the OFC. These regions are engaged generally by reward or punishment cues; thus, the affective node imbues social stimuli with emotional salience. Finally, the cognitive-regulatory node, which comprises the medial and dorsal prefrontal cortex (PFC) and areas of the ventral PFC, including the OFC, performs complex cognitive processes related to social stimuli such

as perceiving others' mental states, inhibiting prepotent responses, and generating goal-directed behavior. The SIPN model suggests that, during adolescence, changes in social-cognitive processing and social behavior reflect alterations across these three neural nodes via hormonal changes, brain maturation, and the influence of experience on neural networks. Because the major social changes in adolescence are intertwined with intense emotions and motivations, and intense emotions and motivations can tip from normative to psychopathological, heightened sensitivity to and enhanced salience of social experiences are particularly relevant to the development of psychopathology. Adolescents also find themselves having to navigate and integrate with new social networks and supports, behaviors that draw on input from key brain regions delineated by the SIPN model. As such, neural activations are expected to be linked to motivation, self-esteem, and being judged in a social context that will be augmented in the affective node of the SIPN during the adolescent period, with extreme activations relating to psychopathology.

An extension of the SIPN model has further suggested that the prolonged maturation of the PFC parallels the slowly emerging ability for flexible social behavior across the adolescent period (Nelson & Guyer, 2011). Flexibility in social behavior is fundamental for competent interactions with others and can buffer some individuals from the development of psychopathology. Three aspects of social flexibility are thought to be supported specifically by the ventral regions of the PFC, including emotional value computation, inhibitory control of behavior, and acquisition and generation of rules. Within the ventral PFC, the more lateral areas of the orbital gyrus and inferior frontal gyrus are suggested to subserve rule use and inhibitory control in social contexts whereas the medial part of the OFC is thought to support valuation of a social stimulus. A body of evidence now documents that the brain is sensitive to social experiences in adolescence and that perturbations in the process of developing social flexibility may relate to some forms of psychopathology in adolescence, such as social anxiety (Guyer, Lau, et al., 2008).

Each of these perspectives—dual systems models, triadic model, and the social re-orientation framework—suggest that the developmental changes in the brain during adolescence incur risk for psychopathology. In the sections that follow, we review the major adolescent changes that occur in biology and in context. We focus on the types of change that may place individuals most at risk for psychopathology and the individuals who are at risk for psychopathology.

MAJOR BIOLOGICAL CHANGES OF ADOLESCENCE

Pubertal development and changes in brain development are the two major biological changes of adolescence. These processes are inextricably intertwined, as puberty can affect the development of the brain during the adolescent years. In this section, we describe pubertal changes, changes in the brain that occur during adolescence, and the links between puberty and brain maturation in both human and animal models. We discuss how each of these major developmental changes increases risk for psychopathology.

Pubertal Development in Humans

The onset of puberty—the developmental process that encompasses the transition from childhood to sexual maturity—is one of the defining milestones of the adolescent transition, so much so, that the terms adolescence and puberty are used interchangeably (Spear, 2010). From a hormonal standpoint, puberty is marked by activation of the hypothalamic-pituitary-gonadal (HPG) axis for the first time since early childhood, with an increasing number and magnitude of gonadotropin-releasing hormone (GnRH) secretions from the hypothalamus that stimulate the production of follicle-stimulating hormone (FSH) and leutenizing hormone (LH) by the pituitary gland. Together, these hormones induce secretion of gonadal steroid hormones (e.g., estrogen, testosterone, other androgens) that lead to gametogenesis, or production of sex-specific cells, such as sperm. The production of gonadal steroids is also responsible for the development of secondary sex characteristics and changes in reproductive behavior, such as increased interest in sex. While the effects of gonadal hormones on the nervous system were originally thought to be organizational and limited to the perinatal period, more researchers have recognized that puberty is yet another ontogenetic period during which gonadal hormones have the opportunity to influence neural development and behavior (see Sisk & Zehr, 2005, for a review).

Puberty and Psychopathology

Although the specific mechanisms connecting pubertal maturation and various psychopathologies in adolescence have yet to be established, there are two areas where considerable research has been conducted. First, much evidence suggests that an early onset of puberty may incur risk for the emergence of psychopathology. Second, evidence is growing to suggest that part of the association between

puberty and risk for psychopathology may be due to the puberty-related changes in affective and motivational systems that regulate emotions and behavior.

Numerous studies have shown that individuals who go through puberty earlier than their same-age peers are especially vulnerable to a wide range of affective and behavioral disorders. Indeed, one of the most robust findings in the literature on pubertal development and adolescent adjustment is that early maturing females, and to a lesser extent early maturing males, evince relatively higher rates of virtually all sorts of adjustment difficulties, including depression and suicide, delinquency, risk taking, and emotional disorders and other psychological difficulties (Ge, Conger, & Elder, 1996; Graber et al., 1997; Orr & Ingersoll, 1995). As with the case of pubertal status and psychopathology, the underlying links between pubertal timing and psychopathology have remained largely unexplained. Some investigators have emphasized the effects of off-time development (i.e., maturing at a different age than one's peers) as the key factor in risk for depression (Graber et al., 1997), whereas others have attributed increased vulnerability of early maturers to a wider array of problems (Stattin, Kerr, & Skoog, 2011). Another strong possibility that has been suggested (e.g., Dahl, 2001) is that the disjunction between changes in affective arousal (which are linked to puberty) and the development of self-regulatory competence (which is likely pubertal-independent) is wider among early maturers than their peers.

Beyond psychopathology, it is important to note that variation in pubertal timing contributes to risk for a broad range of negative health outcomes. Early pubertal timing has been linked to many deleterious health outcomes (Golub et al., 2008), including obesity (Prentice & Viner, 2013), type 2 diabetes (Lakshman et al., 2008), cardiovascular disease (Prentice & Viner, 2013), and reproductive cancers (Hamilton & Mack, 2003). Yet earlier timing of puberty may also relate to the development of psychosocial problems (e.g., sexual abuse, conduct disorder; see Golub et al., 2008).

Part of the reason for the association between pubertal development and risk for psychopathology may be because pubertal development is associated with intense affective experience. From a neuroscience perspective, emotions have been conceptualized as brain states associated with rewards and punishments (Rolls, Critchley, Browning, Hernadi, & Lenard, 1999), with a group of interconnected brains structures including (but not limited to) the amygdala, extended amygdala/ventral striatum, medial cortex and OFC (Davidson, 2000, 2002; Davidson, Jackson, & Kalin, 2000; Drevets, 2003; Rolls et al., 1999) contributing to affect regulation. Not surprisingly, there is evidence that the development of romantic interest and sexual motivation is directly influenced by pubertal processes (Udry, 1987). Furthermore, it has been shown that some aspects of emotional reactivity and intensity (e.g., parent-adolescent conflict) are more closely linked to pubertal maturation and not age (Belsky et al., 2007). Furthermore, evidence has suggested that there is a correlation between pubertal status and processing of facial expressions indicating social threat (Forbes, Phillips, Silk, Ryan, & Dahl, 2011), as well as pubertal status and brain activation patterns induced by reward-related events and depressive behaviors (Forbes et al., 2010). Studies that have indicated a positive association between pubertal status and the risk for affective disorders (Angold & Costello, 2006; Angold, Costello, & Worthman, 1998) provide even more evidence for an influence of pubertal hormones on affective processes.

Finally, part of the association between puberty and externalizing issues during adolescence may be explained by changes in the associations between pubertal development and sensation seeking. During the adolescent transition, risky behavior, and in particular sensation seeking, is prominent (Shek & Yu, 2012; Steinberg et al., 2008), with this behavior escalating significantly from childhood into early adolescence and declining thereafter into adulthood (Steinberg et al., 2008). In 11–14-year-olds, pubertal status, but not age, is positively correlated with measures of sensation seeking (Martin et al., 2002). In another study that investigated the association between self-reported measures of pubertal status and sensation-seeking using a broader age range (i.e., 10–16-year-olds), a significant relationship between sensation seeking and pubertal status was observed for males but not for females (Steinberg et al., 2008). Interestingly, measures of impulsivity were not significantly correlated with pubertal status for either sex in that same study, indicating that the effects were specific to the construct of sensation seeking. More developmental research is needed to identify the role of puberty in the expression of adolescent typical behaviors, as well as to determine the instances in which developmental processes independent of puberty contribute to the adolescent phenotype.

Lessons From Animal Models

The broader adolescent period has been modeled across a variety of mammalian species, including non-human primates and rodents (for a review see Spear, 2000b). The advantage of examining these processes within animal populations is that we are better able to determine the

specific timing and magnitude of developmental change than in humans. Although not all aspects of puberty can be represented using animal models (e.g., menarche), there are physical indications of sexual maturation in rats with which pubertal timing may be assessed, such as a female change in vaginal opening and a male change in preputial separation and presence of sperm occurring within a constrained expectable period that maps to an adolescence (Vetter-O'Hagen & Spear, 2011b). In both humans and rodents, another indication of the onset of puberty, as described previously, is the increase in gonadal hormones (Harris & Levine, 2003; Sisk, Richardson, Chappell, & Levine, 2001; Vetter-O'Hagen & Spear, 2011b). Physiological and hormonal indices of puberty generally begin to emerge at approximately P28 (i.e., postnatal day 28) in rats, with some pubertal processes lasting until about P55, with males usually entering puberty later in life relative to females (Vetter-O'Hagen & Spear, 2011b).

Animal models have also been particularly useful in illuminating possible mechanisms that trigger the onset of puberty that are not possible to study directly in humans. Initiation of the rising and pulsatile secretions of GnRH from the arcuate nucleus of the hypothalamus (ARC) is likely triggered via a constellation of both internal and external/environmental signals. For example, it has been suggested that insulin and leptin levels are potential physiological signals for induction of puberty (for reviews see Kaplowitz, 2008; Shalitin & Phillip, 2003), perhaps as permissive factors that signal adequate nutrition/body fat has been achieved for successful reproduction. In animal models, as in human evidence, other external factors such as social context (Coppola & Vandenbergh, 1985; Slob, van Es, & van der Werff ten Bosch, 1985) may also play a role in the onset of puberty.

Although mechanistically it is not entirely clear what neurobiological events are responsible for the activation of GnRH secretion at the onset of puberty, recent evidence has begun to demonstrate that kisspeptin (and signaling through its receptor, GPR54) is a contributor to this event (for reviews see Popa, Clifton, & Steiner, 2008; Roa et al., 2009), as kisspeptin appears to stimulate GnRH release from the ARC (Castellano et al., 2006; Gottsch et al., 2004). Expression of kisspeptins (a family of peptides encoded by the Kiss1 gene) is low prior to puberty, with abrupt rises in kisspeptin activity associated with the onset of puberty in rats (Irwig et al., 2004) and mice (Gottsch et al., 2004).

Taken together, these studies demonstrate that the onset of puberty is apparent on both a hormonal and neural level in rodents, with the timing relatively consistent across species and strains, and females tending to enter the pubertal transition earlier than males. These data indicate that, indeed, animal models may be appropriate for investigating the extent to which certain adolescent-typical behavioral and neural transformations may or may not be related to activation of pubertal processes.

Pubertal Contributions to Adolescent-Typical Behaviors in Rodent Models

In comparison to their human counterparts, the behavioral repertoire of rodents is more limited and not nearly as complex. Therefore, it is not possible to fully model human adolescence using rodents, and it may be particularly difficult to use animal models as tools to investigate psychopathological conditions. Nevertheless, animal models provide a sound foundation with which we can more directly assess relationships between pubertal development and neurobehavioral changes of adolescence. These models present many experimental advantages that are not possible in human studies, such as tight control of experimental conditions and the subjects' histories, which allows for a more direct assessment of the impact of specific variables. For example, the organizational versus activational properties of gonadal hormones on neurodevelopment and adolescent-typical behaviors can be examined with animal models. Removal of the gonads (i.e., gonadectomy; GDX) prior to or after puberty in combination with hormone replacement strategies can more directly assesses whether the presence of gonadal hormones at a critical ontogenetic period is necessary to observe a particular behavior or neurobiological event (i.e., organizational effect), or if their presence in the system is required for a particular event or behavior to take place (i.e., activational).

Although numerous studies have used animal models to investigate the organizational influence of early life (neonatal period) sex steroids on later behavior, less attention has been paid to the influence of these hormones specifically during the pubertal period. Evidence now suggests, however, that there are indeed many instances in which the presence of pubertal hormones is necessary to observe a variety of behavioral responses, as described below. For instance, when considering adult-typical sexual/reproductive behaviors, evidence has shown that pubertal hormones are directly involved in the onset and continued expression of these behaviors (Schulz, Molenda-Figueira, & Sisk, 2009). Schulz, Sisk and colleagues demonstrated that adult male rodent sexual, agonistic, aggressive, and submissive behaviors were

dependent upon adolescent exposure to pubertal hormones (Schulz et al., 2004; Schulz & Sisk, 2006). In male rats, the typical increased expression of rough-and-tumble play observed during adolescence (Varlinskaya & Spear, 2006) was reported to not occur when rats were castrated prior to puberty (Cooke & Woolley, 2009), suggesting that pubertal hormones are involved in the expression of this adolescent-typical behavior.

Using behavioral tests that are thought to index anxiety-related processes, some studies have shown that pubertal hormones are also involved in the expression of sex-related differences in anxiety-like behavior in adulthood. Male rats given the opportunity to interact with a conspecific in a novel environment will exhibit significantly less social interaction relative to animals that are placed together in a familiar environment. This reduction in social interaction is thought to reflect anxiety-like behavior and has been shown to depend on pubertal exposure to gonadal hormones, as castration before puberty prevents the adult-typical anxiogenic response but gonadectomy in adulthood does not affect this behavior (Primus & Kellogg, 1989, 1990). Using other behavioral assays of anxiety-like behavior, evidence has emerged with both the open field test (Brand & Slob, 1988; Slob, Huizer, & Van der Werff ten Bosch, 1986) and elevated plus-maze test (Zimmerberg & Farley, 1993) to suggest that pubertal sex hormones contribute to the expression of sex-related differences in anxiety later during adulthood, although these effects are complicated and differ according to the behavioral test being examined. Nonetheless, these findings provide some links between pubertal hormones, detrimental social experiences, and anxiety that may relate to the emergence of human adolescent anxiety.

In contrast to the studies described previously, there are instances in which animal models have demonstrated that the expression of certain adolescent-related behaviors is independent of gonadal hormones. Novelty seeking, for instance, is an adolescent-typical behavior that has been observed in both humans and in rodent models (Caster, Walker, & Kuhn, 2007; Collins & Izenwasser, 2002; Stansfield & Kirstein, 2006), with novelty-directed behavior having been found to be especially rewarding during adolescence (Douglas, Varlinskaya, & Spear, 2003). Novelty-directed behavior was systematically assessed across the adolescent-to-adult transition in male and female rats and, although it was reported to peak between P32-P36 in both sexes before declining into adulthood, no significant correlations between physical and hormonal indices of puberty and novelty seeking were found (Vetter-O'Hagen & Spear, 2011b). Subsequently, the same group observed that neither prepubertal nor adult gonadectomy influenced the expression of novelty-directed behavior when animals were tested as adults (Vetter-O'Hagen & Spear, 2012). In contrast to these results, however, administration of Antide (a GnRH antagonist) prior to puberty and throughout adolescence was shown to reduce an adolescent-typical preference for a novel object in male but not female adolescent rats (Cyrenne & Brown, 2011). Although the reasons for these divergent results are as yet unknown, it is likely that different methodologies for elimination of gonadal hormones (e.g., gonadectomy vs. Antide) and measurement of novelty-directed behavior were contributing variables. Nevertheless, these data indicate that more research is necessary to fully elucidate the role of pubertal hormones in adolescent novelty seeking behavior.

Perhaps related to sensation-/novelty-seeking, ethanol consumption also appears to peak ontogenetically during the adolescent transition, both among humans (SAMHSA, 2011) as well as in animal models (Doremus, Brunell, Rajendran, & Spear, 2005; Vetter, Doremus-Fitzwater, & Spear, 2007). Studies from Spear and colleagues have demonstrated that adolescent-associated increases in ethanol intake in male and female rats are largely unaffected by pubertal hormones (Vetter-O'Hagen & Spear, 2011a), with prepubertal gonadectomy not altering ethanol intake during the adolescent period in either males or females. Instead, it seems that testosterone may impart an activational role on ethanol intake of adult males, as gonadectomy prior to puberty or during adulthood reduces ethanol intake only during adulthood (Vetter-O'Hagen & Spear, 2011a) and testosterone replacement reinstates low levels of ethanol consumption that are typical of adult males (Vetter-O'Hagen, Sanders, & Spear, 2011). While the mechanisms underlying adolescent-associated increases in ethanol consumption still are not understood, these data would suggest that organizational effects of gonadal hormones that happened prior to puberty, or puberty-independent neural alterations occurring during the adolescence transition, are contributors to these age-dependent ethanol intake patterns.

As a whole, the emerging literature in this area has begun to demonstrate the complex relationship between sex steroids and expression of certain behaviors. While we may not be able to fully model human psychopathology using animal models, studies like these provide invaluable data for helping to identify certain facets of adolescent behavior that may be influenced (or not) by pubertal changes and, therefore, provide insight into where to focus our research efforts in humans.

Normative Changes in Brain Development

Despite the widely held notion that the brain changes at puberty, only recently have researchers begun to directly examine the links between brain development and pubertal maturation. In this section, we begin by reviewing neuroscience data that has identified general changes in brain development during the adolescent transition, including studies conducted in both humans and animal models. Specifically, we discuss gross brain alterations, as well as changes on a neuroanatomical and functional level. Subsequently, we will discuss research that has attempted to distinguish between aspects of brain development and function that are closely tied to some aspect or facet of puberty and those that appear to occur relatively independent of pubertal processes (i.e., that follow a timeline distinct from that of puberty or are instead influenced by other aspects of development or experience).

Brain development in mammalian species follows an orderly progression that begins with differentiation of the brain and spinal cord in the longitudinal, circumferential, and radial dimensions prenatally. This process is followed by increases in cell numbers (neurogenesis), repositioning of cell locations (migration), and maturation of connections among brain cells and supporting constituents, which can occur through both activity-independent (i.e., innate) and activity-dependent (i.e., dictated by experience–environment) mechanisms (Nowakowski & Hayes, 1999). Later in development, whole brain volume has been reported to increase from childhood into early and mid-adolescence, declining thereafter from mid-adolescence into adulthood (Courchesne et al., 2000). In addition to gross changes in volume, adolescence is marked by significant changes with respect to neurons and synapses. In terms of gray matter (which is comprised of cell bodies and their projections), adolescence is a time of refinement—synapses are culled and, overall, gray matter is pruned, especially within the cerebral cortex (De Bellis et al., 2001; Sowell et al., 2002). Beyond decreases in the total number of neurons, there is evidence of prolonged changes in the morphology and functional integrity of dendrites, as synapses exhibit marked changes in absolute number and precise localization on dendrites during adolescence (Kolb, 1999). Conversely, there is evidence of extensive myelination during adolescence, which is indicated by general increases in white matter (defined mostly as myelinated axons and glial cells) that is also occurring particularly in the cerebral cortex. Together, these reductions in gray matter concomitant with increases in white matter may result in a functionally more efficient adult brain. Some evidence would suggest that synaptic pruning tends to take place earlier in adolescence, whereas proliferation of white matter seems to occur during late adolescence/early adulthood (Sowell, Thompson, Tessner, & Toga, 2001).

Studies in animal models have similarly reported neuronal loss during adolescence that is accompanied by increases in glial cells, with these changes dependent upon brain area of interest (Cressman et al., 2010; Markham, Morris, & Juraska, 2007; Yates, Markham, Anderson, Morris, & Juraska, 2008). Similarly for humans, the timing of these changes during ontogeny has been shown to be regionally specific, and also influenced by sex (De Bellis et al., 2001; Lenroot & Giedd, 2010; Sowell et al., 2001), which will certainly have implications for determining how pubertal processes might influence these alterations, as well as their contribution to adolescent psychopathology.

From a neurocircuitry standpoint, numerous studies have now demonstrated that substantial reorganization occurs in brain regions and circuits important for a variety of processes, including but not limited to emotion regulation, motivation, inhibitory control, and learning and memory (Crews, He, & Hodge, 2007; Doremus-Fitzwater, Varlinskaya, & Spear, 2010; Yurgelun-Todd, 2007). Overall PFC volume declines, while significant synaptic alterations result in a change in balance from excitatory to inhibitory inputs—general decreases in glutamatergic inputs take place and increased dopaminergic afferents occur (Spear, 2000b, 2007). As shown by Benes et al. (2000), at approximately P28 (i.e., postnatal day 28), dopaminergic inputs to the mPFC began to increase in the rat and continued to exhibit ontogenetic increases into early adulthood (Benes, Taylor, & Cunningham, 2000). Mechanistically, electrophysiological studies have indicated that enhanced sensitivity of inhibitory interneurons in the PFC to dopaminergic inputs are involved in this ontogenetic change (Tseng & O'Donnell, 2007), with developmental increases in postsynaptic PKA activity likely driving augmented L-type Ca2+ function that would be responsible for maturation of prefrontal function (Heng, Markham, Hu, & Tseng, 2011). Furthermore, preclinical data have demonstrated that substantial alterations in connectivity between the PFC and subcortical brain areas happen during adolescence. For instance, when considering GABAergic interneurons in the PFC, afferents from the basolateral amygdala to these interneurons are increased during adolescence, which would have implications for emotional and cognitive processes and the development of psychopathology during this developmental period (Cunningham, Bhattacharyya, & Benes, 2008). We discuss

implications for brain maturation and these developmental processes later in this chapter.

Neural connections between the PFC and nucleus accumbens undergo considerable change throughout adolescence as well. Overall, afferent projections from the PFC to accumbens increase in number during adolescence, along with a late-adolescence elevation in the percentage of these cells that express dopamine D1 receptors (D1-Rs) (Brenhouse, Sonntag, & Andersen, 2008). Electrophysiological properties of both D1-Rs and dopamine D2 receptors (D2-Rs) on medium spiny neurons in the nucleus accumbens to NMDA (N-methyl-D-aspartate)-related stimulation and cortical GABA (Gamma-aminobutyric) stimulation, respectively, have also been shown to differ in adolescent rats relative to their adult counterparts (Benoit-Marand & O'Donnell, 2008; Huppe-Gourgues & O'Donnell, 2012a, 2012b). The magnitude and timing of developmental pruning of dopamine receptors in these brain areas seems to be regionally specific, as D1- and D2-Rs have been reported to markedly decline in early adulthood in the PFC (Andersen, Thompson, Rutstein, Hostetter, & Teicher, 2000), whereas pruning of dopamine receptor levels in the nucleus accumbens appears to occur slightly earlier and to a lesser extent than that observed in the PFC or dorsal striatum (Andersen et al., 2000; Tarazi & Baldessarini, 2000). Alterations in cortico-striatal dopamine projections, receptor expression, and receptor functionality that occur during adolescence together suggest that this circuit is a likely contributor to ontogenetic alterations in reward-related behaviors during adolescence, as well as a vulnerable target for abnormal development and psychopathologies.

While we have focused thus far on dopaminergic systems in cortical circuits, there are, of course, many other brain regions, circuits, and neurotransmitter systems that undergo developmental change during adolescence and might impart vulnerability for psychopathologies. For example, the cannabinoid system has been implicated in the etiology of schizophrenia (Bossong & Niesink, 2010; Giuffrida & Seillier, 2012) and adolescence is a time of elevated cannabis use (SAMHSA, 2011) as well as an ontogenetic period characterized by an increase in the onset of symptoms of schizophrenia (Markham, 2012). Current research suggests that presynaptic (CB1) cannabinoid receptors regulate both inhibitory GABAergic and excitatory glutamatergic activity within the brain, thereby functioning as a protective mechanism that would prevent over-stimulation of excitatory activity at critical periods of development (Bossong & Niesink, 2010). Within PFC regions in particular, endocannabinoids seem to play an important role in modulating GABA/glutamate and dopamine interactions. Studies examining the development of the endocannabinoid system have reported ontogenetic alterations, with CB-1 receptors showing developmental patterns of expression in cortex (Heng, Beverley, Steiner, & Tseng, 2011), and striatum (Van Waes, Beverley, Siman, Tseng, & Steiner, 2012) across the transition to adulthood and developmental alterations in endocannabinoid levels reported as well (Ellgren et al., 2008).

While the increased risk for schizophrenia with drug use during adolescence does appear to be relatively specific to marijuana, it is important to consider that the magnitude of the brain alterations occurring during adolescence imparts a significant liability for disruption of normative brain changes by any drug or environmental perturbation. On the other hand, adolescent-related brain maturational processes may impart vulnerability for drug use, whether due to neurobiologically induced increases in sensation-seeking behavior, increases in motivational- and reward-related behaviors, or simply altered sensitivity to certain drugs of abuse. Though likely a combination of these possibilities, drug use during the adolescent transition is a risk factor that may interact with genetic–environmental vulnerabilities and thus contribute to the onset of psychopathology at this maturational interval.

Puberty and Adolescent Brain Development

Brain alterations occurring during adolescence take place on a variety of levels, from neurotransmitter and receptor expression, to synapse formation, to alterations in myelination. Given the vast number of changes, it is not surprising that evidence to date indicates that some brain alterations seem to be puberty dependent, whereas others appear to not be influenced by pubertal maturation. As reviewed by Ladouceur and colleagues (2012) human neuroimaging studies have provided growing, albeit indirect, evidence for an influence of pubertal maturation on white matter development. Furthermore, neuroimaging studies have indicated that some of the sexual dimorphisms in brain anatomy that arise during adolescence (Lenroot & Giedd, 2010) are likely influenced by the presence of pubertal hormones, as there are cases in which adolescents experienced abnormalities in pubertal hormones and did not exhibit typical sex-related differences in brain development (Giedd et al., 2006).

In parallel to these neuroimaging studies with humans, animal models have also been used to more directly assess the influence of pubertal hormones on adolescent-related brain reorganization. The general picture that has emerged

is that some adolescent-associated brain alterations appear to be influenced by pubertal hormones, whereas others occur independent of pubertal processes (Schulz et al., 2009; Sisk & Zehr, 2005). For example, the sexually dimorphic development of the anteroventral periventricular nucleus (AVPV), SDN and medial amygdala appears to be affected by prepubertal gonadectomy, although the nature of the influence of these pubertal hormones is region and sex dependent (for a review see Juraska, Sisk, & DonCarlos, 2013; Schulz et al., 2009). Another instance in which pubertal hormones exert an influence on adolescent brain development is with respect to sex differences in the magnitude of cell death in the visual cortex during puberty, with prepubertal ovariectomy attenuating the sexually dimorphic size differences in this structure during adulthood (Nunez, Lauschke, & Juraska, 2001; Nunez, Sodhi, & Juraska, 2002). In contrast, sex differences in the overexpression and subsequent pruning of D1 and D2 dopamine receptors in the PFC and striatum of rats during the adolescent transition have been reported to occur independently of the presence of pubertal hormones (Andersen, Thompson, Krenzel, & Teicher, 2002). Taken together, results from this growing literature suggest that not all aspects of adolescent brain development are related to puberty. Yet careful examination of these adolescent-related brain alterations using both human neuroimaging studies and animal models will help to fully characterize the influence of pubertal hormones on specific brain changes as potential contributors to the onset of psychopathology during adolescence.

DEVELOPMENTAL PROCESSES CRITICAL IN ADOLESCENT PSYCHOPATHOLOGY

Over the past decade, there has been a tremendous interest, both from the scientific community and the media, in how adolescent neurodevelopment might contribute to the behavioral and emotional health problems that become prevalent during the teen years. Many of these problems have been conceptualized as involving dysregulation of intense emotions (e.g., depression, anxiety disorders) or poor decision making in the face of emotional influences (e.g., unsafe sex, risky driving, substance abuse). As described earlier in this chapter, researchers and policy-makers have emphasized dual process models that seek to explain increased rates of adolescent psychopathology as a function of a gap between input via an affective salience system, believed to be heightened during adolescence, and input from a cognitive control system, which undergoes a prolonged course of development, that serves to regulate the affective system (Casey, Jones, & Hare, 2008; Dahl, 2004; Ernst, Pine, & Hardin, 2006; Steinberg, 2005; Steinberg et al., 2006). Although to date developmental neuroscience research has provided some empirical support for dual process models, the boundaries, and thus operationalization, of what such a gap implies for maturity of adolescent brain anatomy and structure remains unspecified. Researchers have also recently argued for greater recognition of the complex nature of adolescent brain development, indicating that the interrelationships between neurodevelopment and the development of psychopathology may be more complex than previously thought (Crone & Dahl, 2012; Luciana & Collins, 2012; Pfeifer & Allen, 2012). For example, attention is needed on the direct relationship between brain structure and function and its joint association with psychopathology as well as how neural processes change within individuals and in tandem with changes in psychopathology over time. Although many questions still remain to be answered, we review the developmental changes in affective and cognitive control systems that occur during adolescence and discuss their potential role in the development of psychopathology during this period.

Changes in Social Motivation Systems

As we have discussed previously and will discuss in depth later in this chapter, adolescence involves a reorganization of social relationships, with teens investing more time and energy into forging new bonds with peers and pursuing romantic interests, while spending less time with family members (Larson & Richards, 1994; Steinberg & Morris, 2001). Researchers have proposed that the convergence of social changes and neural and endocrine changes in adolescence place an increased motivational salience on the goals of obtaining and maintaining social rewards (i.e., status, admiration, acceptance) and defending against social threats (i.e., rejection, exclusion; Crone & Dahl, 2012; Nelson et al., 2005; Silk, Davis, McMakin, Dahl, & Forbes, 2012). These motivational changes are likely interrelated with processes involved in identity formation (Erikson, 1980), which are strongly influenced by social comparison during adolescence (Pfeifer, Lieberman, & Dapretto, 2007; Pfeifer et al., 2009). In other words, adolescents come to understand who they are largely through the lens of how others view them and how they compare to others. Affiliation, admiration, and acceptance from peers and romantic partners represent salient social rewards during this period, but adolescents are also exposed to

frequent social threats, such as rejection, loss of status, exclusion, or embarrassment. This is particularly true for modern teens, given that they receive status feedback from social media technologies on a near continuous basis. Social threats are among the most highly salient human stressors (Dickerson & Kemeny, 2004) and may be particularly important for adolescents, given that their peer groups involve complex social hierarchies (Brown & Larson, 2009; Connolly, Furman, & Konarski, 2000).

Increased social motivations during adolescence may be related specifically to changes in the dopamine system during this period, which, as discussed previously, tend to increase incentive motivation (Luciana & Collins, 2012). Social incentives, such as obtaining approval from an admired peer, or being asked out on a date, are likely to be particularly salient for teens. Motivational changes during adolescence may also be related to the pubertal rise in sex hormones that occurs during this period. For example, testosterone, which increases in both males and females at puberty, appears to activate motivational tendencies that facilitate an increased orientation toward social status (Forbes & Dahl, 2010; Pfeifer & Allen, 2012).

While there is a pressing need for more research in human adolescents, studies of animals and adult humans converge to support the role of testosterone as a social hormone that enhances motivation to obtain and defend social status (Bos, Panksepp, Bluthe, & van Honk, 2011; Carney & Mason, 2010; Dabbs & Dabbs, 2000; Eisenegger, Haushofer, & Fehr, 2011). For example, in a study of adolescent primates, testosterone was associated with increased social dominance *and* sensitivity to threatening faces, but not with reactions to nonsocial emotional stimuli (Richards et al., 2009). Although the relationship between hormones and behavior is complex, non-human research suggests that it may be at least partially mediated by the influence of sex hormones on neural circuits that support socio-emotional behavior (Hermans et al., 2010; Manuck et al., 2010; Schulz et al., 2009; Stanton, Wirth, Waugh, & Schultheiss, 2009; Van Wingen et al., 2010), as indicated by high densities of steroid hormone receptors in areas involved in social and emotional information processing, such as the striatum, amygdala, hippocampus, and PFC (Sarkey, Azcoitia, Garcia-Segura, Garcia-Ovejero, & Don-Carlos, 2008; Simerly, Chang, Muramatsu, & Swanson, 1990). Although less understood, other hormones, such as estradiol and oxytocin, may also play a role in increasing the motivational salience of social interactions during adolescence (Gabor, Phan, Clipperton-Allen, Kavaliers, & Choleris, 2012). Greater attention to hormones' impact on brain and behavior in human adolescents, especially as a function of pubertal development, is an important priority for future research, and particularly for understanding psychopathology (Paus et al., 2008).

Increased orientation toward the social world beyond the family context is normative during adolescence, yet may also contribute to the development of problems such as substance abuse, anxiety, and depression. The field of social cognitive neuroscience has made major progress in mapping the neural substrates of social interaction and social perception during adolescence. These studies have identified a network of regions known as the mentalizing or theory of mind (ToM) network, which undergoes structural and functional change during adolescence (see reviews by Blakemore, 2008; Burnett, Sebastian, Cohen Kadosh, & Blakemore, 2010). However, relatively little is known about how changes in the mentalizing and ToM network might contribute to the development of psychopathology during this period. In contrast, more research has focused on how adolescent neurodevelopmental changes in the brain circuitry that responds to the affective salience of social stimuli might be implicated in the development of psychopathology. Altered functioning in a ventral affective salience network that includes regions of the brain that are involved in the processing of both negative emotional stimuli and rewards have been identified in some forms of adolescent psychopathology, such as anxiety and depression.

Changes in Reward Systems

We use the term reward systems to refer broadly to interrelated systems involved in approach motivation, sensation seeking, reward processing, and incentive motivation. As summarized in several recent reviews (Ernst, Romeo, & Andersen, 2009; Galvan, 2010; Galvan, 2013; Wahlstrom, Collins, White, & Luciana, 2010), adolescence is associated with an increase in reward-seeking, sensation-seeking, and novelty-seeking behaviors that also occurs in other species (Spear, 2000a, 2011). Self-reported sensation seeking increases from early to middle adolescence before declining from adolescence to adulthood (Harden & Tucker-Drob, 2011). Adolescents appear to seek out experiences that create high-intensity feelings, even when these experiences carry risks (Martin et al., 2002). This shift toward greater novelty-seeking and risk-taking may have evolutionary value, as it would serve to encourage adolescents to explore novel territories and roles beyond the home and interact with new potential mates outside of the family unit (Spear, 2000a). More generally, it may encourage a sense of independence and agency during the transition from childhood to adulthood.

This change in reward-seeking behavior is believed to be related to changes reviewed above in dopaminergic systems in adolescence, including changes in the firing rates, density, and concentration of dopamine fibers and receptors and a shift in the balance of dopamine receptors across brain regions. Luciana and Collins (2012) have argued that the increase in reward- and sensation-seeking behaviors in adolescence could be mediated by increases in tonic levels of dopamine in neural regions supporting affective motivation during adolescence. Others have suggested that heightened dopaminergic prediction error responsivity contributes to adolescent reward seeking (Cohen et al., 2010). However, methods for investigating changes in tonic and phasic dopamine firing in human adolescents are currently limited.

Neuroimaging studies provide some evidence for developmental changes in activation of reward circuitry during adolescence. This circuitry includes the striatum, amygdala, ACC, and mPFC (Depue & Collins, 1999). Most studies of adolescents have focused on the ventral striatum, and have relied on monetary reward tasks to probe neural response to anticipation and receipt of reward. These studies suggest that, relative to children, adolescents show increased striatal activity during the anticipation and receipt of reward (Cohen et al., 2010; Galvan et al., 2006; Somerville, Hare, & Casey, 2011; Van Leijenhorst et al., 2010). When compared with adults, adolescents have also been shown to exhibit increased striatal reactivity to reward (Cohen et al., 2010; Ernst et al., 2005; Galvan et al., 2006; Somerville et al., 2011), although conflicting data also exist (Bjork et al., 2004; Bjork, Smith, Chen, & Hommer, 2010; Forbes et al., 2010). Spear (2011) and Galvan (2010) suggested that these discrepant findings may be related to differences in responding to reward anticipation versus receipt of reward or other contextual features such as the type and magnitude of the reward. For example, it may be that adolescents have a decreased response to small rewards but an increased response to large rewards. This remains an important area for continued research.

Another important question is the extent to which changes in reward processing are related to pubertal development. Martin and colleagues (2002) found that adolescents further along in self-reported pubertal development were also higher in self-reported sensation seeking, even when controlling for the effects of age. Forbes and colleagues (2010) examined puberty-specific changes in reward responding based on a large sample of early adolescents matched for age but differing in pubertal status. They found that adolescents with more advanced pubertal maturation exhibited less striatal and more mPFC reactivity during reward receipt than age-matched adolescents with less advanced pubertal maturation. Similarly, they found that adolescents with higher circulating levels of testosterone exhibited lower striatal reactivity to reward receipt. In contrast, for boys only, testosterone was associated with increased striatal reactivity during reward anticipation, suggesting the possibility of different puberty-related developmental effects on anticipation and receipt of reward. These findings raise the possibility that later stages of puberty are associated with greater involvement of the mPFC, which aids in learning associations between events (e.g., outcome of receiving a reward) and generating adaptive emotional responses (Euston, Gruber, & McNaughton, 2012), and less involvement of the striatal regions implicated in motivation and reward seeking.

Over the past decade more ecologically valid paradigms have been developed that aim to simulate peer interactions during neuroimaging and psychophysiological assessment (Guyer, Lau, et al., 2008; Masten et al., 2009; Silk, Stroud, et al., 2012). This has allowed researchers to study typical and atypical neural responses to social rewards, such as peer acceptance, during adolescence. For example, the Chatroom Task (Guyer et al., 2014; Guyer, Choate, Pine, & Nelson, 2012; Guyer, Lau, et al., 2008; Guyer, McClure-Tone, Shiffrin, Pine, & Nelson, 2009; Lau et al., 2012) has been widely used to investigate adolescents' neural response to anticipated and rigged feedback (both positive and negative) from virtual peers they believe have evaluated them as potential interaction partners for an upcoming online chat session. Davey, Allen, Harrison, Dwyer, and Yucel (2010) investigated how adolescents and young adults respond to being liked by asking participants to view photos of other virtual participants whom they were led to believe had rated them as likable based on their own photographs. These peer feedback tasks have shown that acceptance from virtual peers activates regions involved in reward processing and positive affect, particularly the ventral striatum (Davey et al., 2010; Giedd & Rapoport, 2010; Guyer et al., 2012; Guyer et al., 2009; Moor, van Leijenhorst, Rombouts, Crone, & Van der Molen, 2010). Several studies have now investigated changes across adolescence in response to positive social feedback. Existing data show increased striatal and mPFC activity to happy relative to neutral faces (Pfeifer et al., 2011) and to virtual peer acceptance relative to rejection (Gunther Moor, van Leijenhorst, Rombouts, Crone, & Van der Molen, 2010; Guyer et al., 2012) across adolescence. Silk and colleagues (2012) also found evidence for increased visual biases toward acceptance feedback across adolescence using eye tracking during engagement in a simulated peer interaction task.

Another exciting discovery over the past decade has been the finding that the presence of peers enhances risk taking and reward processing measured through both behavioral and neural indices in adolescents. In a behavioral study, Gardner and Steinberg (2005) demonstrated that adolescents took more risks on a simulated driving task when they were watched by two peers, compared with when they performed the task alone. In the peer condition, these adolescents were more likely to risk crashing to earn a potential reward, whereas they made safer driving decisions when they were alone. Interestingly, the influence of peers on risky driving was stronger in adolescents than in adults, suggesting that the influence of peers on reward seeking and risk taking may be particularly heightened during adolescence. Another study showed that adolescents had a greater preference for immediate over delayed rewards when performing a delay discounting task in the presence of peers than when playing alone (O'Brien, Albert, Chein, & Steinberg, 2011). These effects were replicated even in the presence of unknown peers (Weigard, Chein, Albert, Smith, & Steinberg, 2014) and even when the probabilities of negative outcomes were known (Smith, Chein, & Steinberg, 2014). Through the use of neuroimaging, Chein and colleagues (2010) investigated the neural correlates of this peer enhancement effect on risk-taking behavior by conducting a neuroimaging study in which adolescents completed the simulated driving task in the fMRI scanner while their performance was observed by two peers. Findings showed that increased risky driving in the presence of peers was associated with enhanced activity in the ventral striatum and OFC during the peer observation condition among adolescents but not adults.

Changes in Reward System and Psychopathology

Increases in risk-taking and sensation-seeking behaviors in adolescence likely contribute to adolescent experimentation with rewarding and pleasurable substances and experiences, such as taking drugs and alcohol, and sexual activity (Colder et al., 2013). Most drugs exert their initial reinforcing effects on reward processing through ventral striatal dopamine release (Baler & Volkow, 2006), and heightened reward responsivity has been associated with early onset drinking and substance use problems (Castellanos-Ryan, Rubia, & Conrod, 2011; Crowley, Raymond, Mikulich-Gilbertson, Thompson, & Lejuez, 2006). Data also show that adolescents who tend to respond to rewarding stimuli with greater striatal activation in the laboratory engage in more self-reported risk-taking behaviors (Bjork, Chen, Smith, & Hommer, 2010; Galvan, Hare, Voss, Glover, & Casey, 2007). Furthermore, greater ventral striatal response measured during the simulated driving task discussed previously predicted greater risk taking on the task (Chein et al., 2010).

At the other end of the spectrum, the failure to experience normative levels of reward responsiveness during adolescence may be related to increased risk for depression. Rates of depression rise dramatically during this period of development, especially for girls (Angold et al., 1998). Epidemiological studies indicate that as many as 1 in 7 adolescents will experience an episode of Major Depressive Disorder prior to adulthood (Kessler, 1994; Kessler et al., 2012). While healthy adolescents tend to show increased reward seeking during adolescence, youth with depressive disorders and heightened depressive symptoms show behavioral evidence of reduced positive affect and reward-seeking behaviors (Forbes, Shaw, & Dahl, 2007; Jazbec, McClure, Hardin, Pine, & Ernst, 2005). In neuroimaging studies, adult depression has been associated with reduced activation to positive stimuli in the striatum (Epstein et al., 2006; Lawrence et al., 2004; Surguladze et al., 2005) and enhanced activation in ventromedial areas of the PFC that are involved in evaluating contingencies (Keedwell, Andrew, Williams, Brammer, & Phillips, 2005). Neuroimaging studies of reward processing in adolescents also show decreased striatal activity and increased mPFC activity in depressed youth relative to healthy controls (Forbes et al., 2009; Forbes et al., 2006). Studies have also reported decreased striatal activity in healthy youth at high risk for depression (Gotlib et al., 2010; Monk, Klein, et al., 2008), suggesting that diminished striatal response to reward could be a biomarker for depression risk. Although most of the studies have focused on response to monetary reward, Whittle et al. (2012) demonstrated that adolescents with higher depressive symptoms also show reduced striatal activity to video clips of their own and unfamiliar mothers' positive behavior. Two recent studies, however, have suggested that depressed adolescents may actually show increased activation of the amygdala in response to social rewards (Davey, Allen, Harrison, & Yucel, 2011; Yang et al., 2010), highlighting the potential for a differential depression-related response to stimuli representing monetary and social value.

It is not clearly understood why youth vulnerable to depression might show diminished reward responding during the transition through adolescence compared with typically developing youth. Some data suggest that diminished sensitivity to reward might represent an endophenotype of risk for depression that is present earlier in life (Bress, Foti, Kotov, Klein, & Hajcak, 2013; Olino

et al., 2011), and could be exacerbated during adolescence (Morgan, Olino, McMakin, Ryan, & Forbes, 2013). Given high rates of interpersonal sensitivity and interpersonal concerns among depressed youth (Hammen & Brennan, 2001; Rudolph, Flynn, Abaied, Groot, & Thompson, 2009), it may be that depressed youth are sensitive to both positive and negative social evaluation, but do not experience high levels of social acceptance or positive social reward, or anticipate that they will not receive it and do not pursue it. Overall, future work in this area is needed that integrates neuroimaging approaches with observational and sociometric investigations of peer relationships, to obtain a fuller picture of how the actual social experiences in adolescents' daily lives are linked with their changing neurobiology.

Changes in Negative Affect Systems

Although no longer considered a period of pervasive storm and stress (Hall, 1904), the adolescent period still conjures up images of increased negativity, especially in affect. Consistent with this view, ecological momentary assessment (EMA) studies, in which adolescents' emotions are sampled repeatedly in everyday life, have shown that adolescents do tend to experience more frequent negative emotions than children or adults and that changes in emotional states are linked with changes in daily activities (Larson, 1989; Larson, Csikszentmihalyi, & Graef, 1980). Several neuroimaging studies have demonstrated increased sensitivity to negative emotional stimuli in adolescents compared with adults across regions of the affective salience network, especially the amygdala. For example, adolescents have been found to have greater amygdala reactivity relative to adults to sad and fearful faces (Guyer, Monk, et al., 2008; Killgore & Yurgelun-Todd, 2007) and greater activation in the amygdala, mPFC, and ACC compared with adults during passive viewing of emotional faces (Monk et al., 2003). Research is lacking, however, that tracks neurodevelopmental changes in response to negative emotional stimuli during the transition from childhood to adolescence. One study has shown increased amygdala activity when inhibiting response to negative versus positive emotional faces in adolescents compared with younger children and adults (Hare et al., 2008), but most existing neuroimaging research compares adolescents to adults rather than to younger children. This is partially a methodological issue, as it is difficult to have younger children perform the same complexity of tasks as older individuals and also to require young children to be still in the scanner. Nevertheless, it would strengthen the current literature to have an understanding of these patterns across broader periods of development.

Researchers have also begun to probe the neural correlates of social threat and social rejection using simulated interaction paradigms such as the Cyberball ball tossing task (Eisenberger, Lieberman, & Williams, 2003) and the Chatroom and Likeability social evaluation tasks (Gunther Moor et al., 2010; Guyer, Lau, et al., 2008). Findings indicate that anticipated and perceived social exclusion/rejection in adolescents activates the ventral affective salience network including the amygdala, ACC, and anterior insula, as well as ventrolateral areas of the prefrontal cortex (vlPFC) involved in the regulation of social distress (Guyer, Lau, et al., 2008; Masten et al., 2009; Sebastian et al., 2011). While social exclusion in adults appears to activate a dorsal portion of the ACC (Eisenberger, Gable, & Lieberman, 2007), studies of adolescents implicate the subgenual ACC (sgACC) in response to social exclusion (Masten et al., 2009; Sebastian et al., 2011; Silk et al., 2014). Emerging data suggest that adolescents, especially girls, exhibit age-related increases in the neural response to peer rejection in these affective and self-evaluative networks (Gunther Moor et al., 2010; Guyer et al., 2009; Silk et al., 2014). Youth also show increased pupillary reactivity to peer rejection across adolescence (Silk, Stroud, et al., 2012). Activity in the vlPFC, which is implicated in regulating responses to social distress, also is increased during adolescence (Gunther Moor et al., 2010), but decreased in adolescents compared with adults (Sebastian et al., 2011). Together, these results would suggest that adolescents are less effective at recruiting regulatory resources in response to social exclusion threat.

Only a few studies have investigated responses to negative or threatening emotional stimuli as a function of puberty. Silk et al. (2009) found that mid to late pubertal youth had a greater pupillary response to emotional words than pre- to early pubertal youth, controlling for participants' age, although this effect was seen in both positive and negative emotional words. Similarly, Moore et al. (2012) found increased amygdala reactivity to both negative and positive emotional faces relative to neutral faces among early adolescents more advanced in pubertal status. Moore et al. (2012) suggested that puberty may reorient adolescents toward social stimuli, such that emotional faces become particularly relevant. However, another recent study observed that activity in the amygdala and vlPFC while viewing fearful faces was stronger during early puberty than later puberty (Forbes, Phillips, Silk, Ryan, & Dahl, 2011), indicating potential nonlinear effects. There is also evidence that sensitivity to peer rejection may vary as

a function of puberty, with increased amygdala and sgACC activation to peer rejection among youth more advanced in pubertal development (Silk et al., 2014). New evidence suggests that pubertal testosterone may exert its effects on increased threat reactivity during adolescence partially through disrupting functional connectivity between the amygdala and orbitofrontal cortex (Spielberg et al., 2014). Additional work is needed to pinpoint more precisely which phases of puberty show neural changes to emotional stimuli of various classes, and to link such changes with psychopathology.

Changes in Negative Affect Systems and Psychopathology

Normative increases in reactivity to negative emotional information may lead to the development of problems such as anxiety and depression during the transition to adolescence in vulnerable youth. The role of threat and fear processing has been most strongly investigated in relation to anxiety disorders, although focus has also turned to reward processing in anxiety (Caouette & Guyer, 2014). Although some forms of anxiety, such as separation anxiety and specific phobias, tend to decrease in adolescence, overall rates of anxiety increase, particularly social anxiety (Beesdo, Pine, Lieb, & Wittchen, 2010), and especially for girls, with 11% of 12–19 year olds experiencing clinically significant anxiety (Costello, Copeland, & Angold, 2011). Behavioral studies demonstrate that anxious children and adolescents show an attentional bias toward social threat words and faces (Telzer et al., 2008) and report more threatening interpretations of ambiguous social scenarios (Creswell, Schniering, & Rapee, 2005), although little research has investigated whether these anxiety-related attentional biases are heightened during adolescence. Adolescence is filled with ambiguous social cues that may easily be misinterpreted as threatening by youth vulnerable to anxiety (Creswell et al., 2005). It seems plausible that the increased focus on social status and evaluation during adolescence could contribute to increased vigilance for social threat during this period of development, possibly contributing to increased anxiety during adolescence (Caouette & Guyer, 2014; Silk, Stroud, et al., 2012). Consistent with this possibility, neuroimaging studies show that anxious symptoms in adolescents are associated with increased amygdala and vlPFC activity to threatening faces (McClure et al., 2007; Monk, Telzer, et al., 2008). Several studies have also investigated response to peer rejection in anxious adolescents using the Chatroom task. These studies show that adolescents with anxiety disorders expect peers to rate them as less desirable (Guyer, Lau, et al., 2008), especially peers with which they did not want to interact, while also exhibiting increased insula and amygdala reactivity to rejection feedback (Lau et al., 2012). Two studies also found evidence for altered amygdala–vlPFC connectivity in adolescent anxiety (Guyer, Lau, et al., 2008; Monk, Telzer, et al., 2008), suggesting potential disruptions in top-down regulation of threat responding.

In a recent study that considered both developmental stage and clinical diagnosis, neural responses to emotional facial expressions were compared between adults and adolescents with social anxiety disorder. Greater activation in the amygdala and rostral ACC was found in response to angry and fearful, but not neutral faces in both adolescents and adults with social phobia. Although this was a cross-sectional study, the similar patterns of neural activation in adolescent and adult social anxiety disorder suggest persistence across development in the neural mechanisms underlying social anxiety disorder (Blair et al., 2011).

Changes in negative affect systems during adolescence may also be implicated in increased rates of depression during this period. EMA studies show that depressed adolescents experience more sadness, anger, and anxiety in daily life compared with healthy youth, and these differences are exacerbated by pubertal development (Silk et al., 2010). Specifically, depressed adolescents in the midst of puberty show more marked differences in the experience of negative emotions compared with their healthy postpubertal peers. Neuroimaging studies also provide evidence for a link between heightened responsivity to negative affective stimuli and adolescent depression. Although relatively few studies have been conducted with depressed adolescents, these studies have generally demonstrated amygdala hyper-reactivity in response to negative emotional faces in depressed youth compared with healthy controls (Beesdo et al., 2009; Roberson-Nay et al., 2006; Yang et al., 2010). Recently, two studies have investigated the neural response to peer rejection in adolescent depression. Masten et al. (2011) showed that when adolescents were being socially excluded during the Cyberball task, greater activity in the sgACC and the dorsomedial PFC was associated with increases in depressive symptoms over one year in a community sample of adolescents. Silk and colleagues (2014) demonstrated increased activation to being rejected by peers in a clinical sample of depressed youth, compared with healthy controls, in the same subgenual region of the ACC, and in the amygdala, insula, and nucleus accumbens. Taken together, these data suggest that depression in adolescents is characterized by increased neural reactivity to negative affective stimuli, particularly affective stimuli that

represent potential social threat. Such vulnerability of girls to depression during puberty may relate to a more rapid course of cortical thinning in the frontal lobes in males than in females (Raznahan et al., 2010). As such, a differential tempo in cortical brain development between males and females may create different windows of imbalanced connections between affective and cognitive-control neural systems that render females vulnerable to contextual or other risks that lead to depression. A similar mechanism of vulnerability to depression in girls may also relate to the timing and tempo of pubertal changes instantiated through adrenal and gonadal axes (Berenbaum & Beltz, 2011; Schulz et al., 2009).

Changes in Cognitive Control

The models proposed to understand how adolescent neurodevelopment and psychopathology are intertwined emphasize not only increases in emotional reactivity during adolescence, but also challenges in recruiting cognitive control processes to regulate these emotions. Cognitive control is defined as "a set of neurocognitive processes that are important for achieving short- and long-term goals, particularly when individuals are required to adjust their thoughts and actions adaptively in response to changing environmental demands in order to achieve their goal" (Crone & Dahl, 2012, pp. 636). This includes executive functions such as response inhibition, working memory, and task switching. Research on the neural substrates of cognitive control focuses on lateral portions of the PFC as well as parts of the parietal cortex (Miller & Cohen, 2001). As discussed previously, the PFC undergoes substantial remodeling of neuronal connections during adolescence, as well as changes in the amount of input received from neurotransmitters involved in emotional responding such as dopamine and gamma-amino-butyric acid (Lewis, 1997). Much attention in recent years has been drawn to the fact that areas of the PFC involved in higher order cognitive processing continue to change and undergo refinement through adulthood. For example, the dorsolateral PFC does not reach its adult volume until early adulthood (Giedd, 2004; Giedd et al., 1999). Synapse elimination and gray matter volume reduction in the PFC also continue into early adulthood relative to other areas of the brain (Giedd, 2004; Huttenlocher, 1990).

Despite solid evidence of these structural changes in adolescence, their relationship to functional and behavioral changes is still poorly understood. Specifically, evidence that delayed structural maturation of the PFC translates into immature capacity for cognitive control is unclear (Pfeifer & Allen, 2012). In general, the ability to engage in cognitive control processes improves and becomes more integrated throughout childhood and adolescence (Huizinga, Dolan, & van der Molen, 2006; Luna, Padmanabhan, & O'Hearn, 2010), and this is well established when measured behaviorally but recent reviews highlight the complexity of associating changes in the brain with age-related behavioral improvements (Crone & Dahl, 2012; Pfeifer & Allen, 2012). Some neuroimaging studies suggest that, rather than having *less* PFC activation than adults, adolescents have more diffuse, potentially inefficient patterns of activity in the PFC during cognitive control tasks compared with adults (Andrews-Hanna et al., 2011; Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Geier & Luna, 2009; Luna et al., 2001; Velanova & Luna, 2009). A meta-analysis of neuroimaging studies conducted from 2001 to 2011 found substantial evidence for both increases and decreases in adolescence relative to adulthood or childhood in PFC activity during cognitive control tasks as well as evidence for a mid-adolescent peak in PFC activity during cognitive control tasks (Crone & Dahl, 2012), with the direction of effects differing across PFC subregions and tasks. As a whole, findings from the available literature underscore the importance of examining neural activation patterns in terms of both their magnitude (e.g., height of response), location (e.g., focal or diffuse response), and distribution (e.g., connections within and between regions) at multiple phases of development. As such, future work should compare samples of children, adolescents, and adults longitudinally in that it may demonstrate a progression of cognitive control function that goes from being focal to diffuse to distributed.

The discrepant findings in age-related differences in PFC activity do not necessarily support the idea that adolescents are less able to exert control over their hyperactive affective response systems relative to adults. Given that, it is important to bear in mind that there is no standard benchmark of maturity in the brain systems involved in cognitive control over behavior (or affective systems for that matter), and that assessments of relative neural activity within specific regions cannot solely be used to provide information for establishing such benchmarks. In fact, some studies suggest that by mid-adolescence, teens do not differ greatly from adults in the *capacity* for cognitive control (Luna, Garver, Urban, Lazar, & Sweeney, 2004; Steinberg et al., 2009). For example, Luna et al. (2004) showed that by age 15, most adolescents have reached adult levels of response inhibition. In many ways, an important index of maturity may be in the connectivity between the PFC and other regions, particularly with those within the affective system,

to the extent that tighter and more specific connections between cognitive control and affective regions support more mature or adult-like behavior (Dosenbach et al., 2010). Importantly, the convergence of connections within and between cognitive control and affective systems in adolescence is likely subject to influences such as attentional focus, arousal, or social factors like the presence of peers (Guyer, Lau, et al., 2008). Adolescents may therefore differentially recruit cognitive capacities based on contextual factors, motivational incentives, and affective salience. This perspective is consistent with studies suggesting that when tasks include both a cognitive and affective component, adolescents tend to be more strongly influenced by the affective demands of the task (Monk et al., 2003; Somerville et al., 2011). However, adolescents can improve cognitive performance when the affective salience of the task is enhanced by providing rewards for performance (Jazbec et al., 2005).

Changes in Cognitive Control and Psychopathology

Over the past decade, many researchers have discussed the possibility that problems in emotional and behavioral regulation during adolescence might result from immature cognitive control, as a function of the PFC's protracted period of development, particularly in the context of increased emotional demands during the adolescent transition (Casey et al., 2011; Dahl, 2004; Ernst et al., 2006; Steinberg et al., 2006). Despite the intuitive appeal of this model (see Pfeifer & Allen, 2012), some of the data reviewed above suggests that these "dual process" or "developmental mismatch" models may have oversimplified the relationship between adolescent neurodevelopment and psychopathology (Crone & Dahl, 2012; Luciana & Collins, 2012; Pfeifer & Allen, 2012). This can be seen in the example of risk-taking behavior. Adolescents are more likely than children or adults to engage in risky behaviors, including binge drinking, smoking, unprotected sex, and risky driving (Steinberg, 2008). There is now convincing evidence that adolescent risk taking is *not* a function of limited understanding of the cognitive consequences of risk (Reyna & Farley, 2006). Rather, risk taking may be better thought of as the result of a biasing of behavior by social and motivational factors during adolescence (Dreyfuss et al., 2014; Smith, Chein, & Steinberg, 2013b). In other words, it is not that cognitive control is weak but rather that motivations toward obtaining reward, especially social motivations, are particularly strong. In support of this view, Chein et al. (2010) found that although adolescents showed greater activation of the reward system during peer observation, activity in the cognitive control system did not vary based on the presence or absence of peer observers. This finding supports the suggestion that adolescents are driven to engage in risky and reward-seeking behaviors because social and motivational factors play a stronger role in shaping such behaviors than does cognitive control at this developmental interval, particularly given the interconnected nature of these cognitive control and affective neural systems. More generally applied across forms of psychopathology, it may be that greater connectivity between cognitive control and affective neural systems during adolescence affords some protection from the onset of psychopathology, whereas less connectivity could render an adolescent vulnerable to the influence of intensely felt and reactive emotions, highly arousing motivations, and demanding social-contextual conditions.

Age-related refinement in cognitive control neural systems may play a role in the development of depression during adolescence. Dual process models suggest that rates of depression increase during adolescence as a function of increased negative emotional arousal relative to insufficient regulatory control. However, these models cannot fully account for the fact that rates of depression remain stable from adolescence through adulthood, despite stabilization of structural development of cognitive control neural regions by early adulthood. Davey et al. (2008) have proposed an alternative model, suggesting that increased rates of depression during adolescence might be a function of the more advanced nature of cognitive capabilities seen in adolescence, rather than the relative immaturity of cognitive neural structures reported in adolescence relative to adulthood. Specifically, the model proposes that the continued development of the PFC facilitates advanced hypothetical thinking during adolescence, allowing for representation of increasingly complex social and future-oriented rewards. Yet, these abstract social rewards (i.e., becoming popular, falling in love, being successful) are also tenuous and easily frustrated. Davey et al. (2008) suggest that repeated failure or frustration of these socially oriented rewards during adolescence may lead to suppression of the reward system, eventually resulting in anhedonia and depression (Bogdan & Pizzagalli, 2006; Frewen, Dozois, Joanisse, & Neufeld, 2008). Additional research is needed to support this model, as alternative hypotheses remain to be tested. For example, deficits in cognitive control could lead to excessive rumination, a key component of depression. The model nonetheless highlights an emerging recognition that, despite the historical neurodevelopmental focus on the imbalance of too little cognitive control and too much emotional reactivity, the

progression of cognitive control capacities from childhood to adolescence should also be examined as a contributor to the development of psychopathology during this period.

CONTEXTS OF ADOLESCENT DEVELOPMENT

Adolescence is characterized not only by the biological and cognitive changes within the individual adolescent but also by changes in the contexts in which adolescents live and in their interactions with those contexts. As articulated in ecological models and developmental systems theory (Bronfenbrenner, 1979; Ford & Lerner, 1992; Gottlieb & Halpern, 2002; Thelen & Smith, 2006), individual development is embedded in processes of interaction with family, peers, school, neighborhood, and society. As they age, adolescents in many modern societies spend increasing amounts of time outside the supervision of their parents and in the company of peers, make transitions to secondary schooling, begin to navigate employment and romantic relationships, and engage with media in many forms, often for many hours a week (Brown & Larson, 2009; Brown & Bobkowski, 2011; Steinberg & Morris, 2001). The nature of these contexts and the interactions of adolescents with them have been widely implicated in the development, maintenance, and prevention of psychopathology, although the conceptual models of how and why context and psychopathology may be linked continue to be refined. Moreover, the lion's share of research on contextual influences on the development of psychopathology has not formally examined how context may interact with the biological, emotional, and cognitive changes that concomitantly occur during adolescence.

During the transition from childhood into adolescence, and over the course of early adolescence in particular, contextual interactions may play a key role in protecting or exacerbating the adaptation of individuals who enter the transition with regulatory vulnerabilities. That is, during early adolescence, individuals need the assistance and protection provided by a structured and supportive context. In concrete terms, adolescents need the presence of other individuals and institutions during this potentially challenging developmental transition. At the same time, this ontogenetic period is particularly risky for young people with little or no contextual support and those with high vulnerability.

Context and adolescent psychopathology connections were studied initially in terms of risk factors for psychopathology and problems, such as delinquency, substance abuse, school dropout, depression, eating disorders, and suicidal behavior, all of which were linked in some way to bad environments. Poor parenting, poverty, divorce, and many other stressful life events, as well as unsafe neighborhoods and deviant peers, have each been studied as risk factors for psychopathology. Extensive evidence pointed to unsupportive or dangerous environments and relationships as predictors of psychopathology, although the processes accounting for these outcomes were not well understood. It also became clear that risky conditions often co-occurred, such that some youth faced very hazardous transitions to adolescence, fraught with stressful experiences and little in the way of positive resources; psychopathology was often associated with high net or cumulative risk (Masten & Coatsworth, 1998; Masten & Narayan, 2012; Sameroff, Gutman, & Peck, 2003). Moreover, strong overlap was noted among risk factors, with a given risk factor such as a chaotic home environment or unsafe neighborhood being associated with multiple forms of psychopathology (Monahan, Oesterle, Rhew, & Hawkins, 2014; Steinberg & Avenevoli, 2000).

With the emergence of developmental approaches to psychopathology, thinking about the connections of context and emotional and behavioral outcomes has changed in several respects. First, the role of context in normative developmental transitions has received closer examination, in an effort to use findings from research on typical development to inform our understanding of maladaptive developmental pathways. Second, more dynamic models of person-environment interaction have gained ground, emphasizing the role of adolescents as agents in the shaping of their own experiences and the importance of relationships in the development and course of problematic and positive behavior during adolescence. Attention is increasingly focused on how contexts and adolescents interact or co-act to shape development either toward or away from psychopathology, with more focus on regulatory processes and concepts such as self-regulation, co-regulation, and scaffolding. Finally, there has been a movement toward studying the ways in which multiple, interdependent, and sometimes nested contexts may interact to influence patterns of individual development, rather than investigating the effects of a single context considered in isolation. These changes reflect the influence of developmental systems theory on conceptualizations of normative and deviant development and also herald an evolving framework for a developmental psychopathology of adolescence.

In the three decades since Hill (1980, 1983) first published his framework for research on adolescence, there have been marked changes in the study of context in relation to adolescent development. Studies of traditional

contexts, such as peers, families, and schools continue, but the focus of this work has shifted to addressing more complex and dynamic questions. There has been more intensive and focused investigation of contexts that had previously received scant attention, including romantic relationships, work, extracurricular activities, and media. Emerging technologies have created virtual contexts for adolescent interaction, including electronic friendships, neighborhoods, fantasy worlds, and many other kinds of contexts and contextual interactions. These same technologies have altered the study of context-adolescent interaction as investigators capitalize on computers, tablets, and cell phones to assess the ongoing interactions of adolescents with their environments. This section highlights some of these changes, as investigators try to understand the nature of adolescent interactions with their environments and how these interactions may contribute to the etiology, maintenance, prevention of, or recovery from psychopathology and other problems in adolescent development.

Over the past 20 years, several overarching themes in the study of psychopathology and context in adolescence have emerged. First, there is growing evidence that the role of context in the development of psychopathology is typically nonspecific. That is, it is difficult to find links between specific contextual stressors (either chronic or acute) and specific manifestations of dysfunction. Divorce, poverty, maltreatment, exposure to neighborhood violence, and peer rejection, for example, are risk factors for many types of problems in adolescence (Bond, Toumbourou, Thomas, Catalano, & Patton, 2005; Monahan, Oesterle, et al., 2014; Steinberg & Avenevoli, 2000). Thus, it appears likely that specificity in the manifestations of emotional and behavioral disorder (i.e., why one individual develops depression but another develops alcohol dependence) likely reflects individual differences (genetic or acquired) in biological diatheses rather than specific differences in contextual experience.

Second, the impact of contextual stress on psychopathology is cumulative. Individuals whose lives are characterized by a greater number of contextual risks are more likely to show manifestations of internalizing, externalizing, or addictive problems than are those whose lives are characterized by fewer risk factors.

Third, there are significant links among contextual risk factors that make it difficult to study them as independent influences. Adolescents who grow up in dysfunctional family environments, for example, are more likely to experience poverty, attend inadequate schools, encounter antisocial peers, and witness neighborhood violence. By the same token, adolescents who enjoy one form of contextual benefit (e.g., supportive teachers) are also more likely to have lives that are characterized by multiple advantages. As such, studies that examine one context in isolation ignore that certain risk factors are nested and highly likely to co-occur, and that other factors may protect against risk or promote adaptation more generally (Rutter, 2001).

Fourth, contextual risk exerts its impact on psychopathology through both objective and subjective means (Boyce et al., 1998). Thus, in research on context and psychopathology, it is important to document both the objective level of stress, as well as the adolescent's subjective appraisal of stress. This is especially important in research involving adolescents from various demographic groups, because the same contextual stressor may be appraised differently by individuals from diverse backgrounds. What might be considered harsh parenting among middle-class suburban adolescents, for example, may be considered supportive among impoverished inner-city youth. To the extent that the impact of parenting is mediated by the way it is interpreted by the adolescent, we would expect that parental strictness would have different effects across these various settings. Similarly, the objective assessment of peer characteristics and the subjective report of perceived peer characteristics demonstrate different associations with adolescent psychopathology (Brechwald & Prinstein, 2011)—examination of both is needed.

Fifth, contexts interact in ways that may exacerbate, compensate for, or cancel out each other's influence on normative and atypical development. Additionally, contemporary research on contextual influence, reflecting the work of Bronfenbrenner (1979) and others, has documented the importance of examining how the influence of proximal settings, such as the family, is moderated by factors within the broader contexts that contain them, such as neighborhoods (Leventhal, Dupéré, & Brooks-Gunn, 2009). Understanding the development of psychopathology necessitates that attention be paid to the interactive and nested relations among contexts. Contemporary research also stresses the importance of examining interactions between social and neurobiological contexts. For example, recent studies demonstrate that the quality of parenting influences brain function and structure during adolescence in regions of the brain that respond to social and emotional stimuli (Casement, 2014; Morgan, 2014; Tan, 2014; Whittle, 2014).

Finally, adolescents are not the passive recipients of contextual influence, but are active agents who choose, transform, and recruit contextual resources. Unlike younger children, who have little control over where and with whom they spend time, adolescents are more

active in selecting the contexts to which they are exposed; although adolescents have little say over their family or school environments, they choose their friends, decide whether to work or engage in extracurricular activities, and pick the media to which they are exposed. This fact poses a challenge to researchers interested in demonstrating causal influences of context on psychopathology, because often it is not clear whether it is the context that is driving the psychopathology or the reverse. Thus, for example, the links between externalizing problems and affiliation with antisocial peers may result from the self-selection of antisocial adolescents into deviant peer groups, as well as the recruitment of alienated youth into deviant groups (Monahan, Steinberg, & Cauffman, 2009). Deviant peer association may then function to exacerbate antisocial behavior through reinforcement, modeling, opportunities, or combined influences of this kind. It is not easy to sort out causality when there is so much reciprocal influence. In addition, and operating above and beyond any selection process, is the fact that adolescents actually influence their parents, friends, teachers, and neighbors in ways that affect the home, peer, school, and community contexts, which then, in turn, influence the adolescent's development. An important but understudied issue is how, under what circumstances, and through what processes adolescents actively employ contextual resources (from relationships with parents, friends, and teachers to video games and Internet chat rooms) as a means of protection against the adverse effects of environmental stress, as well as the amelioration of psychological distress. A detailed review of the vast literature on specific aspects of context that have been associated with various forms of psychopathology in adolescence is beyond the scope of this chapter. In the sections that follow, we highlight points of consensus and areas of converging evidence in different contexts.

The Role of the Family

Of the many contexts that have been studied in relation to adolescent psychopathology, none has received as much attention as the family. Parent-adolescent relationships characterized by warmth, support, age- and context-appropriate monitoring, and clear expectations for positive behavior—the kind of parenting known as authoritative in style (Baumrind, 1973, 1991)—continues to be widely associated with positive adaptation in adolescence (Steinberg, 2001), including less psychopathology. Conversely, families that provide little warmth, structure, or resources or that expose the adolescent to high levels of hostility may not only exacerbate risk for psychopathology, but also fail to scaffold successful transitions in adolescence, leaving their adolescent children unprotected during a challenging time of change (Ge, Lorenz, Conger, Elder, & Simons, 1994; Repetti, Taylor, & Seeman, 2002).

If is, of course, quite possible that parents who do not function well transmit genetic vulnerability to psychopathology along with providing a risk-laden or neglectful environment. This is a classic confound in diathesis-stress models of psychopathology, and the issue has reemerged in contemporary debates about the importance of parenting in development (Collins, Maccoby, Steinberg, & Hetherington, 2000; Masten & Shaffer, 2006; Repetti et al., 2002; Scarr & McCartney, 1983). Nonetheless, research implicates parenting as a key mediator of adverse life experiences and psychosocial disadvantage on adolescent behavior (Bowes, Maughan, Caspi, Moffitt, & Arseneault, 2010; Bradley & Corwyn, 2002; McLoyd, 1998; Odgers et al., 2012). In these models, adversity undermines parental functioning, which in turn affects adolescent functioning. Not surprisingly, adolescents who achieve more positive adaptation in the presence of adversity or psychosocial risk often have better functioning parents or other adults who provide effective parent resources for them in spite of high-adversity exposure (Masten, 2001; Odgers et al., 2012). Moreover, high quality parenting appears to buffer against exposure to other risk factors, such as delinquent peers, suggesting that parenting may both promote positive adjustment and also protect against negative adjustment in the presence of risk (Chester, Jones, Zalot, & Sterrett, 2007; Germán, Gonzales, & Dumka, 2009). Studies also hint at the potential role of parenting in scaffolding self-regulation skills in the transition to adolescence. In a study of competence development among rural African American adolescents living in poverty, the effects of effective parenting on competence in young adolescents was mediated by self-regulation in the adolescents (Brody, Murry, Kim, & Brown, 2002). Conversely, in a sample of typically developing community youth, harsh parenting was associated with diminished development of self-control across early adolescence (King, Lengua, & Monahan, 2013). Moreover, interventions to facilitate or protect the quality of parent functioning under adverse conditions appear to be effective in altering the risk for problems developing in children and adolescents (Hawkins et al., 2003; Van Ryzin, Stormshak, & Dishion, 2012; Wolchik et al., 2002). Studies of families also focus on indirect and possible long-term effects that families may have in protecting or harming development during adolescence indirectly, through their influence on the opportunities, peers, schools, and neighborhood resources available to

their children. Long before the challenges of adolescence arrive, effective parents may facilitate the successes of their children in peer relations and schools, indirectly increasing the likelihood of bonding to prosocial peers and school engagement that may be a key to avoiding increases in antisocial and other risk-taking behaviors that tend to accompany transitions to adolescence (Brown & Bakken, 2011; Brown, Mounts, Lamborn, & Steinberg, 1993; Collins et al., 2000; Galambos, Barker, & Almeida, 2003; Pettit, Bates, Dodge, & Meece, 1999).

Understanding of the importance of the parent-child relationship during adolescence must be coupled with recognition that the relationship changes across the adolescent years. A meta-analysis of studies of parent-adolescent conflict indicates that, although conflict generally declines across adolescence, the intensity of affect characterizing these conflicts rises in early adolescence (Laursen et al., 1998). An especially relevant aspect of the parent-child relationship is the negotiation of the child's emerging autonomy needs—a critical task that has been linked to numerous indices of adolescent adjustment (Laursen & Collins, 2009). Parents' role in this process consists of striking a balance between encouraging adolescent independence and maintaining a supportive connection when needed—a balance that bolsters adolescent self-esteem, ego development, and social functioning (Van Petegem et al., 2012). Thus, this transition period may be a time during which responsive changes in parenting behavior are critically important for the child maintaining a positive trajectory of adaptive social behavior; and lack of appropriate parental responsiveness to these developmental changes may deflect this pathway into maladaptive functioning. Sufficient data are not yet available to discern subtle patterns or differentiate age, context, and pubertal effects in these parent-adolescent interactions. However, studies do corroborate the general idea prominent in many theories of adolescent maturation that reorganizations occur in parent-adolescent interactions around adolescence and that these transformations involve affect regulation. It is therefore important to understand how variations in parenting practices may contribute to the development of regulatory competence and how developmental variation in parenting across adolescence is important for the emergence of psychopathology. From a vulnerability perspective, it stands to reason that parents who respond poorly to the changing needs of the adolescent across adolescence may place their child at risk for the development of psychopathology, by failing to provide a supportive and appropriate structural context.

Peers as Positive and Negative Influences on Adolescent Development

During the adolescent years, individuals spend substantial amounts of time in the peer context and simultaneously report greater susceptibility to peer influences than in earlier or later developmental periods. These changes in peer socialization make the peer group one of the most salient contexts for adolescent development. In most modern societies, adolescents spend more unsupervised time in the company of their peers than do younger children, and it is widely accepted that peers play an increasing role in the lives of adolescents as compared with younger children (Brown & Larson, 2009; Steinberg & Morris, 2001). As children grow older, they typically have more freedom of choice about whom they associate with. Adolescents may choose peers who reinforce their own beliefs, enable them to explore new roles, or engage in exciting activities. They also may be recruited by peers for similar reasons. Thus, peers have increasing potential as part of the regulatory systems available to adolescents. Adolescents may self-regulate by actively seeking peer interactions; peers also may deliberately act to cheer up, calm down, or recruit a friend for illicit activities.

Evidence suggests that adolescents actively select peer contexts that reflect their personalities or preferences and that peer groups in turn influence adolescents' mood states and behavior (Brechwald & Prinstein, 2011; Brown & Larson, 2009; Cairns & Cairns, 1994). Across adolescence, more popular teens tend to have higher levels of positive adaptation (i.e., greater prosocial behavior), but also have increased risk for problem behaviors, including aggression (Cillessen & Mayeux, 2004; Rose, Swenson, & Waller, 2004). With respect to psychopathology, antisocial behavior can lead to rejection by normative peers in middle childhood and also to affiliation with deviant peers, who subsequently encourage negative behaviors ranging from delinquent activities to health-risk behaviors (Dishion, Andrews, & Crosby, 1995; Dodge & Pettit, 2003; Laird, Pettit, Dodge, & Bates, 2005). Other children may withdraw from social interaction with peers due to shyness or anxiety and become more lonely and sad as a result (Rubin, Hymel, & Mills, 2006). It is interesting to note that anxious solitude may protect against antisocial behavior in adolescence, suggesting that this characteristic (likely reflecting high inhibition or social anxiety) may function as a risk factor for internalizing problems and a protective factor for externalizing problems (Burt, Obradović, Long, & Masten, 2008; Gazelle, 2010; A. S. Masten et al., 2005; Moffitt et al., 2002; Pine, Cohen, Cohen, & Brook, 2003). In general, individuals who fail to develop appropriate

peer relationships or who associate with peers with negative peer characteristics are at risk for a range of types of psychopathology.

One dimension of peer relationships that has received substantial attention in the past decade is popularity, and specifically perceived popularity, which refers to how much status an individual carries within the peer group (Cillessen & Rose, 2005). Some evidence suggests that perceived popularity is associated with the norms associated with risk taking behavior during adolescence. If, for instance, smoking marijuana becomes something that is valued by the peer group, popular adolescents will start getting high more regularly (Allen, Porter, McFarland, Marsh, & McElhaney, 2005). When popular adolescents start to engage in a particular behavior, that behavior often becomes more admired. Even behaviors such as bullying or carrying a weapon, which most adolescents do not approve of, become more acceptable when popular adolescents start to engage in them (Dijkstra, Lindenberg, & Veenstra, 2008; Dijkstra et al., 2010).

In contrast to popularity, being unpopular with peers is a risk factor for many forms of psychopathology. In general, research shows that unpopular, withdrawn children are excessively anxious and uncertain around other children, often hovering around the group without knowing how to break into a conversation or activity (Rubin, LeMare, & Lollis, 1990). Their hesitancy, low self-esteem, and lack of confidence make other children feel uncomfortable, and their submissiveness makes them easy targets for bullying (Olweus, 1993). Many of these youngsters are especially sensitive to being rejected, a trait that may have its origins in early experiences with parents (Downey, Lebolt, Rincón, & Freitas, 1998). Some youth are depressed, and their depression leads them to behave in ways that make them targets of harassment (generally speaking, people of all ages do not prefer to spend time with depressed individuals; Kochel, Ladd, & Rudolph, 2012). Unfortunately, the more these children are teased, rejected, and victimized, the more hesitant they feel around others, and the more they blame themselves for their victimization, which only compounds their problem—creating a cycle of victimization (Graham & Juvonen, 1998). Interestingly, children who are victimized but who have a best friend are less likely to be caught in this vicious cycle than those who are friendless (Hodges, Boivin, Vitaro, & Bukowski, 1999).

Although psychologists used to believe that aggressive adolescents are likely to be rejected by their classmates, it turns out that some teenagers are both aggressive and popular (de Bruyn, Cillessen, & Wissink, 2010). Evidently, it is not aggression alone, but the combination of aggression and difficulty controlling emotions or a lack of social skills, that leads to problems with peers (Dijkstra, Lindenberg, Verhulst, Ormel, & Veenstra, 2009; Farmer, Estell, Bishop, O'Neal, & Cairns, 2003). Interestingly, adolescents who see themselves as well-liked and socially competent fare well over time, regardless of whether they are genuinely popular among their classmates (McElhaney, Antonishak, & Allen, 2008).

Although relational aggression was first noticed in observations of girls, studies show that both genders employ it, but that girls are more aware of it, more distressed by it, and more often the victims of it (Card & Hodges, 2008; French & Conrad, 2001; Pronk & Zimmer-Gembeck, 2010; Sullivan, Farrell, & Kliewer, 2006). One study of adolescents' reasoning about excluding people from group activities found, for example, that girls are more likely than boys to say that it is morally wrong to exclude someone simply on the basis of the crowd to which he or she belongs (Horn, 2003). Although relational aggression is more covert than fighting or yelling, the use of relational aggression is nevertheless associated with rejection by peers (Crick, 1996; Rys & Bear, 1997). Interestingly, adolescents whose aggression is atypical for their gender (that is, girls who are highly physically aggressive and boys who are highly relationally aggressive) show more maladjustment than their peers whose aggression is more gender-stereotypic (Crick, 1997). As psychologist Amanda Rose has pointed out, however, preventing relational aggression is easier said than done (Rose et al., 2004). She has shown that adolescents who use relational aggression are more popular than their peers. In some ways, this is hardly surprising, because the whole *point* of using relational aggression is to maintain one's status and popularity, and because the same social skills that make one popular (e.g., learning how to read other people, adjusting one's behavior to maintain one's status) are useful when one is spreading rumors, gossiping, or trying to undermine someone else's reputation.

Much evidence suggests that rejection from peers incurs risk for psychopathology. Peer rejection and friendlessness are associated with subsequent depression, behavior problems, and academic difficulties (Bellmore, 2011; French & Conrad, 2001; Wentzel, 2009). But studies show that the specific consequences of peer rejection may differ for rejected youth who are aggressive versus those who are withdrawn. Aggressive individuals who are rejected are at risk for conduct problems and involvement in antisocial activity as adolescents, not just as a direct result of their rejection, but because the underlying causes of their

aggression (for instance, poor self-control) also contribute to later conduct problems (Laird et al., 2005; Rubin, Chen, McDougall, Bowker, & McKinnon, 1995). In contrast, withdrawn children who are rejected are likely to feel exceedingly lonely and are at risk for low self-esteem, depression, and diminished social competence—again, both as a result of being rejected and in part because the underlying causes of their timidity (for instance, high anxiety) also contribute to later emotional problems (Card & Hodges, 2008; Hoza, Molina, Bukowski, & Sippola, 1995; Pedersen, Vitaro, Barker, & Borge, 2007; Rubin et al., 1995). Rejection is especially likely to lead to depression in adolescents who place a lot of importance on their standing in the peer group and who believe that they, rather than the peers who reject them, are at fault (Prinstein & Aikins, 2004). Adolescents who are both aggressive and withdrawn are at the greatest risk of all (Rubin et al., 1990).

Peer–Family Joint Effects on Psychopathology

One of the advances in the study of peer and family contexts in recent years has come in the form of considering how each of these systems may influence the effects of the other. Parents vary significantly in the extent to which they attempt to manage their teenagers' peer relationships, and some evidence suggests that more active management is associated with more positive peer relationships (e.g., higher quality, less delinquency) (Mounts, 2002, 2004, 2007; Stattin & Kerr, 2000; Tilton-Weaver & Galambos, 2003). Poor parenting may elevate the risk for association with deviant peers; concomitantly, lack of monitoring may increase unstructured time with antisocial peers, facilitating deviancy training (Dekovic, Wissink, & Meijer, 2004; Dishion, McCord, & Poulin, 1999; Dishion, Nelson, & Bullock, 2004; Oxford, Harachi, Catalano, & Abbott, 2001; Werner & Silbereisen, 2003). Negative peer relations have been found to increase the influence of negative parenting on externalizing behavior (Lansford, Criss, Pettit, Dodge, & Bates, 2003). High quality attachment to parents is linked with better peer interactions and fewer emotional and behavioral problems (Allen, Porter, McFarland, McElhaney, & Marsh, 2007). On the positive side, close parent-adolescent relationships may enhance the likelihood of exposure to positive peer networks as well as the socioemotional skills to engage effectively with peers (Chester et al., 2007). Evidence also suggests that good-quality relationships with parents may moderate the influence of deviant friends (Galambos et al., 2003).

Romantic Relationships and Adolescent Development

One of the key psychosocial milestones of adolescence is the development of romantic relationships. Increasingly, researchers have begun to focus on the context of adolescents' burgeoning romantic relationships (Collins, Welsh, & Furman, 2009). Romantic relationships emerge in adolescence, though they may remain exploratory until early adulthood; this domain can be conceptualized as an emerging developmental task in adolescence and a salient developmental task of early adulthood (Collins et al., 2009; Roisman, Masten, Coatsworth, & Tellegen, 2004). These special peer relationships, spurred by new motivational systems, pubertal processes, and a culture promoting adolescent sexuality and romance, offer a new realm of possibilities for adolescents to experience emotional extremes of happiness, excitement, disappointment, and despair.

Romantic feelings appear to be powerful activators of behavior; concomitantly, romantic relationships appear to be powerful regulators of arousal and affect (Collins et al., 2009; Connolly & McIsaac, 2009; Furman, Brown, & Feiring, 1999; Larson, Clore, & Wood, 1999). We noted previously that early maturing is a risk factor for a variety of problems; for some girls, this risk appears to be mediated by romantic relationships with older boys (Steinberg & Morris, 2001). Breakups of romantic relationships also may trigger great distress in adolescents (Larson et al., 1999) and have been linked to subsequent emotional disorders such as depression (Hankin & Abramson, 2001). Much like the classic finding that associating with deviant peers is linked with antisocial behavior, dating a partner who is high in antisocial influence and behavior is associated with maintaining involvement in antisocial behavior across adolescence and into early adulthood (Cauffman, Farruggia, & Goldweber, 2008; Monahan, Dmitrieva, & Cauffman, 2014). Though still limited, the growing literature on romantic relationships in adolescence suggests that these relationships may play complex roles in social development and the regulation of affect, with positive and negative ramifications. In general, individuals who are more susceptible to romantic partner influence and those with more difficult or low-quality romantic relationships may be the most vulnerable to psychopathology, due to increased sensitivity to the social influence and increased risk for negative socialization.

Schools and Psychopathology in Adolescence

School contexts play a salient role in the lives of modern youth for many years and in multiple ways. The transition

to secondary schooling in adolescence presents new challenges and opportunities for learning, peer relationships, and extracurricular activities, with all the attendant complexities of cognitive, emotional, social, and cultural processes (Elmore, 2009). Transitions into junior high school and high school often are accompanied by normative changes in motivation, attendance, involvement, and achievement. Psychopathology has been linked to school failure and disengagement in various ways. For example, adolescents who are antisocial, anxious, or depressed may not go to school or perform well when in attendance; academic failure may increase the likelihood of dropping out, affiliating with deviant peers, or developing internalizing symptoms; or youth may be victimized at school (Masten et al., 2005; National Research Council and Institute of Medicine, 2009). Perhaps the most striking conclusion to be drawn from studies of competence in the school context and either externalizing or internalizing symptoms in adolescence is the *salience* of academic success or failure to an adolescent as a mediator, outcome, and predictor of adolescent symptoms and disorders (Burt et al., 2008; Burt & Roisman, 2010; Hawkins, Kosterman, Catalano, Hill, & Abbott, 2005; Hawkins et al., 2003; A. S. Masten, 2003).

Interventions to promote positive bonding to school and academic achievement have shown success, increasing academic attainment and reducing dropout and delinquency. The mediating processes by which these interventions work are not well understood, though increasingly, interventions are designed strategically to shed some light on the mediating processes. Hawkins and colleagues (Hawkins et al., 2003), in the Seattle Social Development Project, have shown that multifaceted elementary school interventions increase positive bonding to school in the high school years, which is associated with school success and lower risk for multiple problems. Moreover, the positive effects of this intervention for youth outcomes are documented into adulthood (Hawkins et al., 2005), suggesting that earlier intervention may engender long-term benefits. A study of mentoring as an intervention suggested that the Big Brother Big Sister program improves relationships with parents along with school involvement and achievement (Rhodes, Grossman, & Resch, 2000). Mentoring may have some direct influences on school values and behavior, but these interventions also may provide indirect benefits in the lives of adolescents that are mediated by parent-adolescent relationships.

Recent attention also has focused on the role of extracurricular activities in adolescent development (Mahoney & Vest, 2012). Such activities may provide opportunities for personal ups and downs in accomplishments, but also may serve the more mundane but important function of bonding youth to the normative school context, peers, and behaviors, with important socialization sequelae. Little is known about the general regulatory role sports and other activities may play in the healthy development of adolescents, although studies of the joys and stresses of sport involvement suggest intense possibilities for affect regulation, for good or ill (Gatz & Messner, 2002; R. E. Smith, Smoll, & Cumming, 2009). For example, engagement in sports provides many youth with social bonds, goals, and exercise; however, participation in sports can also introduce opportunities for underage drinking or other risky behaviors. Structured activities of diverse kinds could play a powerful regulatory role in stress management and arousal regulation, may help adolescents acquire self-control and related regulatory competencies, and may serve to facilitate relationships with peers and coaches who can also play such regulatory roles. Moreover, these activities may provide a positive outlet for increases in sensation seeking that are noted during adolescence.

Work as a Context for Adolescent Development

During adolescence, individuals typically begin their foray into the world of employment. The impact of work on adolescent development and psychopathology has received increased attention, particularly with respect to the relative risks and benefits of work (Monahan, Lee, & Steinberg, 2011; Mortimer, 2003; Mortimer, Staff, & Oesterle, 2003; Roisman et al., 2004). In terms of psychopathology or positive adaptation, work may exacerbate stress and distress or increase self-efficacy, take time from schoolwork or motivate youth to succeed in school. Generally, moderate work hours in the lives of ordinary adolescents who are succeeding in other aspects of their lives appear to have at least short-term benefits (e.g., extra money and self-confidence) and few costs. For some youth, steady low-intensity work during adolescence may also have long-term benefits in vocational development (Mortimer, 2003). However, working long hours at unskilled jobs may contribute to symptoms of psychopathology, either directly (stress) or indirectly, by contributing to school problems, psychosocial development, and increased behavioral problems (Monahan et al., 2011). Indeed, even in high-risk samples—whom work is suspected to benefit—long hours employed during adolescence is a risk for antisocial behavior *unless* youth are also engaged in school (Monahan, Steinberg, & Cauffman, 2013).

The extent to which work may contribute to regulatory competence likely depends on the nature of the work environment, the number of hours per week the adolescent works, and the extent to which working facilitates or interferes with the successful negotiation of other tasks, such as those affecting achievement in school (Roisman et al., 2004). In an appropriately challenging job with adequate supervision, where the adolescent is acquiring skills and not unduly stressed by demanding work hours, employment may contribute to the development of responsibility, time management skills, and self-confidence. However, in a menial job with inadequate supervision, where work is stressful and hours long, employment may contribute to mental health problems, alcohol and drug use, and diminished attachment to school (Monahan et al., 2011; Monahan et al., 2013; Staff, Messersmith, & Schulenberg, 2009). These adolescents in menial, stressful jobs working at a high intensity of hours are likely at risk for psychopathology.

Community, Society, and Culture

One of the marked changes characteristic of adolescence in many modern societies is the increased level of mobility in society and the potential for engaging and being engaged by more aspects of community, culture, and society outside the family and school contexts. Evidence suggests that neighborhoods are potent sources of risks, assets, and moderators of adolescent development (Duncan & Raudenbush, 2001; Leventhal et al., 2009). There are hints in this literature that social structures in neighborhoods may function as regulatory systems for the behavior of youth, although it is difficult methodologically to sort out the role of larger social systems from the influence of the individuals and families that compose them (Duncan & Raudenbush, 2001). Studies of resilience in youth at risk due to family adversity or poverty suggest that external regulatory systems in communities (e.g., provided by churches, boys' and girls' clubs, recreational centers and teams) may play a protective role for the development of competence (Masten & Coatsworth, 1998). Who chooses to engage such systems and why remains an intriguing mystery. Coaches and youth ministers may seek out youth, youth may seek out competent and trustworthy adults, or juvenile systems may assign youth to some of these connections. Yet, for these external systems to work, adolescents must participate, and it seems likely that the bonding of youth to positive community systems is scaffolded through the relationships they form with mentors and other program participants.

Community based efforts at prevention have received increasing attention in recent years. The Community Youth Development Project addresses individual risk and protective factors at a community level, allowing communities to pick and choose from a menu of tested and effective individual- and school-based programs. The result is a community-specific approach to prevention that serves the needs of the youth in a given community. Evidence suggests that these approaches to prevention hold promise for reducing youth externalizing behaviors during the adolescent years (Hawkins, Oesterle, Brown, & Arthur, 2009; Hawkins et al., 2012).

Macrosystem influences on the regulation of adolescent risk behavior and, accordingly, vulnerability to certain forms of psychopathology, also have been studied. Examples include studies of cigarette tax policy on adolescent tobacco use (Chaloupka, Cummings, Morley, & Horan, 2002), the impact of gun-control policies on access to weapons (Elliott, Hamburg, & Williams, 1998), the effects of condom distribution in school-based health (Blake et al., 2003), and the impact of graduated driver's licensing policies on automobile accidents (Ulmer, Ferguson, Williams, & Preusser, 2001). Although these policies are rarely thought of as interventions designed to prevent or reduce psychopathology, they can be viewed as attempts to impose external regulation on individuals whose judgment and regulatory competence is not yet fully mature. One interesting but unstudied question is the relative effectiveness of policies designed to impose regulatory control on adolescents as a means of limiting risk behavior versus those designed to limit risk behavior by increasing adolescents' regulatory competence (e.g., through educational intervention).

Media and Virtual Contexts

Whereas many of the traditional contexts of adolescence development—involving family, peers, school, neighborhoods, and work—readily fit an embedded systems model of development, as proposed by Bronfenbrenner (1979) and others, other elements of context in adolescents' lives do not fit so neatly. Yet, these experiences may play an enormous and growing role in adolescent development. In particular, music, movies, and television, as well as the new virtual worlds of electronic games, web sites, and social media, saturate the lives of many adolescents many hours a day, penetrating most other contexts of interaction. The media diet (Brown & Bobkowski, 2011; J. D. Brown & Witherspoon, 2002) of American teenagers reflects a rapidly changing and increasingly

individualized context for learning, self-regulation, victimization, friendship formation, sex, violence, illegal activity, and self-discovery, among other processes. Teenagers clearly utilize music, phones, movies, games, chat rooms, instant messaging, email, and other electronic media to meet all kinds of needs. Increasingly, these media can be tailored to individual desires, so that adolescents can fine-tune their own experiences. Concomitantly, the same strategies can be utilized by marketers to recruit teenagers as consumers, often with the promise of happiness or sex appeal through consumption of food or drugs or the purchase of goods and services. The role of these transactions in the development or avoidance of psychopathology, misery, antisocial behavior, or risk-taking behavior is only beginning to be considered, as concern grows about the unmonitored interactions of adolescents through these media on violence, depression, self-injurious behavior, substance use, and many other problems or risky behaviors (Brown & Bobkowski, 2011). While exposure to types of media may not change per se from childhood to adolescence, it is the case that adolescents have more autonomy when selecting media exposure than previous developmental periods.

With the rise in exposure to various forms of technology during adolescence, the past decade has seen an increase in studies of how technology, such as Facebook, video games, or cyberbullying are associated with psychopathology. Although the study of these issues is nascent, in general, there is weak evidence of an association between exposure to these forms of media and psychopathology. Studies of Facebook have generally suggested that social media use can influence mood, with positive feedback boosting self-esteem and negative comments causing increase in negative mooed (Valkenburg, Peter, & Schouten, 2006). The increased feelings of social connectedness and inclusion that Facebook leads to may actually promote better adaptation in individuals, especially when they feel isolated from people in the real world (Sheldon, 2008). Increased social evaluation that has come about in part because of increased exposure to social media has raised general public concerns about cyberbullying. Yet cyberbullying appears to be less prevalent than media reports would suggest. For example, in a study of two large longitudinal samples of adolescents, one from the United States and one from Norway, Olweus (2012) documented that cyberbullying is a low-prevalence phenomenon. However, the negative effects of the cyberbullying have not received much attention from the research community. Greater investigation of the effects of media usage on psychopathology is needed.

New Approaches to Context in Relation to Adolescent Psychopathology: A Call for Future Research

Over the past 30 years, there has been a rapid expansion of research and theory on the significance of context-adolescent interactions for adolescent development and psychopathology. Work, romantic relationships, and media have gained more attention, as have the moderating and mediating roles of one context in regard to another. A profound change has occurred in the conceptualization of context in relation to adolescent development. Relationships, media, drugs, food, and activities, for example, are viewed as ways for adolescents to develop and exercise regulatory competence and to modulate levels of negative affect. Our point is that entry into adolescence is marked by changes in these types of contextual experiences: some new contextual experiences emerge, as is the case with work and romantic relationships, and others lead to increases in adolescent autonomy and control, such as provided by media. Moreover, the extent to which adolescents may be more or less sensitive to these contextual influences on affect developmental and regulation, and how in turn these contexts may stimulate different development of affective and motivational processes, remains unknown.

Concerns about deviant outcomes from adolescents' experiences in the contexts they come into contact with because such experiences have increased, perhaps in part as a function of the decreasing control of adults over these adolescents' time. Major concerns include social contagion of maladaptive behaviors, such as violence, self-injury, depression, or suicide. On the other hand, emerging contexts for adolescent development, such as virtual friends and support networks, could conceivably offer just as many positive as negative opportunities (Brown & Bobkowski, 2011; Brown & Witherspoon, 2002). The extensive and expanding contexts available to adolescents may be challenging and overwhelming or supportive and protective. As adolescents, who might be viewed as novice adults, negotiate the many changes of adolescence and the transition to self-regulated behavior, they may call on people in the various contexts of their lives for help. At the same time, adults, especially parents, may deliberately scaffold this long-term transition to adulthood through provision of adequate structure, support, and opportunities to facilitate success. If disparate developmental timing occurs in the functional maturity of affective, sexual, cognitive, and social systems utilized by adolescents to adapt, resources in the external context, in relationships, and in formal and informal institutions may provide compensatory or

protective effects that temporarily close the functional gaps in emotional and cognitive maturity with and across individuals. Conceptualizing the role of context in this way may offer important perspectives for interventions to prevent and ameliorate behavioral and emotional problems in adolescence, particularly when coupled with the study of the biological and cognitive changes that mark this developmental period.

CONCLUDING COMMENTS AND FUTURE DIRECTIONS

The framework we have advanced in this chapter articulates psychopathology during adolescence that is grounded in the understanding that the biological, cognitive, and contextual transitions of adolescence are dynamic, dramatic, and potentially determinative of psychopathology. In the past 10 years we have seen an explosion of research on the neurobiological changes of adolescence, and the framework we propose for the development of psychopathology is grounded in the notion that these neurobiological changes affect, and are affected by, the adolescent's social-contextual world.

We begin from the premise that adolescence is characterized by an increased need to regulate affect and behavior in accordance with long-term goals and consequences, often at a distance from the adults who provided regulatory structure and guidance during childhood. From this vantage point, adolescence is a time of especially heightened vulnerability to psychopathology specifically as a result of disjunctions between and among developing brain, behavioral, and cognitive systems that mature along different timetables and under the control of both common and independent biological processes. These disjunctions, in turn, create gaps between affect, thinking, and action. Viewed from this perspective, symptoms of various types of psychopathology in adolescence can be profitably understood as reflecting difficulties in the coordination of emotional, intellectual, and behavioral proclivities, capacities, and capabilities. By all indications, adolescence may well be a sensitive or critical developmental period for both normative and maladaptive patterns of development through the shaping of future trajectories and in the biological embedding of developmental experiences as the principal method through which this occurs.

Although adolescence is a time of increased vulnerability to psychological dysfunction, the fact remains that only a minority of adolescents develop psychopathology. To be useful, then, any framework that purports to aid in our understanding of psychopathology in adolescence must account not only for the heightened vulnerability that is characteristic of the period in general, but also for the wide variability between individuals in whether and to what extent this vulnerability is ever actualized. Virtually all adolescents will experience the sorts of disjunctions between affect, cognition, and behavior to which we have alluded, but most individuals will weather these difficulties and move into adulthood having experienced no or few serious difficulties.

In our view, individual differences in emotional and behavioral dysfunction during this period exist among adolescents in the nature and extent of these dysfunctions and in the availability of contextual support and the presence of contextual risk during times of heightened neurobiological vulnerability. Research on early maturing girls is a case in point. As we have noted, early maturing girls are, on average, at greater risk for the development of emotional and behavioral problems than their on-time or late-maturing peers. This is likely because earlier pubertal maturation brings with it changes in arousal that precede, by a fairly long stretch of time, the development of the regulatory competence necessary to modulate these drives; this is the sort of disjunction between arousal and regulatory competence that heightens vulnerability to problems. Moreover, the physical changes that accompany puberty also elicit new interactions with context (e.g., attracting attention from older peers and unwelcome advances from adult strangers) that may be difficult for a young girl to handle. Yet, most early maturing girls do not develop psychopathology. This is because early puberty is a risk factor for psychopathology among adolescent girls only under conditions of specific contextual risk: in families that expose the adolescent to stressful life events, in schools in which older boys are present, in communities in which students are especially body conscious, and in cultures that place a premium on thinness (Steinberg, 2011).

The past decade has seen considerable progress in our understanding of the most important sources of contextual risk and support. We now have a very good sense of what adolescents need in the family, school, peer, and neighborhood contexts to maximize positive youth development and minimize emotional and behavioral problems. There is an especially rich literature on familial risk and protective factors and, to a lesser extent, on the influence of peer, school, and work settings and media. Overall, the study of environmental influence on psychopathology in adolescence has yielded a solid basis for the development of preventive interventions and treatments, but research has focused largely on the influence of family and friends,

and much work remains to be done on understudied contextual influences, such as those of romantic partners, neighborhoods, and electronic media. This is particularly challenging in the changing landscape of society and culture, both of which dictate youth exposure to these various contexts.

There is no doubt that today we are on the cusp of a biological revolution in the study of normative and atypical adolescent development—a revolution made possible by tremendous advances in the study of molecular genetics, endocrinology, neurotransmission, and brain structure and function. These advances will enable the field to move beyond sweeping generalizations about the significance of puberty, or of changes in certain brain regions in the development of psychopathology in adolescence, and to begin to identify the specific characteristics and indices of pubertal maturation and brain development that are linked to specific forms of psychological malady. This will require a careful unpacking of puberty as a multifaceted phenomenon that involves endocrinological, neuroendocrinological, somatic, and social processes, and an equally careful unpacking of brain development in adolescence that links maturational change within and across specific systems to changes in behavior, cognition, and affect. Recent breakthroughs in neuroscience generate considerable enthusiasm for expanding knowledge on the mechanisms behind adolescent changes in behavior associated with successful or unsuccessful transitions in development.

For the field to advance in its understanding of how context and biology shape the emergence of psychopathology during adolescence, it is necessary for scholars to engage in collaboration with others trained in different disciplines. Although calls for interdisciplinary work are undoubtedly clichéd, there is no better way to begin to understand the interplay between biology, cognition, and context. At the nexus of these interdisciplinary efforts will be key information for translation of findings to prevention and intervention science. Indeed, beyond building interdisciplinary collaborations, it is our hope that this chapter spurs scientists to engage in translational efforts, moving science into prevention and intervention practice. Despite its obvious importance, the biological revolution that is currently unfolding in the study of adolescence will not suffice in the search for a complete understanding of the development, prevention, and treatment of psychopathology during this stage of life. Biological vulnerabilities may set the stage for psychopathology, but they by no means determine its course. Nor will the answer to questions about the onset, nature, and course of psychopathology be found in the study of context alone. We have noted numerous times in this chapter that the sources of contextual risk and protection in adolescence are nonspecific, interactive, and cumulative. Ultimately, we believe that the dramatic changes of adolescence are a paradox, in that adolescence is a developmental period with a heightened risk for psychopathology, but it is also a time of plasticity and has a potential to be a final developmental period for the successful implementation of prevention and intervention efforts.

Future progress in the developmental psychopathology of adolescence demands an integration of research on biology, cognition, and context. This will require cross-training and collaboration of scientists who specialize in neuroscience, behavioral development, and influential contextual systems, including families, peers, communities, media, policy, and multiple aspects of culture. Finally, it will also require a generation of scientists who are active in prevention science. In this chapter, we have offered a framework that we hope will launch many such efforts.

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CHAPTER 20

Developmental Social Neuroscience

JEAN DECETY and JASON M. COWELL

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Social neuroscience is an examination of the associations and influences between social and biological levels of organization, particularly of the underlying neural, hormonal, cellular, and genetic mechanisms of interpersonal behaviors and cognitions. Traditionally, the development of the nervous system has been studied in isolation, ignoring the influences of the social environments in which humans and nonhuman animals live and grow. Yet, humans are a social species, and as such organizational structures naturally emerge, ranging from individual dyads to families, groups, and cultures (Cacioppo & Berntson, 1992). Like other social species, humans cannot survive and reproduce without others. Even our day-to-day existence is governed by direct and indirect contact with others. Consider the case of a solitary walk: we almost always bring others with us and virtually all of our actions are directed toward or are responses to others (Batson, 1990). Human social organizations, civilizations, cultures, and institutions are extensively developed, particularly in comparison to other species on the planet. These emergent structures have evolved hand in hand with neural and hormonal mechanisms to support them, as their consequent social behaviors helped these organisms survive, reproduce, and care for offspring sufficiently long that they too survived to reproduce (Cacioppo & Decety, 2011a).

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Changes in the environment are thought to feed into individual biology, and their effects may travel into the storehouse of genes (Gottlieb, 1998; Gazzaniga, 2008) and there is growing evidence that social context (including cultures) fundamentally impacts living organisms at various levels across species, including their genetic expression (Rogers, 2014). For instance, physiological differences between mature queens of the two social forms (monogynous or polygynous) of the fire ant *Solenopsis invicta* are due largely to differences in the social (pheromonal) environment of the colonies in which the adults mature, rather than being due to intrinsic genetic differences between the forms (Keller & Ross, 1993). In primates (including humans), there is a relationship between social group size and the volume of the neocortex (Byrne & Bates, 2007; Dunbar, 2014). Thus the social brain must be studied in the context of the environment in which it develops and thrives. A diverse variety of organisms, from simple to complex, share many common behaviors including courtship and mating, aggression, and parenting. Indeed, many of the social behaviors exhibited by simple animals harken to social behaviors in complex animals, and their underlying neurobiological mechanisms—from cellular to neural networks—are highly conserved across species (Sokolowski, 2010).

The social environments humans have created shape our genes, genetic expression, brains, and bodies. While humans uniquely impact the environment and vice versa, much of the biological heritage is shared with other species.

For that reason, translational animal models testing specific aspects of human functioning and investigations of our evolutionary lineage are extremely valuable. Even though humans are what we are ultimately interested in, we share a lot of genes with other animals, even with simple organisms such as *C. elegans*. In order to understand how biological systems implement social behavior, it is imperative to investigate how the molecular and cellular mechanisms underpinning social interaction have evolved across species, using translation animal models. While research across multiple domains has helped to elucidate many of the complexities of the developing social brain, much remains to be explored about how the social and cultural environment influences genetic, hormonal, neural, and behavioral development (Ebstein, Israel, Chew, Zhong, & Knafo, 2010).

This chapter begins with a focus on the promises and challenges of developmental social neuroscience. Next, three specific illustrations of research in developmental social neuroscience are discussed: moral cognition, theory of mind, and empathy. These programs are led by interdisciplinary efforts, within multiple domains (social, cognitive, and neural), using multiple methods (EEG/ERP, fMRI, MRI, eye-tracking, hormonal measures, psychophysiological methods), and across multiple levels of analysis (behavioral, functional, neural, genetic). These examples highlight the utility of a multiple-level, contextually informed approach to the understanding of both normative and abnormal development. Finally, we discuss attempts to translate evidence from social neuroscience into research and policy regarding specific developmental psychopathologies.

SHAPING THE DEVELOPING BRAIN

The brain is not a static object that is the same from birth through adulthood. Rather, it is dynamic, plastic for much of development, experiencing periods of growth and pruning long after an infant has left the womb. For example, children's prefrontal cortex (PFC) is functional by age 4, yet it undergoes extensive fine-tuning and specialization over childhood and adolescence (Tsujimoto, 2008). This dynamic development is further evidenced by the longitudinal studies indicating peak cortical density in the PFC around age 8, followed by rapid pruning of neural pathways (Giedd et al., 1999). Many networks become increasingly integrated through myelination of pathways over development and maturation continues to late adolescence. Social experience is thought to be a primary driving factor enhancing certain networks (the ones often recruited together) and allowing others (less recruited) to be pruned for neural efficiency. To this point, both increases in functional connectivity and decreases in other networks have been documented across development (Stevens, 2009).

Early adversity in rodents' caregiving relationships impacts amygdala–medial prefrontal cortex (mPFC) circuits that in adulthood serve to regulate the activity of the amygdala circuits (Quirk et al., 2003). Analogously, in humans, previously institutionalized children, who experienced early maternal deprivation, also exhibit atypical amygdala–mPFC connectivity characterized by adolescent-like maturation of the connectivity (negative amygdala–mPFC coupling) (Gee et al., 2014). This connectivity is mediated by cortisol levels (collected immediately before and after MRI scanning), suggesting that stress-induced modifications of the hypothalamic–pituitary–adrenal axis impact the development of the amygdala–mPFC circuitry. Another example of this can be seen in the development of emotion processing. Children, as well as adults, will usually engage a large network of neural circuits, including the ventromedial prefrontal cortex, the amygdala, and visual cortices when emotional information is presented. This fine-tuned network, pruned through early experience, allows for the simultaneous perception, experience, and regulation of an emotion (e.g., Wismer Fries & Pollak, 2007). In studies of early deprivation, where children have not received extensive social input in infancy and early childhood (e.g., post-institutionalization), children's behavioral emotion processing appears limited and the structure and function of neural structures in this network are modulated (Pollak et al., 2010). What is clear from nearly two decades of research in developmental psychology, developmental social neuroscience, and behavioral neuroscience, is that environment and experience bi-directionally influence both structural and functional brain development.

MULTIPLE LEVELS OF INFORMATION

Since the mid-twentieth century, theorists in cognitive science, psychology, and neuroscience have argued for the integration of multiple levels of information in the study of any behavior. Forging an analogy with the computer, Marr (1982) introduced the notion of computational, algorithmic, and implementational levels of analysis. Marr's levels and corresponding emphasis on the computational and algorithmic levels were born out of the early movements of artificial intelligence, cognitive psychology, and cognitive

science, which were based on the idea that one could ignore the underlying biological mechanisms of cognition, focusing instead on identifying important computational or cognitive level properties. Indeed, these traditional approaches assumed that the brain works like a standard computer, and that Marr's computational and algorithmic levels were much more important than the mere details of the underlying neurobiological implementation (O'Reilly & Munakata, 2000). Naturally, few scholars in social and affective neuroscience today would agree with Marr's view that the implementational level is largely irrelevant. On the contrary, there is mounting evidence that the cellular level (e.g., genetic polymorphisms) has an impact in brain-behavior relationships, and the brain cannot be seen as a computer (Decety & Cacioppo, 2011).

Social neuroscience is an incorporation of information from multiple levels of analysis towards an understanding of behavior, similar to the developmental psychopathology approach (Cicchetti & Valentino, 2007; Gottlieb, 1998). Human behavior can be parsed into levels of organization, ranging from the atomic to the societal (Bronfenbrenner, 1995). Often what guides a level of organization, at least at the lower scales of representation, is knowledge of genetics, anatomy, and physiology, but the ultimate criterion is the usefulness of the organization in shedding light on some type of behavioral outcome. Social neuroscience, as a theoretical approach, describes a complementary relationship between the different levels of organization, spanning the social and biological domains (e.g. molecular, cellular, system, person, relational, collective, societal) and advocates for the use of multilevel analyses to explore the mechanisms underlying the human mind and behavior without needing to specify each individual action by its simplest components (Cacioppo, Berntson, Sheridan, & McClintock, 2000). It can help us understand developing brain function and, in turn, can be informed and refined through integration with theories and methods from social and behavioral sciences. Generative theories lead to hypotheses about the manifestation of behavior across multiple levels of organization, and provide a platform for conducting empirical tests, which can be used to support, reject, or refine these theories (Gergen, 1985).

THE COMPLEX INTEGRATION FROM MULTIPLE LEVELS OF ANALYSIS

As a social species, our behavioral and psychological functions can be best interpreted as the confluence of information processing from multiple levels: social, behavioral, neural, and genetic. This is the heart of social neuroscience and facilitates the focusing of intellectual energy and the unification of scholarly activity across levels of organization to produce more comprehensive accounts of the human brain, mind, and behavior (Cacioppo & Decety, 2011b). The study of developmental social neuroscience necessitates a large amount of information from multiple levels of analysis, using multiple methods, and from multiple informants, thus a more comprehensive account of a phenomenon can be forwarded. However, the challenge lies in creating the inclusive account, assimilating information from so many sources and levels. In incorporating evidence in developmental social neuroscience, three principles are key: multiple, nonadditive, and reciprocal determinism.

1. A target behavior at one level of organization can have multiple antecedents within or across levels of organization (multiple determinism; akin to equifinality; Cicchetti & Rogosch, 1996). On the biological level, for instance, scientists might identify the contribution of individual differences in the endogenous opioid receptor system in drug use, whereas on the social level investigators have noted the important role of social context. Both are important and inform our more complete understanding of the same outcome, drug abuse (Dalley et al., 2007). Similarly, immune functions were once considered to reflect specific and nonspecific physiological responses to pathogens or tissue damage. It is now clear that immune responses are also influenced by central nervous processes that, in turn, are affected by social interactions (Hawkley, Bosch, Engeland, Marucha, & Cacioppo, 2007). Human immunocompetence can thus be considered the consequent of either, or both, and any theoretical conception of it would be inadequate in the absence of considerations of social and behavioral factors. Theories of behavior will require information on comprehension of factors from multiple levels of analysis. Accordingly, advances in the neurosciences and the social sciences may occur by increasing the scope of analysis to include the contributions of factors and processes from both social and neuroscientific perspectives. Yet with additional levels of analysis, integrating and mapping becomes more complex (e.g., many to many). The likelihood of overly complex and potentially obscure mappings increases as one skips levels of analysis. This is perhaps one reason that going from the genotype to endophenotype and from endophenotype to phenotype has proven to be more fruitful than going directly from the genotype to phenotype (Bell, Richerson, & McElreath, 2009).
2. Properties of the whole are not always the simple sum of the properties of the parts (nonadditive determinism). Consider an illustrative study of the effects of

amphetamine on primate behavior (Haber & Barchas, 1984). The behavior of nonhuman primates was examined following the administration of amphetamine or placebo. No clear pattern emerged between the drug and placebo conditions until each primate's position in the social hierarchy was considered. When this social factor was taken into account, amphetamine was found to increase dominant behavior in primates high in the social hierarchy and to increase submissive behavior in primates low in the social hierarchy. The importance of this study derives from its demonstration of how the orderly mapping between the biological and social levels of organization would remain opaque until knowledge of the modulatory social status of the primates is included. A strictly physiological or social analysis, regardless of the sophistication of the measurement technology, would not have revealed the orderly relationship that actually existed.

3. Biological and social factors can be mutually influential in producing behavior and often bi-directionally interact with each other in such production (reciprocal determinism). To illustrate this point, consider that not only has the level of testosterone in nonhuman male primates been shown to promote sexual behavior, but the availability of receptive females influences the level of testosterone in nonhuman primates (Bernstein, Gordon, & Rose, 1983). This principle, too, implies that comprehensive accounts of behavior cannot be achieved if the biological or the social level of organization is considered unnecessary or irrelevant.

Overall, social neuroscience is characterized by its multilevel, integrative analyses across species. The conceptual questions in social neuroscience have captured the imagination of a talented, new generation of scientists. To address many of the big questions in the field requires larger and more interdisciplinary teams than were common in the prior century, however, and this is certainly the case in social neuroscience and developmental psychopathology as well.

METHODS IN SOCIAL NEUROSCIENCE

In social neuroscience, multiple methods at each level of analysis provide a more complete understanding of a behavior. These levels include behavioral, molecular, neurophysiological, social, and environmental. Common behavioral-level assessment methods include self-questionnaires, computerized experimental tasks, paper-and-pencil surveys and paradigms, as well as desktop games, quite common in developmental studies. Similarly, the children's behavioral characteristics and social interaction abilities are often measured using surveys of parents and teachers (multiple informants are crucial for providing a full picture of the environment, as well as the child's daily behaviors), as well as observation in various social interactions. Measuring the social and environmental levels varies greatly based on the nature of the subjects. As nonhuman research plays a critical role in social neuroscience, many researchers can systematically control both the social and general environment. In humans, strategic control of the social environment is limited and as such, measurement is based heavily on self, parent, and teacher reports.

The use of behavioral and molecular genetic methods has become common in social neuroscience. Many methods are used in the study of genetics in humans and nonhumans. Some of the earliest methods used in humans were twin, family, and adoption studies. These investigations were based on the knowledge that identical twins share (on average) all of their genes, whereas fraternal twins or siblings share half, allowing for heritability estimation. Other human genetic approaches include: linkage analyses (studying the transmission of particular genes in families with respect to other genes), candidate gene (tracking the association of particular behavioral characteristics of groups with varying alleles of a gene), and recently, DNA/ genomic sequencing (for a review of behavioral and molecular methods with humans, see Wilcutt et al., 2011). Human studies provide valuable information regarding genetic level differences, however. Due to ethical and feasibility constraints, studies using genetic methods in humans are limited to correlations and observations. In contrast, nonhuman animal studies provide the ideal venue for researching genetic contributions to behavior. Commonly used genetic methods in animal research include: transgenic or knockout methods (inserting a foreign gene or deleting a specifically targeted gene in a new strain of animals), phenotypic selection studies (selecting for animals that display extreme high or low phenotypes and selectively breeding them over successive generations), and inbred strain methods (animals who are the offspring of generations of siblings).

In addition to behavioral, social, environmental, and genetic research, several different methodologies within the neural level of analysis will be discussed. In developmental neuroscience, the most common methods utilized are electroencephalography (EEG), event-related potentials (ERPs), structural magnetic resonance image (MRI), functional magnetic resonance imaging (fMRI), functional near infrared spectography (fNIRS), pupillometry, and

TABLE 20.1 Techniques for Studying the Developing Brain in Humans

Technique	Description
Postmortem analysis	Brains are retrieved and processed after death to allow analysis of macroscopic and microscopic features of brain tissue.
Structural MRI	Noninvasive method that provides high spatial resolution (1 mm) images of the living brain and features of brain tissue.
Diffusion Tensor Imaging	Relies on the detection of microscopic movement of water within brain tissue to allow visualization of white matter and effective connectivity.
Functional MRI	Measures changes in blood oxygenation. Provides good spatial resolution but more limited temporal resolution.
Electroencephalography	Measures the electrical activity of the brain via electrodes placed on the scalp. Provides excellent temporal resolution, but limited spatial resolution.
Event-related potentials	Refers to averaged EEG responses that are time-locked to more complex processing of stimuli.
Near-infrared spectroscopy	Measures blood oxygenation. Limited currently to cortical regions.

eye tracking. Many developmental scientists have also integrated measures of autonomic arousal, such as heart rate variability (EKG) and skin conductance (GSR).

Each method can provide interesting and useful information, but all have drawbacks. A brief description of each method can be found in Table 20.1. For an extensive review of developmental neuroimaging methods see de Haan & Gunnar (2009).

Moral Cognition

The past decade has seen an explosion of empirical research in the study of morality. Among the most exciting and novel findings and theories, evolutionary biologists and comparative psychologists have shown that moral cognition has evolved to facilitate cooperation and smooth social interactions, and that certain components of morality are present in nonhuman animals (Decety & Howard, 2013). Moreover, the precursors to complex morality have been demonstrated much earlier in development than originally thought, and are clearly in place before children turn 2 (Hamlin, 2014). In several studies, infants as young as 6 months of age appear to be sensitive to an agent that helps another versus hinders another (Hamlin, Wynn, & Bloom, 2007). Additionally, infants as young as 12–15 months of age look longer at unequal distributions of resources (Schmidt & Sommerville, 2011; Sloane, Baillargeon, & Premack, 2012). Around 14–18-month-old infants exhibit spontaneous, unrewarded instrumental helping behaviors (Warneken & Tomasello, 2009). These early attention differences to fair versus unfair distributions have consequences in the behavior of infants and toddlers as well. Those who looked longer at an unequal distribution of resources were also the first to offer a preferred toy to another individual (compared with an unattractive toy; Schmidt & Sommerville, 2011).

Behavioral investigations of moral development in the last decade have been dominated by infant and toddler research; however, there is a rich history of studying moral development in later childhood and adolescence (Kohlberg, 1976; Turiel, 1998). For decades, children's moral knowledge and judgment have been documented and segregated into stage-type progressions. Behavioral level analyses of moral development across all ages of childhood have led to several prominent conceptions in the field, primarily the early onset of rudimentary moral sensitivities, the discrepancy between early sensitivity and later integration the activity into verbalized moral knowledge and subsequent moral behavior, and the importance of social context in morality, namely, situational constraints to moral judgment as well as domain-general mechanisms that may underlie moral thought and action (Blasi, 1980; Hoffman, 1977). To tease apart many of these conceptions, information about neural structure and function is useful.

Social neuroscientists have begun to map brain circuits implicated in moral decision making and identify the contribution of neuropeptides to moral sensitivity (Young & Dungan, 2012). Much of current social neuroscience research on morality with adults uses a classic philosophical thought experiment. Participants are provided with hypothetical moral dilemmas and asked to determine the morality of the agent in the story's actions. For example, in several studies, the trolley dilemma was used as a tool for differentiating emotionality and reasoning (Foot, 1967; Thomson, 1976). In the trolley dilemma, a trolley is bounding down a train track toward a group of individuals. The individuals are tied to the track and cannot escape. The study participants are asked: should they divert the trolley to a track where there are only two people tied down as opposed to six (i.e. should they kill two to save the six)? This is compared with a situation where the individual is asked if they should push a large man off a bridge in front of the trolley, saving the six but killing the one. In the first, the decision is impersonal, whereas the second involves a personal level of violation. In one functional MRI study, participants responding to personal moral dilemmas, compared with impersonal and nonmoral dilemmas,

produced increased activity in regions associated with social-emotional processing, including the medial frontal gyrus, posterior cingulate gyrus, and bilateral STS (Greene et al., 2001). By contrast, impersonal and nonmoral dilemmas compared with personal dilemmas produced increased activity in areas associated with working memory: dorsolateral prefrontal and parietal areas. Another study used similar moral dilemmas to look at the role of intentionality in moral decision making (Young & Saxe, 2008). Participants had greater activation in the posterior STS (also called the temporal-parietal junction [TPJ]) as well as the anterior cingulate cortex (ACC), when judging the intentionality of an individual in a moral dilemma (i.e., one person purposefully poisoning another compared with one person accidentally poisoning another). Our current knowledge of the neural bases of moral judgment also relies on lesion studies (e.g., Gleichgerrcht, Torralva, Roca, Pose, & Manes, 2011). Patients with vmPFC damage exhibit increased utilitarian judgments (Koenigs et al., 2007), which support the crucial role of this region in judgments and knowledge of right and wrong. In recent studies, patients with developmental-onset lesions to the vmPFC, unlike patients with damage during adulthood, made significantly more self-serving judgments that break moral rules or inflict harm on others than those with adulthood damage (Taber-Thomas et al., 2014).

Consistently, all studies implicate the vmPFC in moral decision-making, as a region argued to be important in processing aversive emotions that arrive from perceiving or imagining harmful intentions (Blair & Cipolotti, 2000; Koenigs et al., 2007). This part of the prefrontal cortex projects to the basal forebrain (the major cholinergic output) and brainstem regions, which contain all the afferent and efferent systems necessary for survival, including basic affective responses (Ongür & Price, 2000). It is also reciprocally connected with the amygdala and hypothalamus, and is therefore involved in the autonomic component of emotion and is essential in the evaluation of harmful intent. In studies using EEG recording, signals from the vmPFC and amygdala regions have been shown to encode the emotional value of stimuli (Decety & Cacioppo, 2012; Elliott, Agnew, & Deakin, 2010), and impairments of that region are not associated with deficits in mental states understanding, suggesting no effects on cognitive reasoning (Young et al., 2010).

The integration of neural and psychophysiological level analyses into the study of moral development is more recent. One functional MRI study, involving a large sample of individuals aged 4 to 37 years, combined moral evaluations, eye-tracking, and fMRI measures in response to short animated visual scenarios (Decety, Michalska, & Kinzler, 2012). Participants were shown sequences of pictures that depicted either people or objects being injured, intentionally or unintentionally. Intentionality is a critical aspect in this design because its detection is postulated to be the primary cue in determining whether an action is malicious or not (Cushman 2008; Killen et al., 2011; Malle & Guglielmo, 2012). After scanning, they were presented with the same stimuli and were asked to judge whether the action performed by the perpetrator in the video clip was intentional or not. Participants were also asked to respond to a set of questions probing moral judgment (wrongness and punishment), empathic concern for the victim, personal distress, and understanding of the perpetrator's mental state. Perceived intentional harm to people (as opposed to accidental harm) was associated with increased activation in brain regions sensitive to the perception, prediction, and interpretation of others' intentions such as the right pSTS/TPJ (Blakemore et al., 2003; Pelphrey & Carter, 2008) as well as regions processing the affective consequences of these actions, namely, the temporal poles, insula, vmPFC, and amygdala. The more participants reported being personally distressed about harmful actions, the higher the activity in the amygdala. Interesting developmental trends were also examined. For example, age was negatively correlated with empathetic sadness for the victim of harm in the video clips, with the youngest participants exhibiting the greatest personal sadness. Ratings of sadness for the victim correlated with activity in the insula, thalamus, and subgenual prefrontal cortex. This latter region has extensive connections with circuits implicated in emotional behavior and autonomic/neuroendocrine response to stressors, including the amygdala, lateral hypothalamus, and brainstem serotonergic, noradrenergic and dopaminergic nuclei (Drevets et al., 1997). Damage to the subgenual prefrontal cortex is associated with abnormal autonomic responses to emotional experiences and impaired comprehension of the adverse consequences of pernicious social behaviors (Bechara et al., 1996). Moreover, the BOLD (blood oxygenated level dependent) signal in older participants increased in the mPFC and vmPFC, regions associated with cognitive representation and decision making that enable us to reflect on the values linked to outcomes and actions.

That study also demonstrated that patterns of functional connectivity between prefrontal cortex and amygdala during the perception of intentional harm relative to accidental harm were different with age. The functional integration between vmPFC and amygdala were observed, such that the older participants showed significant

coactivation in these regions during the perception of intentional harm relative to accidental harm, whereas the youngest children only exhibited a significant covariation between the vmPFC and periaqueductal gray. Moreover, young participants showed weaker connectivity between vmPFC and pSTS/TPJ while viewing moral relative to nonmoral actions than adult participants, suggestive of developmental changes in functional integration within the mentalizing system.

In another study, 51 healthy male participants aged 13–53 were scanned while viewing international affective picture system (IAPS) pictures that did or did not depict situations considered to represent moral violations, and were asked to rate the severity of moral violation (Harenski et al., 2012). These severity ratings were associated with increased activity in the amygdala, pSTS/TPJ and posterior cingulate cortex activity in both adolescents and adults, however the magnitude of activity in the pSTS was positively correlated with age. Given the role of the pSTS region in mentalizing, and the fact that its underlying neural substrates undergo extensive developmental changes from adolescence to adulthood, the authors hypothesized that adolescents use these types of theory of mind inferences less during moral judgment than do adults.

Overall, findings from affective developmental neuroscience indicate that both affective reactions and cognitive reasoning contribute to moral judgments, yet in many contexts, automatic affective processes dominate. Converging results from lesion and functional neuroimaging studies implicate the specific role of a neural circuit of reciprocally connected regions in moral cognition (Moll, de Oliviera-Souza, & Eslinger, 2003). Moral reasoning has been argued to be supported by specific neural circuitry, but in fact these circuits are not necessarily unique to morality (Decety et al., 2012; Young & Dungan, 2012). Rather, morality involves regions and systems, which underlie various states of feelings, cognitive, and motivational processes. Most importantly, moral reasoning involves a complex integration between affective and cognitive processes that gradually changes with age and can be viewed in dynamic transaction across the course of ontogenesis. Finally, taken together, evidence from lesion studies and functional neuroimaging, offer compelling support for the proposal that early dysfunction in the systems underlying morality, particularly vmPFC and amygdala, may constitute a neuropathophysiological mechanism for the development of psychopathy (Taber-Thomas et al., 2014), a neurodevelopmental disorder associated with callous disregard for the well-being of others, guiltlessness, and little appreciation of moral wrongdoing.

Theory of Mind

The development of social cognition, particularly the understanding of others, is critical for social and peer interactions, and general social competence (Dunn & Cutting, 1999). Theory of mind (ToM; also called mentalizing) is the ability to explain, predict, and interpret behavior by attributing mental states such as desires, beliefs, intentions and emotions to oneself and to other people. Research in ToM and early social cognition has traditionally focused on behavioral development, characterized by task-related increases in overall performance (e.g., Wellman & Liu, 2004). Through the use of behavioral testing measures, children have been shown to have a step-like progression in their ability to pass false-belief tasks, false-appearance tasks, and even deception tasks (Wellman, Cross, & Watson, 2001). In a standard false-belief change location task, children witness two individuals in a room. One hides an object in A location, then leaves the room. The other individual moves the object from A location to B location. When the first individual comes back to the room, the child is asked where the individual will look for the object. To pass the task, children have to understand that the individual will not have the same knowledge of the change-of-location that they themselves have and will search in the original location (Wimmer & Perner, 1983). In meta-analyses of theory of mind development, the ability to pass this task is often not expressed in children until late preschool (Wellman & Liu, 2004). However, rudimentary theory of mind abilities have been shown in children only 15 months old (Onishi & Baillargeon, 2005). Infants look longer at instances where the individual who left the room searches in the B location than in the A location. These results suggest early knowledge of theory of mind, but the lack of an explicit ability to act upon this knowledge, hence children's apparent failure in change-of-location tasks in early preschool.

Complementary findings from developmental literature suggest that by as young as the second year of life, and definitely by preschool age, children are able to integrate conceptions of others into their choice of whom to learn from, a phenomenon referred to as selective trust (Koenig, Clement, & Harris, 2004). In selective trust experiments, children are shown familiar objects and two speakers label the objects, one does so correctly and the other does so incorrectly. Both speakers then label novel objects for the child, and the child is asked what the object is called. This early calculation of another individual's knowledge is also a form of early social cognition (Koenig, Clement, & Harris, 2004).

Recently, developmental and social neuroscientists have also investigated theory of mind and social cognition, including the temporal, developmental, and spatial dynamics of neural and electrophysiological activity underlying behavioral performance and developmental transitions between stages of theory of mind. Several methods have been employed in the study of ToM from a neural level including functional neuroimaging (fMRI), electroencephalography (EEG), event-related potentials (ERP), eye tracking, and pupillometry.

The spatio-temporal dynamics of developing social cognition have been characterized using two methods: collecting resting state electrophysiology (continuous recording while the participants closes and opens their eyes), and analyzing alpha or gamma band frequency frontal asymmetry or coherence (as they relate to behavioral outcomes; e.g., Sabbagh et al., 2009) and collecting stimulus/time locked recordings, wherein discrete waveform/latencies are examined during task acquisition (e.g., P300, LSW studies) (Sabbagh & Taylor, 2000). The event related potential (ERP) technique examines the exact timing of electrophysiological signals after a particular stimulus is presented; however, in order to perform reliable ERP analyses, many trials are needed (e.g., Luck, 2005). In the examination of theory of mind behaviorally, it is common to have a single false-location or false-contents trial. However, in electrophysiology, the variability in waveform latency and amplitude is quite large on a single-trial basis (Luck, 2005), leading to results that may depend on the neurological equivalent of outliers.

In one study using an ERP design, the change in location task was modified such that participants (adults) were shown a number of short stories. In half of the stories, the character's belief regarding the location of two objects was described and the other half, a character was described taking a photograph of two objects (Sabbagh & Taylor, 2000). Thus, most features of the vignettes were matched, except the belief dimension (belief or photo). Significantly greater amplitude in the p300 (a positive deflection approximately 300–400 ms post stimulus) was found for belief versus photo trials. The p300 waveform is oftentimes an index of differential attention allocation, and as such, belief understanding was theorized to depend on additional attention allocation when compared to simply taking a picture (with no mentalizing component). Additionally, differences in late slow wave (LSW) (approximately 900 ms post stimulus, argued to indicate secondary reappraisal) were observed for belief *versus* photo trials. Differences in temporal signatures related to ToM understanding, particularly LSW, were also explored in a series of studies with adults and children (Bowman et al., 2012). In this study, children and adults who could pass false belief (versus children who failed a false belief paradigm) showed a modulated LSW over frontal electrodes for belief versus reality, suggesting the necessity of secondary reappraisal and controlled cognitive processing in focusing on the mental states of others.

For several decades, EEG resting state activity, particularly alpha (or theta) frequency activity and coherence (6–9 Hz in children, 8–13 Hz in adults) have been seen as a relatively stable dispositional state (see Coan & Allen, 2003 for a review). The relationship between EEG resting alpha coherence and ToM development has also been explored (Sabbagh et al., 2009). In this study, frontal scalp alpha power density asymmetries were localized to the dorsolateral prefrontal cortex (dlPFC) and the posterior superior temporal sulcus and predicted children's behavioral representational ToM ability. Source localization, which attempts to provide information on the likely underlying neural sources that would produce scalp electrical signatures consistent with those present in the study, were employed (Phillips, Rugg, & Friston, 2002). Such algorithms attempt to solve what is known as the inverse solution; the use of these algorithms in developmental psychology has become more common (Reynolds & Richards, 2009), but remains a source of contention.

In sum, studies utilizing ERP/EEG methodologies have provided evidence that representational and belief understanding can be characterized by unique temporal neural signatures, primarily by differences in Late Slow Wave and p300 amplitudes. Additionally, resting state alpha frequency asymmetries predict representational ToM abilities. While ERP/EEG methods have provided a great deal of information regarding temporal neural responses related to ToM, their spatial resolution is not ideal and the use of source localization methods, particularly in children, remains contentious. Thus in order to more accurately examine the spatial aspect of neural activation of social cognition, functional magnetic resonance imaging (fMRI) has been the primarily utilized method. Several studies have documented the role of areas such as the medial prefrontal cortex (mPFC) and the dorsolateral prefrontal cortex (dlPFC) as well as the posterior superior temporal sulcus (pSTS) (e.g., Brunet et al., 2000; Fletcher et al., 1995; Ruby & Decety, 2003; Saxe, Xiao, Kovacs, Perrett, & Kanwisher, 2004) in mental states understanding and perspective-taking ability. The specificity versus generality of regions involved in social cognition and representational understanding remains an outstanding issue. One argument has been the importance

of a relatively domain-specific intentionality area specialized for processing information related to intention, the right pSTS (e.g., Young & Saxe, 2008). However, given the relative inability to disentangle cognitive aspects of ToM (e.g., executive function abilities) from the assessment of intentional understanding, many have argued for the necessity of a network of areas working together that are also involved in attention, executive function, and working memory (Decety & Lamm, 2007; Griffith, Pennington, Wehner, & Rogers, 1999). This debate is particularly salient when the information from the neural level of analysis with respect to representational understanding is integrated into our conceptions of abnormal development, particularly in populations where intentional and representational understanding are impaired (e.g., autism spectrum).

Empathy

The operational and conceptual definitions of empathy are both numerous and highly debated (Batson, 2009; Coplan, 2011; Decety & Jackson, 2004). While empathy to most theorists entails feelings of concern for others (known as empathic concern, a motivational state aimed at improving another's welfare), the definition also includes the capacity to take the perspective of another to understand her subjective experiences—feelings, desires, beliefs, and intentions. An additional and crucial component of empathy involves the natural ability to share or become affectively aroused by the emotions of others, referred to as emotional sharing or contagion (Decety, 2010a).

While empathic understanding is often considered as relatively specific to humans (and perhaps apes), emotional contagion and empathic concern are shared with other primates and mammals and depend on evolutionarily ancient systems for attachment, caregiving, and social communication. These systems rely on subcortical neural pathways (connecting the brainstem, hypothalamus, amygdala, basal ganglia and ventromedial prefrontal cortex) and hormones (Decety, 2011).

Several studies have documented empathetic-like behaviors in nonhuman animals. For instance, rodents exhibit emotional contagion and helping behaviors. Rats in an arena with a cagemate trapped in a restrainer learned to intentionally and quickly open the restrainer and free their cagemate, even when social contact was prevented (Ben-Ami Bartal, Decety, & Mason, 2011). When liberating a cagemate was pitted against chocolate contained within a second restrainer, rats opened both restrainers and typically shared the chocolate. To investigate whether pain behavior can serve the function of soliciting a primitive form of empathic concern, Langford and colleagues (2010) used a social approach paradigm to test mice in various dyadic or triadic conditions. In this study, some mice were restrained and administered an intraperitoneal injection of acetic acid to incite pain. A similar group of test mice were unrestrained, free to approach or avoid the distressed conspecifics. Only female mice approached a familiar same-sex conspecific in pain (suggesting empathetic arousal), and the frequency of contact by the test mouse was negatively correlated with the pain behavior of the jailed mouse, suggesting that the proximity of a familiar unaffected conspecific may have analgesic properties. Interestingly, genetic relatedness alone does not motivate helping as demonstrated by a new study that fostered rats from birth with another strain. Results showed that, as adults, fostered rats helped strangers of the fostering strain but not rats of their own strain (Ben-Ami Bartal et al., 2014). Thus, strain familiarity, even to one's own strain, is required for the expression of pro-social behavior in rodents. Additional evidence for empathy-elicited behaviors has been also well documented in chimpanzees and capuchins. For instance, chimpanzees will actively sooth fellow chimps that are distressed or are the targets of aggression (Flack & de Waal, 2000) and capuchins have been found to prosocially offer food to familiar monkeys (de Waal, Leimgruber, & Greenberg, 2008).

Foundational to the experience of empathy in adults and children is the ability to emotionally resonate with the affective states of others (Decety & Sveltova, 2012). Human infants are sensitive to the emotional expressions of others, especially when these expressions are vocalized. This predisposition for sensitivity has been shown in neural approaches to the study of the development of empathy. Neonates appear to possess a neural mechanism for vocal affective discrimination, as demonstrated by a mismatch electroencephalographic response over the right hemisphere in response to emotionally laden (happy and fearful vs. neutral) syllables within the first few days of life (Cheng, Lee, Chen, Wang, & Decety, 2012). In 3–7-month-olds, said vocalizations are associated with a selective increase of hemodynamic activity in brain regions involved in the processing affective stimuli, such as the orbitofrontal cortex and insula (Blasi et al., 2011). The results of these two studies suggest remarkably early functional specialization for processing the human voice and emotions.

Due to the methodological constraints of functional neuroimaging with children, much of our knowledge of regions of the brain associated with empathy come from studies with adults. In adult participants, numerous neuroimaging studies have demonstrated the reliable

activation of a neural network involved in pain perception, including the anterior mid-cingulate cortex (aMCC), anterior insular cortex, supplementary motor area (SMA), and periaqueductal gray area (PAG). Activation in this network has been reported in response to facial expressions of pain (Botvinick et al., 2005; Lamm, Batson & Decety, 2007), body parts being injured (Cheng, Yang, Lin, Lee, & Decety, 2008; Jackson, Meltzoff, & Decety, 2005), imagining the pain of others (Decety & Porges, 2011; Jackson, Brunet, Meltzoff, & Decety, 2006), or simply observing a signal indicating that someone will be receive a painful stimulation (Singer, Seymour, & O'Doherty, 2004). These vicariously instigated activations of the pain matrix are not specific to the sensory qualities of pain, but instead are associated with more general survival mechanisms such as aversion and withdrawal when exposed to danger and threat (Decety, 2010b). In fact, based on a systematic review of electroencephalographic and functional MRI studies that examined neural systems triggered by nociceptive stimuli, activity of this cortical network reflects a salience system involved in detecting, processing, and reacting to the occurrence of salient sensory events regardless of the sensory channel through which these events are conveyed (Legrain, Iannetti, Plaghki, & Moureaux, 2011), which elicit defensive and protective behaviors.

Of particular importance is the aMCC, a region that implements a domain-general process integral to negative affect, pain and cognitive control, which contains pain-responsive neurons that are activated by both anticipation of pain, and instrumental escape from pain (Shackman et al., 2011). Furthermore, activation of the anterior insula is clear in studies of pain empathy. This response can even be elicited automatically, as shown when participants viewed color photographs depicting human body parts in painful or neutral situations and performed either pain judgment (painful–nonpainful) or laterality judgment (left–right) of the body parts in the absence of explicit task requirements and attentional demands (Gu et al., 2010).

One study has attempted to investigate the development of empathy using functional neuroimaging methods. In this cross-sectional study participants ranging from 7 to 40 years of age were shown visual stimuli depicting individuals being physically injured by accident or intentionally by another (Decety & Michalska, 2010). In subjective evaluations of the stimuli, collected after scanning, a gradual decrease in the judgment of pain intensity for both conditions (accidental vs. intentional) across age, with younger participants rating the scenarios as significantly more painful than older participants, was observed. For younger participants, greater activation in amygdala, posterior insula, and medial OFC was seen when watching others in painful situations. In contrast, a positive correlation was found in the anterior portion of the insula. A posterior-to-anterior progression of increasingly complex rerepresentations in the human insula is thought to provide a foundation for the sequential integration of the individual homeostatic condition with one's sensory environment, and motivational condition (Craig, 2003). The posterior insula receives inputs from the ventromedial nucleus of the thalamus, an area that is highly specialized to convey emotional and homeostatic information, and serves as a primary sensory cortex for both of these distinct interoceptive feelings from the body. In response to others' physical distress, younger participants recruited the posterior portion of the insula, in conjunction with the amygdala and medial OFC, more than adults. This finding speaks to the children's tendency to be aroused by the perception of others' distress in a more direct sense leading to a heightened experience of discomfort associated with a visceral response to a potential threat, whereas adult participants tend to use more abstract secondary representations of pain when perceiving others in distress.

This latter study also found that age was related to activation in the prefrontal regions, such as the dlPFC and IFG, areas involved in cognitive control and response inhibition (Aron, Robbins, & Poldrack, 2004; Swick, Ashley, & Turken, 2008). Similarly, age-related change was observed in the OFC in response to the pain inflicted by another, shifting activation from the medial portion in younger participants to the lateral portion in older participants. The OFC has intrinsic networks that are defined on the basis of their cortico-cortical connections and also connections with other parts of the cerebral cortex and subcortical structures. These connections extend to the mediodorsal nucleus of the thalamus, sensory areas, and virtually all limbic structures (including the amygdala and brainstem), each subserving distinct functions (Ongur & Price, 2000). Since the medial part of OFC is involved in regulating both motor and visceral responses, and its lateral part is involved in executive control of emotion reactivity (Hurliman, Nagode, & Pardo, 2005), this pattern of developmental change is indicative of a gradual shift from the monitoring of somatovisceral responses in young children (consistent with their tendency to process others' pain information at a proprioceptive level) to a more cognitive evaluative level associated with executive control of higher order emotion processing in older participants.

TRANSLATIONAL DEVELOPMENTAL SOCIAL NEUROSCIENCE

As developmental social neuroscience is a relatively new field, the predominant focus of research has been on normative populations, answering first-level questions of observation, as is evidenced by our three examples (i.e., moral reasoning, theory of mind, and empathy). However, recent investigations have begun to use this knowledge from the developmental social neuroscience approach to inform the investigation of abnormal development and psychopathology. Two areas where this translation of social neuroscience is most evident are in the study of autism and in the study of conduct disorders, antisocial behavior, and callous unemotionality.

Autism

Children with autism spectrum disorder (ASD) exhibit widespread deficits in social cognitive abilities such as ToM and executive functions (Baron-Cohen, Campbell, Karmiloff-Smith, Grant, & Walker, 1995; Hughes, Russell, & Robbins, 1994; Ozonoff, Pennington, & Rogers, 1991; Russell, 1997). Decades of research with twins and siblings have shown that ASD and the range of social cognitive deficits associated with it, are highly heritable, with some studies reporting over 70% heritability (e.g., Constantino et al., 2013; Hallmayer et al., 2011). In the last 20 years, preliminary investigations of the genetic underpinnings of ASD have identified dozens of candidate genes in which specific mutations are associated with the severity of certain ASD symptomatology, such as the neurexin 1, neuroligin 1, RELM, OXTR, and AVPR1 genes (e.g., Kim, et al., 2008; Marshall et al., 2008; Persico & Bourgeron, 2006; for a review of the current state of behavioral and molecular genetics of autism, see Krumm, O'Roak, Shendure, & Eichler, 2014). However, recent estimates suggest that variations in these candidate genes accounts for less than 20% of ASD cases (Geschwind, 2011). Phenotypic differences in ASD, such as deficits in face processing, social affiliation, motor imitation, working memory, executive function, and phonological processing are unlikely to be based on the mutation of a single gene. Instead, mutations to multiple genes, each a risk factor for the diverse syndrome, are presumed to account for variability (Dawson et al., 2002).

Starting from an early age, children with autism appear to lack the appropriate emotional response to another person's distress or fear (Sigman, Kasari, Kwon, & Yirmiya, 1992). Moreover, infants with autism are far less likely to engage in the imitation of adult facial gestures (Griffith et al., 1999). This early (1–3 weeks of age) normative developmental ability (Meltzoff & Moore, 1977) is likely to interfere with social cognitive experience, leading to future domain-general deficits. Infants can first distinguish between familiar and unfamiliar faces around 3–4 months of age (Tronick & Cohn, 1989). At around 4 months of age infants begin to become sensitive to emotional and social responsiveness of their caregivers. These abilities may be viewed with step-wise progression, wherein, the inability to distinguish between familiar and unfamiliar faces at early ages, may illustrate a general inability to recognize one's familiar sources of support (caregivers). This lack of recognition, coupled with the later inability to attune to a caregiver's emotional responses, can lead to interactional synchrony (Isabella & Belsky, 1991). In this situation, the infant and caregiver's discrepant patterns of responsiveness toward each other in the dyadic relationship predict abnormal social development.

Since the discovery of the mirror neurons in the primate brain (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992) and the finding of a supposedly similar set of circuits in the human brain (Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995), many studies have explored the mirror neuron system (MNS) as it develops in individuals with autism. The predominant function of mirror neurons was thought to relate to action understanding (Rizzolatti & Craighero, 2004), but it is also theorized to be important for other social-cognitive processes, including imitation, theory of mind and empathy (Gallese & Goldman, 1998).

Early developmental failure of the MNS has been postulated to contribute to imitation deficits followed by varied social-cognitive difficulties characteristic of ASD (Williams, Whiten, Suddendorf, & Perrett, 2001). Importantly, in the studies investigating MNS functioning in individuals with autism, results are inconsistent (e.g., Katagiri, Inada, & Kamio, 2010).

In particular, some studies have reported that activity in the MNS of individuals with ASD differed from those of control participants through indirect measures of neural activation, such as resting-state EEG (*mu*) suppression over the sensorimotor cortex (Oberman et al., 2005), or BOLD signal (fMRI; Dapretto et al., 2006) during the observation of goal-directed hand actions and emotional expressions. However, other studies have reported a normal MNS response in individuals with ASD (Dinstein et al., 2010). In one study, the observation of action without requesting imitation elicited significant mu suppression (Bernier, Dawson, Webb, & Murias, 2007), particularly when the action was attributed to a familiar individual

(Oberman, Ramachandran, & Pineda, 2008). In another study, individuals with ASD and control subjects were shown a series of videos depicting standard goal-directed actions, while using the EEG coupled with eye tracking (Fan, Decety, Yang, Liu & Cheng, 2010). Participants with ASD watched a right hand manipulating objects, and showed significant suppression of the mu rhythm, similar to the mu suppression shown in control participants (nondifferentiation between ASD and controls). These results, in conjunction with other recent findings challenge the notion that individuals with ASD have an abnormal mu suppression in response the observation of hand movement (Oberman et al., 2005) or retain their imitation ability to hand–object interaction (Hamilton, Brindley, & Frith, 2007). A recent study using fMRI and EEG in individuals with ASD exhibit heightened empathic arousal but impaired social understanding when perceiving others' distress. Furthermore, both ASD and control groups showed comparable mu suppression, indicative of typical sensorimotor resonance (Fan, Chen, Chen, Decety, & Cheng, 2013).

The last two decades have seen a focus on the role of the MNS in the developmental psychopathology of autism, yet the results have not provided a clear picture that the MNS is of primary importance from a neural level of analysis. Other studies investigating neural developmental differences in individuals with autism have focused either on specific target areas (e.g., the FFA) or diffuse networks of difference (e.g., a combination of frontal, temporal, and parietal areas) (Pelphrey & Carter, 2008).

Several studies indicate that the perception of faces is associated with the specific activation of the so-called fusiform face area (FFA; Weigelt, Koldewyn, & Kanwisher, 2012). In populations with autism, the FFA is activated when processing both faces and objects (not necessarily due to visual expertise; Dalton et al., 2005). However, most studies have documented atypical response in a network of regions, comprised of the FFA, as well as the orbitofrontal cortex (OFC), the medial prefrontal cortex (mPFC), the amygdala, the posterior superior temporal sulcus (pSTS) and the inferior frontal gyrus (IFG; Pelphrey & Carter, 2008). This network view of the abnormal processing in ASD further illustrates differences seen behaviorally in social perception, goal-directed action understanding, social cognition, gaze processing, and executive functioning (Kaiser et al., 2010).

As is quite clear from the brief review of the findings regarding ASD, a multiple-levels-of-analysis approach to understanding this psychopathology, and its underlying mechanisms, is necessary. Preliminary investigations have shown developmental differences in behavioral functioning, differential temporal and spatial processing of belief, desire, and representational understanding, both for children that cannot pass theory of mind tasks, as well as individuals with autism.

Conduct Disorders and Callous Unemotional Traits

Another example of translational developmental social neuroscience is the study of conduct disorders, aggressive behavior, and callous unemotional traits. Socioemotional dysfunction has dire consequences in social cognitive development that dramatically impact interpersonal relationships. This is particularly the case in children with conduct problems or conduct disorders (CD), a serious behavioral and emotional disorder that can occur in children and teens. Children with CD and high levels of antisocial behavior and callous-unemotional traits usually lack guilt and remorse and have difficulty in social situations, showing deficits in affective arousal and empathic concern for the well-being of others (Hawes & Dadds, 2012). The capacity to experience the distress of others as aversive is critical for the development of moral emotions (e.g., guilt and remorse) as distress cues are assumed to activate tendencies to withdraw (Blair, 1999). Moreover, adolescents with higher psychopathy scores also tend to interpret both moral and conventional violations as more permissible than adolescents with low psychopathy scores (Dolan & Fullam, 2010).

Atypical responses to the distress of others are evident as early as childhood and have long-term consequences. For instance, general disregard for others, particularly for the distress of others, as early as 14 months of age is related to later development of antisocial behavior in middle childhood and adolescence (Rhee et al., 2013). Some evidence suggests that there are consistent patterns of psychophysiological empathic responding in both aggressive and nonaggressive toddlers (Gill & Calkins, 2003). Indeed, a meta-analysis of the developmental links between empathic development and aggressive behavior indicated that adolescents exhibit a greater negative relationship between affective empathy and aggressive behavior than children (Lovett & Sheffield, 2007). Gender differences, particularly earlier in development, have been shown in the relationship between empathic responding and conduct disorder/antisocial behavior, wherein young males showed the highest relation between antisocial behavior and lower empathic responding (Dadds et al., 2009). Moreover, from extensive evidence with school age children and adolescents, the mechanisms

that lead to aggressive or antisocial behavior can be identified across multiple domains, from genetics (there is a high incidence of intergenerational aggressive antisocial behavior) to environment (see Tremblay, 2010 for a full review).

Children with psychopathic tendencies also exhibit reduced electrodermal responses to distress cues (e.g., a crying face) and threatening stimuli (e.g., a pointed gun) relative to controls (e.g., Blair, 1999). A study using electroencephalography recently examined this phenomenon by assessing how callous-unemotional traits in juvenile psychopaths are related to empathic arousal deficits (Cheng et al. 2012). In this study, juvenile offenders with high callous-unemotional traits, juvenile offenders with low callous-unemotional traits, and age-matched typically developing adolescents were shown images of people in physical pain while EEG/ERPs were recorded. Results demonstrated that youth with high callous-unemotional traits exhibit atypical neural dynamics of pain empathy processing in the early stages of affective arousal. This abnormality was exemplified by a lack of the early ERP negative deflection (N120), thought to reflect an automatic attention to negative stimuli, and was coupled with relative insensitivity to actual pain (as measured with the pressure pain threshold). Nevertheless, their capacity to understand intentionality was not impaired. This uncoupling between affective arousal and emotional understanding likely contributes to psychopaths' callous disregard for the rights and feelings of others. A recent emphasis has been placed on exploring the genetic and biological mechanisms underlying the expression of callous unemotionality. In a sample of urban and rural children, differences in several genetic polymorphisms related to oxytocin receptors predicted callous unemotional traits in children and adolescents (Dadds, Moul, Cauchi, Dobson-Stone, Hawes, Brennan, Urwin, et al., 2014). High callous unemotionality was also associated with greater methylation of oxytocin receptor genes and lower blood concentration of oxytocin (Dadds, Moul, Cauchi, Dobson-Stone, Hawes, Brennan, & Ebstein, 2014).

Functional MRI studies have reported that adolescents with disruptive psychopathic traits show reduced activity to increasing perceived pain intensity within structures typically implicated in affective responses to others' pain, including the anterior cingulate cortex, insula, and amygdala (Marsh et al., 2013). Another recent study found reduced neural response to others' physical pain in children with conduct problems in the insula and ACC (Lockwood et al., 2013). Youths with psychopathic traits exhibit reduced amygdala responses to fearful facial expressions and during affective theory of mind tasks (Marsh et al., 2008). Adolescents with conduct disorders also show reduced activation in the amygdala and right anterior insula during affective ToM tasks than non-conduct disordered adolescents (Sebastian et al., 2012). It is worth mentioning that psychopathic traits are not exclusively associated with amygdala hyporeactivity. A study that included 200 young adults with self-reported psychopathy assessment found that amygdala reactivity to fearful facial expressions is negatively associated with the interpersonal facet of psychopathy, whereas reactivity to angry expressions is positively associated with the lifestyle facet (Carré et al., 2013). Interestingly, one functional neuroimaging study of youth with aggressive conduct disorder and psychopathic tendencies found increased activation in the ventral striatum and amygdala when adolescents viewed people being intentionally hurt by others (Decety, Michalska, Akitsuki, & Lahey, 2009). The extent of amygdala activation to viewing others in pain was positively correlated to the participant's number of aggressive acts and their ratings of daring and sadism scores. These results are consistent with the view that increased activity in the amygdala, particularly when coupled with the ventral striatum, reflects a general arousing effect of reward (Murray, 2007).

Much of our knowledge on psychopathy/callous unemotionality comes from a rich literature with adults, primary incarcerated psychopaths (e.g., Harenski, Harenski, Shane, & Keihl, 2011). In these studies, several consistent findings have arisen. Adult psychopaths consistently fail to experience distress cues as aversive. They lack fear of punishment, have difficulty regulating their emotions, and do not experience insight into or empathy for the effect their poor behavior has on others (Blair & Blair, 2009). Offenders with high levels of psychopathy show reduced autonomic arousal when viewing a confederate receiving electric shocks (Aniskiewicz, 1979), and often exhibit weaker psychophysiological reactions to emotional stimuli (for example, decreased skin conductance reactivity) and poor passive-avoidance learning (Kosson et al., 2006). Structural neuroimaging studies associate psychopathy with a host of morphological brain abnormalities, including reduced gray matter volumes of the amygdala, temporal poles and temporal cortex (particularly in the right pSTS), and increased volume of the striatum. Furthermore, psychopaths often exhibit signs of reduced structural integrity of the uncinate fasciculus (Koenigs, Baskin-Sommers, & Newman, 2010) connecting areas of the limbic system (such as the hippocampus and amygdala) with the ventromedial prefrontal cortex. The integrity of this circuit

seems to be necessary for moral decision making and empathic concern.

Overall, a lack of affective arousal in psychopathic individuals reinforces the importance of emotion stimulation and perception in the development of care-based morality. This type of moral reasoning necessitates that distress cues become associated with representations of stimulus–outcome learning. Affective arousal plays an important role in eliciting empathic concern (Barnett & Thompson, 2001). The dysfunction of the connectivity between the amygdala and vmPFC partially explains low socioemotional responses to others' distress, though it is important to note that blunted empathic arousal alone does not explain offensive behaviors. Behavior is caused by rewards and stopped by punishments, with the former influencing behavior more effectively than the latter in most individuals. Offending behavior exists and persists because it is rewarding, and these rewards in turn affect the activity of the mesolimbic dopamine system (one of the dopaminergic pathways). For example, pathological reward seeking in individuals with impulsive-antisocial psychopathic traits increases the likelihood of engaging in behaviors that are dangerous to others and themselves, and predicts ventral striatum dopamine release in response to pharmacological and monetary reinforcers (Buckholtz et al., 2010).

Most social interactions hinge on the degree to which individuals have the ability to process socioemotional information and make inferences about another person's cognitive and emotional states in the service of adaptive interpersonal behavior. A lack of emotional response to the distress of others is generally associated with psychopathic and antisocial tendencies, suggesting an important link between arousal and empathy. Integrating our understanding of conduct disorder and callous unemotional traits with adult psychopathy clarifies both normative and atypical development of socioemotional responding.

CONTROVERSIES AND FUTURE DIRECTIONS

Controversies

Developmental psychologists have long debated about domain-general versus domain-specific mechanisms (e.g., Gallistel, Brown, Carey, Gelman, & Keil, 1991). As social neuroscience and its theoretical approach have gained popularity, conceptions of the social brain as a domain-specific set of neural networks or regions interacting or the social brain as the integration of domain-general mechanisms or networks have been in conflict. This debate is particularly pertinent to developmental psychopathology in that many identified neural regions of interest, or even circuits, are postulated to be solely responsible for social cognitive function (e.g., the Facial Fusiform Area; Downing, Jiang, Shuman, & Kanwisher, 2001; Gauthier, Skudlarski, Gore, & Anderson, 2000). Oftentimes these areas show deficits in either structure or function in abnormal populations (e.g., ASD spectrum individuals). Thus, attempting to use a domain-specific approach to social neuroscience may yield potential information for psychopathology and intervention. However, it is important to emphasize that conceptions of domain-specific areas for theory of mind or intention understanding are now commonly being replaced by more complex understandings of multiple overlapping neural networks, not specific to a particular behavioral phenomenon (Decety et al., 2012). In addition, current research shows that complex socioemotional cognitions and behaviors have their neural bases in dynamic coalitions of networks of brain areas, none of which should be conceptualized as specifically affective or cognitive (Pessoa, 2008). As illustrated with examples from the literature in social neuroscience, both types of interpretations still abound. Some neuroscientists argue for specific areas of functioning, others argue for networks of interconnected functioning. The aim of social neuroscience is not the discovery of social modules in the brain. Rather, it is to understand the reciprocal relationships between social, cognitive, and neurobiological levels, and not brain systems specific to social information (Ochsner & Lieberman, 2001).

In interpreting data from multiple levels of analysis, two meta-integration methods have come to the forefront: integrative approaches and reductionist approaches. Similar to biology, physics, and chemistry, developmental neuroscientists have been encouraged to discover explanations of behavior that are at the most scientifically basic levels: molecular, genetic, and biological. Reductionist thought in developmental science is the idea that all explanations should be founded in one of these basic scientific levels.

Ultimately, the study of developmental psychopathology and social neuroscience necessitates an integrative, multiple-level-of-analysis approach (Cicchetti & Valentino, 2007). All the complex constructs that are studied in social and affective neuroscience such as self-regulation, attachment, empathy, trust, and moral reasoning, can hardly be seen as specialized somewhere in the brain or relying on a single region, the consequence of a specific genomic mutation, or the product of a specific hormone. Instead, they need to be broken down into sub-components with

the challenge of avoiding narrow definitions that fail to capture the breadth of a function and vague concepts that may well resonate with lay knowledge and common sense but have little if any scientific validity and utility.

Future Directions

There is great excitement in developmental social neuroscience and developmental psychopathology regarding the potential integration of commonly used behavioral methods with genetic, hormonal, and neural analyses. While these analyses provide insight into development, and may help to clarify some theoretical and behavioral distinctions, it is clear that the methods available and the subsequent information from studies using multiple levels of information are not sufficient to unravel the neurobiological mechanisms mediating social cognition and interaction. However, it is equally clear that, because many of these analyses, such as behavioral, genetic, hormonal, neuroimaging, and electrophysiological measures are noninvasive, they have an important role to play in testing and refinement of developmental theories of complex psychological processes that are difficult to study in nonhuman animals.

Future studies in developmental social neuroscience research need to take into account three primary considerations. First, behavioral analyses and assessments of complex psychological constructs are important and are the core of the field of developmental social neuroscience (Cacioppo & Decety, 2009). In order to use multiple levels of analysis, psychological constructs need to be broken into their component, representations, and processes that could plausibly be implemented by the brain. These behavioral investigations allow for a fine-tuning of tasks and measures that can be used in the study of the genetic, neural, and development change in any construct. Moreover, a strong theoretical perspective will be able to easily integrate evidence from multiple-levels of analysis.

Second, multiple methods at each level of analysis are key. In the neural level, the brain does not operate exclusively at the spatial level of molecules, cells, nuclei, regions, circuits, or systems, nor does it operate exclusively at the temporal level of milliseconds, seconds, minutes, hours, or days. Neuroimaging provides a partial view of brain activity within a very limited range of spatial and temporal levels. For instance, the smallest regions detectable by fMRI still involve hundreds of thousands of cells, cells that are seldom homogeneous in their function or connections, so such studies identify neural circuitry only in a gross sense. Different cells within the amygdala have been identified that respond to appetitive versus aversive stimuli (Paton, Belova, Morrison, & Salzman, 2006). Detection of amygdala activation by fMRI in response to appetitive and aversive stimuli does not mean the same neural circuitry has been activated. Therefore, converging evidence from measures in each level of analysis (e.g., neural, behavioral, environmental) that gauge similar events from different informants, perspectives, or scales (e.g., fMRI and EEG) leads to a more complete picture of any given phenomenon and allows for greater scope in future hypothesis testing.

Third, human and nonhuman animal investigations are critical to the future of developmental social neuroscience. The field of developmental social neuroscience is not limited to the study of humans. In fact, much of the current knowledge comes from neural, behavioral, and environmental translational animal models. These are crucial as human neuroimaging, behavior, and surveys are, by nature, correlational measures. Experimental studies including lesion, transcranial magnetic stimulation, and pharmacological interventions (e.g., ligands, drugs) in human and nonhuman animals are essential to further elucidate the causal role of any given neural structure, circuit, or process in a given task. Lesion methods in particular remain a fundamental and indispensable approach. Lesion is a means to test, at the system level, the necessity and specificity of a particular region and can thus provide complementary information to neuroimaging and behavioral data.

New investigations conscious of these considerations can facilitate advances in our understanding of brain function, development, and psychopathology. The primary message is that multiple levels of analysis, when implemented and interpreted with caution, are critical to the study of development, particularly developmental psychopathology.

Conclusions

The integration of multiple levels of information into developmental social neuroscience and psychopathology results in a reconceptualization of the division between psychological, hormonal, genetic, and neural functions. The presence of so many open questions in the field is both a daunting challenge and an exciting opportunity. With genetic sequencing, hormone analyses, and neuroimaging and electrophysiological measures becoming increasingly affordable and commonplace, the field of developmental science and developmental psychopathology is on the brink of a series of breakthroughs. We encourage this exploration and at the same time advise caution in the

nature of interpretation, particularly in reducing complex psychological phenomenon to activation in areas of the brain, or mutations in a single candidate gene. We should always be cautious that there is no 1:1 relationship between a psychological construct and its neurobiological instantiation.

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CHAPTER 21

Stress Neurobiology and Developmental Psychopathology

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INTRODUCTION

Research into the long-term consequences of early adverse life experiences, such as childhood abuse, neglect, or loss, on subsequent emotional, social, cognitive and physical development has gained increasing attention in recent years. As early as at the end of the 19th century, Sigmund Freud already had recognized that stressful or traumatic experiences in early life play an important role in the development of later mental disorders, such as melancholia (Freud, 1896). Today, an abundance of epidemiological and clinical studies supports that early-life stress (ELS) is an extraordinarily common and potent risk factor for the development of a wide range of psychiatric disorders as well as certain classic medical diseases in adulthood (e.g., Anda et al., 2006; Felitti et al., 1998; Heim, Shugart, Craighead, & Nemeroff, 2010; Shonkoff et al., 2012). Among the psychiatric disorders, depression and anxiety disorders have been most prominently linked to ELS. In addition, ELS induces risk for including ischemic heart disease, lung disease, cancer or cancer progression, gastrointestinal disorders, and chronic fatigue and pain syndromes among others. Many of these disorders are elicited or aggravated by acute stress, and individuals with ELS have decreased thresholds for exhibiting symptoms, even upon mild challenges (Hammen, Henry, & Daley, 2000). The precise mechanisms that mediate the detrimental and persistent impact of ELS on long-term health and adaptation have been subject to intense inquiry over decades. Advances in neuroscience have provided compelling insights into the enormous plasticity of the developing brain as a function of experience. For example, visual sensory input early in life is required for normal development of the visual cortex and perception, and disruptive experiences during such critical periods of plasticity lead to lifelong and sometimes irreversible damage (Weiss & Wagner, 1998). The same principle may be applied to early traumatic experiences during critical periods that may permanently impact on the development of brain regions implicated in the regulation of emotion and stress responses. Such enduring programming effects of ELS on the brain and its regulatory outflow systems, i.e., the autonomic, endocrine and immune systems, may then lead to the development of a vulnerable phenotype with increased sensitivity to

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subsequent stress and risk for a range of psychiatric and somatic disorders (Heim, Plotsky, & Nemeroff, 2004). Indeed, a rapidly accumulating body of research suggests that there are pronounced alterations in stress physiology and the immune system as well as brain anatomy and function in regions relevant to emotional processing and stress regulation that occur as a function of ELS in humans. In addition, there is increasing insight into gene–environment interactions predicting the pathologic outcomes after ELS at the symptomatic and biological levels as well as changes in the molecular or epigenetic regulation of gene activity that mediate some of the outcomes of ELS in humans (Heim & Binder, 2012).

The present chapter aims to provide an overview of the contribution of ELS to the development of psychopathology and medical disease throughout the life span. We will first discuss the definition and prevalence of ELS as well as the association of ELS with psychopathology and medical disorders in adulthood. We will then provide an overview of the neurobiology of stress by describing the major regulatory outflow systems of the brain: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenomedullary system (SAM), central nervous system (CNS) stress mediators, and brain structures and neurocircuits implicated in the regulation of stress responses and emotion. We will further discuss interactions between the neuroendocrine stress response system and the immune system. Based on this overview, we will then discuss the impact of ELS on stress neurobiology and the relationship of these biological effects of ELS to the development of psychopathology and medical disease. Given that some individuals remain resilient despite significant exposure to ELS, whereas others develop disorders, we next focus on factors that mediate the emergence of interindividual differences in the effects of ELS. In this context, we will discuss the role of sex differences in the effects of ELS as well as the potential existence of sensitive developmental periods, during which the brain might be particularly vulnerable to the effects of ELS. In addition, the role of genetic disposition in moderating the effects of ELS will be discussed. Finally, we will discuss more recent insights into the molecular mechanisms of gene regulation by stress that may account for the development of altered stress responsiveness and risk for psychiatric and medical disorders after ELS, including epigenetic programming with long-term impact on gene expression. We will conclude this chapter by discussing the implications of insights from neurobiological research on the long-term consequences of ELS for novel diagnostic and therapeutic approaches that target the mechanisms involved in the persistent effects of ELS, to prevent or reverse the detrimental long-term consequences and thereby reduce the manifestation of negative health outcomes in these victims.

DEFINITION AND PREVALENCE OF EARLY-LIFE STRESS

To define ELS, two main criteria must be considered: the developmental age range that is subsumed under *early life* and the characteristics of the events that would be considered as stressful. There is no such generally agreed upon definition of ELS in humans. Many investigators use an upper age limit to define the early-life criterion, usually between 12 and 18 years. More appropriate approaches refer to the developmental stage by using the onset of sexual maturation (i.e., menarche in females, to more precisely define the early-life period). As for the stress criterion, prevailing models suggest that stress is generally experienced when an individual is confronted with a situation, which is appraised as personally threatening and for which adequate coping resources are unavailable. In addition, threats to physiological homeostasis, such as injury or illness, elicit stress responses. Any such situation occurring within the defined developmental period may be classified as ELS in humans.

The most salient forms of ELS include different forms of maltreatment or deficient caregiving, such as physical, sexual or emotional abuse as well as emotional or physical neglect, as well as exposure to domestic violence. In the following, we provide definitions of each form of maltreatment:

- *Physical abuse* is defined as the intentional use of physical force against a child causing impairment to the child's health and development, which can even cause infanticide. Violent actions like hitting, beating, kicking, shaking, biting, strangling, scalding, burning, poisoning, and suffocating can be subsumed under physical abuse (Martins, Baes, & Juruena, 2011). A particular form of physical maltreatment is the so-called shaken baby syndrome, mainly occurring in infants younger than 1 year. This vigorous manual shaking of the baby is a leading cause of death and disability in childhood (Vitale, Vicedomini, Vega, Greco, & Messi, 2012).
- *Sexual abuse* of a child can be defined as engaging a child in sexual activities that the child is not able to comprehend or to consent to. It includes fondling, rape, and exposing a child to other sexual acts that the child is not mentally prepared for or that violate the

laws of collective taboos of society. Often, perpetrators are known to the child, and sexual offenses are committed by a parent, caregiver, or another person in a custodial role.

- *Emotional or psychological abuse* refers to a failure of a parent or caregiver to provide a developmentally appropriate and supportive environment for the child. Abuse of this type includes behaviors that harm a child's self-esteem, mental health, dignity or safety by restriction of movement or hostile treatment, shaming, blaming, rejecting, threatening, discriminating or withholding love (Martins et al., 2011).
- *Emotional or physical neglect* refers to the failure to meet a child's basic needs in one or more areas, including health and access to medical care, education, emotional development, nutrition, shelter, and safe living conditions. It can occur as isolated incidents or in terms of enduring patterns (Martins et al., 2011).
- *Exposure to domestic or intimate partner violence* of caregivers can also be considered as a form of ELS, because the child experiences stress from witnessing violent actions or by getting directly involved in conflicts, for example by the attempt to intervene. Observing consequences of intimate partner violence such as noticing bruises or sadness and despair of one of the parents can be a further psychological burden (Simmel & Shpiegel, 2013).

Other forms of ELS include accidents, physical illness, surgeries, natural disasters and war or terrorism-related events. Less obvious experiences, that pose significant distress on a child, include unstable families, inadequate parental care due to mental or physical illness, and poverty. Another form of ELS that often goes unidentified is factitious disorder by proxy, a complex condition in which a parent or caretaker induces or invents illness in a child combined with unnecessary, often invasive medical treatments (Berg & Jones, 1999; Shaw, Dayal, Hartman, & DeMaso, 2008). It should be noted that ELS is often complex, inasmuch as various forms of ELS coexist or are associated among each other. While ELS may be a single event, in most cases it occurs as chronic or ongoing adversity in most cases. Unfortunately, lack of identification of maltreatment cases contributes to the fact that these children often live under chronic adversity. Enhanced recognition of child maltreatment cases will be a critical step in reducing the long-term outcomes and devising early interventions.

Early-life stress can only be a significant risk factor with public health relevance, if it occurs frequently enough in the population to explain the relatively high prevalence of disorders associated with ELS, such as depression. However, precise prevalence estimates of ELS are difficult to obtain. Data obtained from child protection agencies are underestimating the prevalence of child maltreatment, as many cases are never reported. Data obtained from retrospective studies in adults are based on retrospective case reports with questionable validity. Indeed, statistics of maltreatment cases tend to underestimate the prevalence (Gilbert, Kemp, et al., 2009). Nevertheless, the prevalence of ELS in these studies is exceedingly high and child maltreatment constitutes a major public health and social-welfare problem.

The National Child Abuse and Neglect Data System (NCANDS, 2009) of the U.S. Children's Bureau provides data on the prevalence of reported and identified cases of child maltreatment. These numbers are derived from data collected by child protective services from 52 states in the United States. Each state frames its own definitions of child abuse and neglect, whereas most states apply the four major types of maltreatment: neglect and physical, emotional, and sexual abuse. In 2011, approximately 3.4 million referrals were received by the child protective services. These referrals were estimated to include 6.2 million children. Of these referrals, 60.8% of the allegations were screened in and received an investigation or assessment for abuse and neglect. More than 3.7 million children were subject to at least one report. 681,000 unique victims were counted in the year 2011. The number of victims slightly decreased compared with the previous years, but it can be assumed that this number only represents the tip of the iceberg, while most cases go unreported. Among reported cases, more than 75% are victims of neglect, 17.6% experienced physical abuse, and nearly 10% suffered sexual abuse. Important to note is the fact that the youngest age group (birth to 1 year) had the highest rate of victimization. One explanation could be that these cases are more often detected and reported. Nearly 1,600 children died as a result of abuse or neglect in 2011 in the United States. Among these children, 81.6% were younger than 4 years of age. Also, as reports show, about 80% of maltreatment cases were committed by parents or caregivers. Furthermore, the majority of the infanticides (78.3%) were caused by one or more parents. With regard to sexual abuse, statistics indicate that in most cases perpetrators are relatives or other persons in the child's immediate environment (Gilbert, Kemp, et al., 2009).

Girls seem to be more often exposed to sexual abuse (Gilbert, Kemp, et al., 2009). Of note, children with other developmental disorders, disabilities or complex medical

problems are also at greater risk to become victims of violence in comparison with healthy children at the same age. A record-linkage study from the United States showed a cumulative prevalence of maltreatment of 9% for nondisabled children and 31% for disabled children. The overall prevalence of any recorded disability was 8%, whereas a quarter of all identified maltreated children had a disability (Jones et al., 2012).

As an alternative methodological approach to estimate the prevalence of ELS, retrospective studies have been conducted to assess the frequency of different forms of maltreatment in the population. For example, Briere and Elliott (2003) presented results from a survey in a community sample: among female respondents, 32% reported experiences of sexual abuse before the age of 18, whereas 14.2% of the male participants were victims of sexual abuse. Approximately 20% (22.2% of men, 19.5% of women) of the total sample experienced physical abuse. More than one third (37%) of the respondents were victims of either type of abuse, 21% experienced both forms of abuse. In a study by Gould et al. (1994), similar numbers have been reported: 44% experienced any type of sexual, physical or emotional abuse, 22% reported multiple types of early maltreatment. Retrospective studies confirm that girls are 2.5 to 3 times at higher risk to experience sexual abuse compared with boys (Fergusson, Horwood, & Lynskey, 1996; Finkelhor, 1993; Sobsey, Randall, & Parrila, 1997). Data from the National Comorbidity Study suggests that nearly 16% of women experience childhood sexual abuse (Molnar, Buka, & Kessler, 2001). The Adverse Childhood Experiences study, a large population-based study conducted by the U.S. Centers for Disease Control and Prevention (CDC) in a sample of more than 17,000 members of an health maintainance organization (HMO) in the San Diego area, reported prevalence rates of 21.6% of sexual abuse, 20.6% of physical abuse, and 14% of witnessing domestic violence; 34.6% of these cases reported exposure to multiple types of ELS (Edwards, Holden, Felitti, & Anda, 2003). Inconsistencies in prevalence rates across studies may reflect differences in the definition or assessment of ELS. A point of criticism with regard to these studies is the retrospective and noncorroborated assessment of childhood maltreatment. Problems concerning the credibility of self-reports of childhood trauma include simple forgetting, nonawareness, nondisclosure, and reporting biases due to mood states. Moreover, declarative biographical memory before the age of 5 years is sparse because the hippocampus is not fully developed. ELS itself leads to hippocampal damage, a brain structure relevant to declarative memory, which might impair recall of childhood experiences. However, a meta-analysis of studies using external corroboration of self-reports revealed that false-negative reports are more frequent than false-positive ones, leading to downward biases in estimated associations between ELS and outcome variables (Hardt & Rutter, 2004).

Taken together, it can be concluded that both the definition of ELS is complex and the estimation of its prevalence is hampered by methodological difficulties. Nevertheless, it can be stated that ELS, in its many forms, clearly is common enough in our society to represent a significant risk factor for the development of diseases later in life, such as depression and other disorders.

RELATIONSHIP BETWEEN EARLY-LIFE STRESS AND RISK FOR PSYCHIATRIC AND MEDICAL DISORDERS

An enormous body of literature from epidemiological, clinical, and twin studies provides strong evidence that ELS is one of the most potent risk factors that predisposes individuals to develop a wide range of psychiatric disorders and classical medical diseases throughout the life span. Given the high prevalence of ELS and the large effect sizes in the prediction of psychiatric and medical disorders, ELS is one of the most significant public health problems in our society. Of note, the association of ELS with disease risk seems to be nonspecific: for example, different types of ELS increase the risk for major depression (e.g., Maniglio, 2013), and conversely, similar types of ELS increase the risk for a wide variety of different disorders. It should be further noted that ELS-related disorders often occur in comorbidity with each other and manifest or aggravate in response to additional stresses (see, e.g., Martins et al., 2011), suggesting that ELS induces a core dysfunction, likely located in stress-regulatory systems, that is common across disorders related to ELS. In the following, we will selectively describe some of the seminal studies that confirm ELS as a major risk factor for psychiatric or medical disorders.

The aforementioned Adverse Childhood Experiences studies conducted by the CDC have provided particular strong data on the link between ELS and a range of adverse health outcomes in a large sample representative of the population. The aforementioned study by Edwards et al. (2003) not only suggested high prevalence rates of different types of ELS, but also showed that there was a clear dose–response relationship between degree of exposure and mental health problems in adulthood. A generally unstable family environment further

accentuated this relationship (Felitti et al., 1998). In terms of specific disorders, results from the same population suggest a 4-fold increase in the risk of depression as well as a dose–response relationship between the number of exposures to different types of ELS and the presence of a major depressive episode in the past year or lifetime chronic depression (Chapman et al., 2004). The experience of any ELS increased the risk of attempted suicide in childhood, adolescence or adulthood 2- to 5-fold; in persons who experienced 7 or more types of ELS, risk for attempting suicide was 31-fold increased (Dube et al., 2001). These CDC studies are in line with other epidemiological studies. For example, McCauley and colleagues (1997) recruited more than 1900 women from internal medicine practices and found that childhood sexual or physical abuse was associated with increases in symptoms of depression, anxiety, addiction, and suicide attempts. Findings of the National Comorbidity Survey (Molnar et al., 2001), the Ontario Health Survey (MacMillan et al., 2001), and a New Zealand community survey (Mullen, Martin, Anderson, Romans, & Herbison, 1996) have provided concordant findings. A role of ELS in the development of major depression, beyond genetic factors, has been confirmed in twin studies (Kendler et al., 2000; Nelson et al., 2002). In addition to maltreatment, parental loss due to death or separation is also associated with increased risk for depressive disorders (Agid et al., 1999). An adverse family environment characterized by poor paternal relationships or maternal overprotection is also associated with increased risk for depression (Lizardi et al., 1995). These selected studies illustrate the general association between various forms of ELS and later depression. In addition, a recent meta-analysis of 16 epidemiological studies suggests that ELS is also associated with a less favorable course in individuals suffering from major depression, as characterized by more recurrent and more chronic depressive episodes as well as a higher likelihood of treatment resistance (Nanni, Uher, & Danese, 2012).

While depression is probably the most extensively studied outcome of ELS, ELS is also associated with the development of various anxiety disorders in adulthood, including social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder (PTSD) (Chou, 2012). Depression and anxiety disorders in particular often coincide in individuals with ELS. The relationship between ELS and PTSD is more complex and can be direct or indirect. In the case of a direct relationship, the ELS experience itself represents the index trauma, to which the PTSD symptoms are related. PTSD related to ELS can then persist into adulthood and may be elicited or aggravated by other events (Pine & Cohen, 2002). Indirect relationships between ELS and PTSD occur in at least two ways: (1) ELS increases the risk of later trauma exposure that may, in turn, elicit PTSD (Sassetti, 1993); and (2) ELS increases the risk for the development of PTSD in response to traumas occurring in adulthood, such as combat (Bremner, Southwick, Johnson, Yehuda, & Charney, 1993).

Other psychiatric disorders that have been consistently linked to ELS include alcohol and substance abuse and dependence in adolescence and adulthood (Gilbert, Widom, Browne, Fergusson, Webb, & Janson, 2009), self-injurious behavior (Klonsky & Moyer, 2008; Yates, Carlson, & Egeland, 2008), eating disorders (Chou, 2012), bipolar disorder (Watson et al., 2013), and psychosis (Dvir, Denietolis, & Frazier, 2013). Personality disorders including borderline personality disorder are also more common after ELS (Ball & Links, 2009). Generally increased risk for psychiatric morbidity after ELS is further reflected in reports suggesting an increased frequency of psychiatric hospital admissions in individuals with ELS exposure (Chou, 2012; McCauley et al., 1997). It can be concluded that ELS is a potent developmental risk factor for psychiatric mental health problems that spans across nosological disease categories and reflects a core dysfunction that is common to these disorders.

Many medical health problems are also part of a spectrum of disorders linked to ELS. These include functional somatic disorders, such as chronic fatigue syndrome (Heim et al., 2006), fibromyalgia and other chronic pain syndromes (Imbierowicz & Egle, 2003), as well as functional gastrointestinal disorders (e.g., Goodwin & Stein, 2004). In addition, ELS promotes many of the illnesses that are leading causes of death in our society. These include ischemic heart disease (Dong et al., 2004), stroke (Felitti et al., 1998), metabolic syndrome and diabetes (Danese & McEwen, 2012), and lung disease (Felitti et al., 1998). In addition, ELS promotes autoimmune disorders, inflammation, and the progression of cancer (Danese & McEwen, 2012; Fagundes et al., 2012). The effect sizes are relatively large. For example, the risk for developing ischemic heart disease is increased by 360% after exposure to multiple types of ELS (Dong et al., 2004). Of note, depression in part mediates the association between ELS and heart disease and other medical diseases. In line with the notion that ELS is a significant risk factor for many illnesses that are the leading causes of death in our society, the Adverse Childhood Experiences Study of the CDC found that adults who reported 6 or more types of ELS experiences

died nearly 20 years earlier on average than those who did not report ELS, showing a detrimental impact of ELS on life expectancy (Brown et al., 2009).

The association between ELS and medical disease risk in adulthood is also in part mediated by a higher prevalence of health risk behaviors in individuals with ELS. These include smoking, inactivity, obesity, and promiscuity, resulting in higher prevalence of sexually transmitted disease (Felitti et al., 1998). In addition to these disorders and health risk behaviors, ELS further interferes with educational achievement and cognitive development, as evidenced in lower academic outcomes, poorer school performance, and more special educational needs (Shonkoff et al., 2012).

In sum, ELS is a major nonspecific risk factor for an array of psychiatric and medical disorders and health risk behaviors. These disorders often coincide and seem to share a common core dysfunction that may be programmed by experience early in life. This core dysfunction is likely located at the level of neurobiological systems mediating stress and emotion regulation. Upon further challenge (physical or emotional), the system may fail to adapt or compensate, leading to maladaptive responses in several physiological regulatory systems and behavior, which underlie the symptoms that reflect the clinical phenotypes of these disorders. This risk is then transmitted into the next generation, as children of mothers with ELS have increased rates of mental health problems (Beardslee, Gladstone, & O'Connor, 2011). A precise understanding of the psychobiological mechanisms that link ELS with this negative developmental trajectory is critical to identify modifiable targets for prevention and intervention.

NEUROBIOLOGICAL EFFECTS OF EARLY-LIFE STRESS

The enduring effects of ELS on disease risk is likely mediated by programming effects on stress neurobiological systems during periods of heightened plasticity throughout early development. Such developmental programming may lead to persistent changes in the set-point of stress response systems and the ability of the brain and organism to adapt or compensate in response to additional challenge, which ultimately might set the stage for the development of stress-related disorders. In the following, we provide an introduction to the neurobiology of stress, followed by a discussion on how ELS impacts on these systems in animal models and human studies.

Neurobiology of Stress

Two main outflow systems of the brain regulate the adaptation of the mammalian organism to stress, i.e., the sympathetic adrenomedullary system (SAM) as a component of the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. Both of these regulatory outflow systems are activated in response to stress, as a result of coordinated input from a neural network of brain regions implicated in the mediation and regulation of stress and emotion. We first describe the regulatory outflow systems, followed by a discussion of brain regions implicated in their control. We conclude this section with a discussion of neuroendocrine-immune interactions.

Sympathetic Adrenomedullary System

As early as in 1932, Walter Cannon suggested in his pioneering work that acute responses to threat involve the release of catecholamines and activation of the sympathetic nervous system, which serves to redistribute blood into muscles and to provide energy to the organism, while shutting down functions that are not instrumental for survival in this situation of threat, such as feeding, reproduction or sleep. This adaptive fight-or-flight response is evolutionary adaptive and serves to increase the likelihood of survival.

Anatomically, the cell bodies of the SAM are located in the interomediolateral cell column of the spinal cord. These sympathetic preganglionic neurons send axons from the spinal cord via the ventral route and form cholinergic direct synapses on the chromaffin cells of the medulla of the adrenal glands. When these chromaffin cells are stimulated, they release catecholamines in different proportions. Whereas stimulated chromaffin cells mainly secrete the hormone epinephrine (80%), smaller amounts of the hormone norepinephrine (20%) are released from the adrenomedullary neurons (Gunnar & Quevedo, 2007). Increases in epinephrine and norepinephrine ensure a rapid mobilization of metabolic resources and, hereby, enable the fight-or-flight response. More specifically, catecholamines, once secreted into the blood circulation, act on organs and tissues by binding to adrenergic receptors. As a consequence, for example, heart rate and pulmonary function are increased, blood vessels are constricted, and stomach, and upper intestinal actions are inhibited to slow down digestion. Further, glycogenolysis in the liver is stimulated leading to increases of glucose levels, which provide the energy for defensive responses. Even though the catecholamines epinephrine and norepinephrine do not

cross the blood–brain barrier, effects of these hormones are paralleled in the brain by norepinephrine production in the locus coeruleus. During stress, norepinephrine supports vigilance, arousal, and attention. Furthermore, norepinephrine in the CNS participates in the activation of the HPA axis (Gunnar & Quevedo, 2007).

Hypothalamic-Pituitary-Adrenal Axis

In addition to the fast-reacting SAM, the slower actions of the HPA axis are initiated as a consequence of internal or external stress experiences. This activation is mediated via ascending brain stem pathways that project to the parvocellular divisions of the paraventricular nucleus (PVN) of the hypothalamus. For example, the nucleus of the solitary tract (NTS) as well as C1-C3 regions project to the PVN via catecholaminergic connections. In addition, the PVN also receives input from the midbrain through serotonergic projections of the median raphé nuclei. The hippocampus and prefrontal cortex exert inhibitory influences on the hypothalamic PVN, via indirect connections (Ulrich-Lai & Herman, 2009). Upon stress, the secretion of corticotropin releasing hormone (CRH; also referred to as corticotropin-releasing factor [CRF]) and arginine vasopressin (AVP) is stimulated as a net result of these inputs from cells of the PVN. The axons of these neurons terminate in the median eminence onto small blood vessels, which is the site of neuroendocrine transmission, where a neuronal signal is translated into a hormone signal in blood. CRH and AVP are released into the portal circulation of the pituitary gland and reach the anterior pituitary corticotrophic cells, where they induce the secretion of adrenocorticotropic hormone (ACTH). ACTH stimulates the synthesis and release of glucocorticoids (corticosteroids in rats, cortisol in humans) from the adrenal gland into the blood circulation.

The release of glucocorticoids in response to stress serves to optimally adapt the organism to the change in demand, to ensure survival. Glucocorticoids exert important effects on the metabolism, by increasing blood sugar through gluconeogenesis and by breaking down proteins. With these actions, glucocorticoids make energy resources available to the organism. Glucocorticoids further have immune-regulating effects during stress. Importantly, glucocorticoids mediate negative feedback effects on their own release by binding to specific receptors at multiple levels of HPA axis control, including the hippocampus. Glucocorticoids also exert inhibitory feedback on locus coeruleus noradrenergic neurons, and hence serve as a stress brake into the brain to control endocrine, autonomic, and behavioral responses to stress.

The effects of glucocorticoids are dependent on specific receptors located in the cytoplasm of cells throughout body and brain. Upon activation, the hormone-receptor complex develops affinity for the nucleus, which induces translocation to the nucleus of the cell. In the nucleus, the activated glucocorticoid receptor (GR) binds to glucocorticoid response elements to regulate gene expression of various target genes. Because glucocorticoids act via the transcription of genes in the nuclei of cells, the effects of these hormones are slower and longer lasting than the fast actions of the SAM (e.g., Scheinman, Cogswell, Lofquist, & Baldwin, 1995). Essentially, there are two types of receptors to which glucocorticoids can bind, that is, the mineralocorticoid receptor (MR) and the GR (De Kloet, 1991). In the brain, glucocorticoids bind to both receptor types, whereas outside the brain, glucocorticoids solely act via GR. Important with regard to the regulation of the stress response is the fact that glucocorticoids have a higher affinity to bind to MR. Therefore, under nonstress conditions, when glucocorticoid levels are normal, mainly MR are activated, which serves to regulate basal functions such as maintaining the HPA axis circadian rhythm and maintaining homeostatic blood pressure. Upon acute stress, when glucocorticoids levels increase, GRs become involved to regulate the stress responses. As noted already, the activity of the HPA axis is subject to negative feedback mechanisms that are mediated via glucocorticoids. Here, limbic forebrain structures are critically involved in the inhibition of the HPA axis via GR and MR that are expressed in these sites. For example, the hippocampus is rich in both receptor types. The medial prefrontal cortex also expresses high levels GR; however, less expression of MRs can be observed, indicating the mPFC being less responsive to lower levels of glucocorticoids. Experiments in rodents show that deletion of the GR in the cortex, hippocampus, and the basolateral amygdala is associated with increased levels of basal glucocorticoids as well as persistent glucocorticoid responses to psychogenic stressors. In addition, these animals do not exert negative feedback inhibition of the HPA axis as a consequence of exogenous glucocorticoids (Boyle et al., 2005). In addition to these findings, the overexpression of GR in the forebrain has been linked to reduced HPA axis activity, supporting the assumption of the forebrain's role in the attenuation of the stress response (Wei et al., 2007; Wei et al., 2004).

It is important to note that the release of glucocorticoids during stress is highly adaptive and necessary for survival. However, under conditions of severe or chronic stress, overexposure of the brain to glucocorticoids can become toxic to neurons, leading to damage particularly in the

hippocampus, but also in the prefrontal cortex. Effects of heightened levels of glucocorticoids in the hippocampus include reduced excitability of cells, dendritic atrophy, and neuronal death particularly in the CA3 region, and decreased neurogenesis in the dentate gyrus (Lupien, McEwen, Gunnar, & Heim, 2009). These effects can lead to perpetuation where increasing damage to the hippocampus leads to further disinhibition of glucocorticoid release with further damaging effects to the brain, which may ultimately underlie the development of symptoms such as depression. Conversely, insufficient release of glucocorticoids may also have adverse effects due to lack of regulatory effects of the hormone on controlling central stress responses as well as immune activation in response to stress (Heim, Ehlert, & Hellhammer, 2000). Lack of glucocorticoid effects on the brain may also be observed if receptors for glucocorticoids become resistant in target cells (Raison & Miller, 2003). Hence, an optimal balance of glucocorticoid release during stress and a functional GR are essential for healthy adaptation to stress.

Corticocotropin-Releasing Hormone System: Integrator of Stress Responses

Corticotropin-releasing hormone neurons integrate information relevant to stress not only at the hypothalamic PVN, which forms the central component of the HPA axis, but also act in a widespread circuitry throughout the brain, including the neocortex, limbic regions, and brain stem. The 41-amino acid peptide is generally accepted to be the main CNS coordinator of the mammalian stress response, including behavioral, autonomic, immune, and endocrine components (Heim & Nemeroff, 2001). Injection of CRH directly into the brain of laboratory animals produces an integrated endocrine, autonomic, and behavioral response that closely parallels signs and symptoms of stress, depression, and anxiety. The behavioral effects of CRH include disruption of slow wave sleep, reduced reproductive behavior, reduced appetite, altered locomotor activity, increased startle response and facilitated fear conditioning as well as a behavioral despair syndrome in nonhuman primates. These global effects of CRH in integrating stress responses are possible due to the strategic localization of CRH neurons and their receptors in circuits linking the amygdala and the hypothalamus with brain stem nuclei.

There are two well-known CRH receptors, CRH-R1 and CRH-R2, distributed in the CNS. CRH-R1 deficient mice show a reduced hormonal stress response and blunted anxiety-like behaviors (Smith et al., 1998; Timpl et al., 1998). CRH-R2 deficient mice show exaggerated anxiety behaviors and are hypersensitive to stress (Bale et al., 2000; Coste et al., 2000). This would suggest that CRH-R1 is the primary CRH receptor mediating the stress response and CRH-R2 may help in modulating this response (Bale et al., 2002).

Microinjection studies in animals have shown that the behavioral effects of CRH are localized in an extrahypothalamic circuit, connecting the amygdala and hypothalamic PVN with the locus coeruleus in the brain stem. CRH and norepinephrine form a feedforward cascade in this circuit that integrates behavioral responses with endocrine and autonomic activation during stress. As noted before, glucocorticoids exert negative feedback effects on this circuit. Further inhibitory influences are exerted by gamma-amino-butyric-acid (GABA)-ergic neurons as well as oxytocin and neuropeptide Y (Arborelius, Owens, Plotsky, & Nemeroff, 1999; Heinrichs, Lapsansky, Lovenberg, De Souza, & Chalmers, 1997). Taken together, central nervous system (CNS) CRH neurons play a cardinal role as the main integrator of the behavioral, endocrine, and autonomic stress responses (Figure 21.1). Overproduction of CRH in these circuits, as a potential consequence of ELS, may conceivably produce sensitization to stress and vulnerability to depression and anxiety disorders.

Stress-Buffering Effects of Oxytocin

Early-life stress might also impact on neurobiological systems that are involved in buffering stress responses. Of particular relevance in this context is the neuropeptide oxytocin. Oxytocin is produced in magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus. It is transmitted to the posterior pituitary, from where it is released into circulation. Oxytocin is mostly recognized for its role as a peripheral hormone regulating parturition and lactation. However, oxytocin is additionally represented throughout the CNS where it affects a variety of neurobehavioral functions. In the brain, oxytocin serves as a neuropeptide transmitter with a critical role in mediating social cognition and prosocial behaviors. For instance, oxytocin has been demonstrated to promote pair bonding and maternal care behavior, mother–child bonding, trust, and the use of social support. In addition, oxytocin exerts anxiolytic effects, as it dampens amygdala reactivity, and exerts inhibitory effects on HPA axis responses to stress (e.g., Heinrichs, 2000; Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003). Because ELS oftentimes represents an adverse early social learning experience in the child's primary caretaker relationship, it may be hypothesized that ELS disrupts the optimal development of the brain's oxytocin system, which may then contribute to heightened stress reactivity

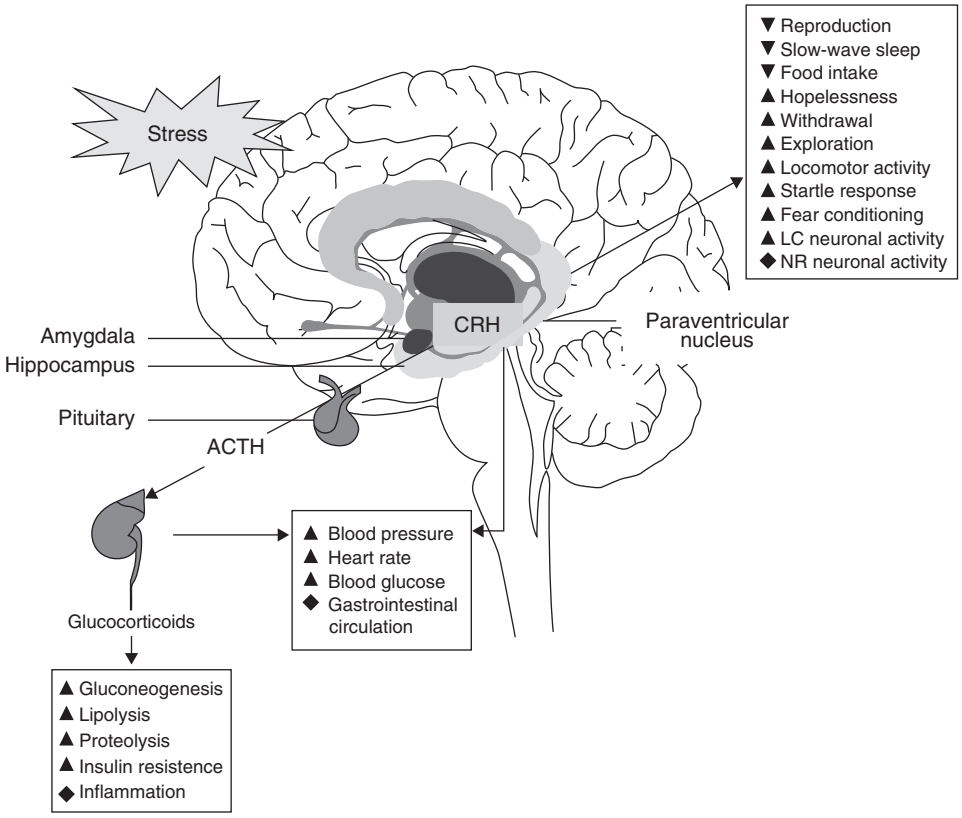


Figure 21.1 Central nervous system (CNS) corticotropin-releasing hormone (CRH) system and its effects in integrating endocrine, autonomic and behavioral responses to stress. Central effects of corticotropin releasing hormone. Symbols: ▲ = increase; ▼ = decrease; ◆ = bidirectional alterations. Abbreviations: ACTH = adrenocorticotropic hormone; CRH = corticotropin releasing hormone; LC = locus coeruleus; NR = nucleus raphé; PVN = paraventricular nucleus. *Source:* Adapted from L. Arborelius, M. J. Owens, P. M. Plotsky, & C. B. Nemeroff, The role of corticotropin-releasing factor in depression and anxiety disorders, *Journal of Endocrinology, 160*(1), p. 3, 1999.

as well as vulnerability for anxiety and depression. Deficits in oxytocin function may then also contribute to the transmission of ELS across generations, as oxytocin is critical for maternal behavior.

Brain Circuits Implicated in the Stress Responses

While systemic stressors and threats to homeostatic balance can readily induce a stress response at the hypothalamic and brain stem level, the response to psychological or emotional stressors requires appraisal and processing activities that involve higher brain regions. The activation of the HPA axis and a sympathetic stress response is the result of the interaction of a number of brain regions that exert influences on the regulatory outflow system.

As has been mentioned previously, brain stem nuclei as well as parts of the spinal cord are involved in the activation of the SAM and the HPA axis via several pathways. In addition to these ascending projections, several top-down processes are involved in tuning the stress response. Limbic forebrain structures, specifically the amygdala, the hippocampus, and the prefrontal cortex are involved in the processing of psychogenic stress. These limbic regions receive input from structures that are involved in higher order sensory processes (subcortical and cortical areas), memory (medial septum, entorhinal cortex, insular cortex), attention, and arousal (e.g., locus coeruleus, raphé nucleus). In turn, limbic structures project to subcortical relay sites and affect the HPA axis response (Ulrich-Lai & Herman, 2009).

Of special interest with regard to the modulation of the stress response is the central nucleus of the amygdala, which is critically involved in autonomic regulation and fear responses. In contrast to homeostatic perturbations and systemic stressors, the central nucleus of the amygdala is not directly activated by psychogenic stressors. However, studies indicate that lesions of the central nucleus of the amygdala impair bradycardic responses during psychosocial stress (Roozendaal, Koolhaas, & Bohus, 1990, 1991). On the other hand, the medial and basolateral amygdala are mainly activated in response to psychosocial stressors

and were shown to reduce HPA axis activation in the case of damage (Bhatnagar, Vining, & Denski, 2004; Dayas, Buller, & Day, 1999).

In addition to the amygdala, the hippocampus has been shown to be involved in the modulation of the HPA axis. Specifically, activation of the hippocampus is associated with a decreased glucocorticoid secretion in rodents as well as in humans (Dunn & Orr, 1984; Rubin, Mandell, & Crandall, 1966). Hippocampal lesions lead to increases in the release of glucocorticoids (Jacobson & Sapolsky, 1991), whereby effects of hippocampal damage appear to be especially prominent in the termination of the HPA axis response to stress. In addition, the hippocampus seems to affect autonomous responses indirectly via the medial prefrontal cortex as it does not directly connect to the brainstem. The stress response is further modulated by the medial prefrontal cortex, which has been linked to the inhibition of autonomous (Akana, Chu, Soriano, & Dallman, 2001) and HPA axis activity, again mainly affecting the termination of the HPA axis response (e.g., Radley, Arias, & Sawchenko, 2006). Overall, the PFC is assumed to constitute the top of the hierarchical stress response in terms of a limbic coordination of the stress response.

Intermediate connections transmit information from the medial prefrontal cortex, the amygdala, and the hippocampus to the PVN and the medulla. Here, excitatory (amygdala) as well as inhibitory (hippocampus) limbic information is integrated. In addition, the brain stem and the PVN receive ongoing homeostatic feedback, which in turn is translated into appropriate HPA axis and SAM activation.

As noted already, CRH, norepinephrine, serotonin, GABA, oxytocin and other transmitters interact in these neural circuits. Stimulatory influences are mediated by CRH and norepinephrine on the stress responses, whereas inhibitory influences are mediated by GABA-ergic neurons and oxytocin. Serotonin exerts modulatory effects on stress responses. Glucocorticoids exert regulatory effects on these brain regions, given that there is a broad distribution of GR in these regions. Neurostructural and functional changes in these brain regions after ELS, as a consequence of experience-dependent developmental programming or glucocorticoid overexposure, may contribute to the manifestation of stress vulnerability and certain mental disorders.

Stress and the Immune System

In addition to the HPA axis and the SAM, the immune system is another regulatory system that is activated in response to stress. Indeed, there are complex interactions between these regulatory systems. Immune activation stemming from the periphery can induce stress responses in the brain, leading to signs and symptoms of stress and depression. Conversely, psychosocial stress alone can activate inflammatory responses in the organism. Hence, the relationship between the brain and the immune system is bidirectional (Raison, Capuron, & Miller, 2006; Raison & Miller, 2003).

Typically, the innate immune system is activated by a peripheral injury or infection, leading to activation of nuclear factor kappa B (NFκB) through Toll-like receptors, which then leads to an inflammatory response with release of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukins 1 (IL-1) and 6 (IL-6). Of note, these cytokines can access the brain. Because these are large molecules, it has been discussed that access to the brain is possible through leaky regions in the blood–brain barrier, active transport molecules, or afferent nerve fibers. In the brain, cytokines impact on circuits implicated in stress responses and depression, including the monoaminergic neurotransmitters as well as the CNS CRH system. For example, administration of proinflammatory cytokines stimulates the HPA axis. In addition, proinflammatory cytokines have potent effects on synaptic plasticity through effects on growth factors, such as brain-derived neurotrophic factor (BDNF). Through such pathways, it can be explained that some individuals who suffer from infections develop a so-called sickness behavior that parallels depressive syndromes.

Conversely, exposure to psychosocial stressors can promote activation of inflammatory signaling via top-down influences. It has been suggested that sympathetic nervous system responses via release of norepinephrine stimulates the induction of NFκB, which then translates the stress signal into an inflammatory response. In addition, stressors also interfere with inhibitory motor vagal input. Accordingly, increases in proinflammatory cytokines have been observed in the periphery and in key brain sites implicated in stress regulation as a consequence of psychosocial stress in animal models (Madrigal et al., 2002; O'Connor et al., 2003). Studies in humans support these findings, as both, acute and chronic stress have been linked to increased concentrations of proinflammatory cytokines (e.g., Maes et al., 1999; Song et al., 1999). Increases in NFκB and inflammatory cytokines have been confirmed in humans in response to psychosocial laboratory stress (Bierhaus et al., 2003).

It is well known that glucocorticoids have suppressive effects on innate immunity. These suppressive effects are mediated by GR in immune cells. High levels of

inflammation in depression or stress-related states may be explained by the fact that the GR can become resistant. Of note, immune activation itself can contribute to the development of GR resistance through activation of protein kinase pathways, which would then lead to lack of inhibitory control of NFκB release by glucocorticoids during stress (Miller & Raison, 2006). It has been suggested that increased pro-inflammatory activity as a consequence of stress has an adaptive function as it allows a fast control of injuries and infections during periods of stress. However, increased innate immune activity as a consequence of stress might come at the prize of decreases in cellular and humoral acquired immune functions (Raison & Miller, 2003).

Given these complex interactions between stress pathways and the immune system, it can be assumed that ELS may also exert effects in immune function, which may contribute to elevated risk for certain immune-related disorders after ELS in humans.

Taken together, this section aimed to provide an overview of neurobiological systems that might be modified by ELS. In the following sections, we focus on the effects of ELS on these systems in animal models and human studies.

Summary of the Effects of Early-Life Stress on Neurobiological Systems in Animal Models

Numerous rodent and nonhuman primate studies have revealed a number of persistent neurobiological consequences of ELS (e.g., reviewed in Francis, Caldji, Champagne, Plotsky, & Meaney, 1999; Heim & Nemeroff, 2001; Kaufman, Plotsky, Nemeroff, & Charney, 2000; Ladd et al., 2000; Meaney, 2001). We here summarize selected results.

As early as the 1950s and 1960s, the pioneering work of Seymour Levine revealed that manipulation of neonatal rats, such as handling or mild shock, permanently alters behavior as well as corticosteroid responsiveness to later stressors (e.g., Levine, 1967; Levine, Chevalier, & Korchin, 1956). Levine's studies provided evidence that early handling, which involves brief separations (3–15 minutes) of pups from their mothers, improves developmental outcomes. More potent early stressors, such as maternal separation, which involves longer separations (3 or more hours) of pups from their mothers, have adverse effects on development. Maternal separation of rodents early in life is often used as a model of human parental neglect. Maternal separation in rats in the first 2 weeks of life has been found to result in heightened neuroendocrine and autonomic responses to stress as well as depression-like behavior (e.g., decreased preference for sucrose), anxiety (e.g., increased startle), alcohol preference, and cognitive impairment in adulthood. These changes that occur as a function of early maternal separation persist throughout life (Huot, Thrivikraman, Meaney, & Plotsky, 2001; Ladd et al., 2000). Similar changes have been observed in rats that were reared by mothers with naturally occurring low expression of maternal caregiving behavior (Meaney, 2001). In contrast, rats that were reared by mothers expressing high levels of care developed into adult rats with less anxiety and more stress resilience (Meaney, 2001). In fact, levels of maternal care are critical in mediating the positive effects of early handling: it has been shown that dams increase licking and grooming of rats that have been briefly handled (Barnett & Burn, 1967; Francis, Diorio, Liu, & Meaney, 1999).

These peripheral and behavioral changes that occur as a function of early environment occur due to changes in neural circuits that coordinate stress responses and behavior. Thus, maternal separation has been found to impact on several neurotransmitter systems, most notably central CNS CRH circuits. Maternal separation in rats results in increased CRH concentrations and increased CRH mRNA expression in the hypothalamus, locus coeruleus, and the amygdala (Plotsky et al., 2005). Further, maternal separation is associated with upregulation of CRH-R1 receptors in various brain regions and increased noradrenergic activity, which contribute to increased stress responsiveness (Plotsky et al., 2005). It should be noted that increased central CRH activity along with increased anxiety have been observed in a nonhuman primate model, in which infant macaques are exposed to a variable foraging demand condition that produces chronically stressed mothers which display decreased maternal care (Coplan et al., 1996).

Increased stress responsiveness might be mediated through impaired glucocorticoid feedback due to impaired glucocorticoid receptor function. Accordingly, decreased glucocorticoid receptor density and mRNA expression have been reported in the hippocampus and frontal cortex of rats exposed to maternal separation. Seminal studies by Meaney and coworkers have demonstrated the existence of direct epigenetic effects of variations in maternal care on a neuron-specific promoter region of the glucocorticoid receptor gene (Weaver et al., 2004). Specifically, altered cytosine-methylation of this gene has been documented as a function of early maternal care, leading to silencing of the gene and thus glucocorticoid resistance. Such early programming results in life-long effects on stress reactivity.

In addition, reduced neurogenesis has been observed in the hippocampus of maternally deprived rats, which might further contribute to disinhibition of the stress responses (Mirescu, Peters, & Gould, 2004). Other CNS changes reported after early maternal deprivation in rats include a decrease in 5-HT_{1B} receptor expression (Gutman & Nemeroff, 2002), decreased expression of $GABA_A$ receptors (Caldji, Francis, Sharma, Plotsky, & Meaney, 2000), and impaired dopamine transporter (DAT) expression (Meaney, Brake, & Gratton, 2002). Of note, early nurturing experiences also induce persistent changes in CNS oxytocin receptor expression in rats (Francis, Champagne, & Meaney, 2000). Nursery-reared rhesus monkeys exhibit decreased central oxytocin concentrations compared with mother-reared controls (Winslow, Noble, Lyons, Sterk, & Insel, 2003), suggesting that ELS in animals interferes with optimal development of the central oxytocin system.

Taken together, such preclinical studies provide unequivocal causal evidence that ELS induces a phenotype with multiple structural, functional, and epigenetic changes in brain regions implicated in stress and emotion regulation, which converge into increased physiological responsiveness to the environment and behavioral changes that are reminiscent of depression, anxiety, and substance abuse. These preclinical studies, which we selectively summarized here, served as an impetus for a large number of studies over the recent years that have investigated the neurobiological consequences of ELS in humans.

Neurobiological Effects of Early-Life Stress in Human Studies

Over the past two decades research has focused on whether findings on the effects of ELS in animal models can be transferred to humans.

Neuroendocrine and Autonomic Stress Responses

A number of studies have investigated whether ELS in humans is associated with persistent sensitization of the HPA axis and the autonomic nervous system to stress in adulthood. To test this hypothesis, our group (Heim et al., 2000) employed a standardized psychosocial stress protocol that consists of a public speaking and mental arithmetic task in front of an audience and which has been shown to reliably induce HPA axis and sympathetic activation (Kirschbaum, Pirke, & Hellhammer, 1993). This test was administered to 4 groups of women stratified by ELS and major depression. This design allowed for separating effects of ELS from correlates of Major Depressive Disorder (MDD). In remarkable parallel to results from animal models, women with a history of childhood abuse without and with current major depression exhibited increased ACTH responses to stress compared with controls. Net ACTH response was more than 6-fold greater in abused women with current major depression than in controls. These women also demonstrated increased cortisol and heart rate responses to psychosocial stress. Abused women who were not currently depressed exhibited normal cortisol responses, despite their increased ACTH response, perhaps suggesting adrenal adaptation to central sensitization as a marker of resilience against depression after early stress. Depressed women without abuse demonstrated normal neuroendocrine responses (Figure 21.2). These findings suggested that HPA axis and autonomic nervous system hyperreactivity, presumably due to CRH hypersecretion, may be a persistent consequence of ELS in humans that may contribute to the risk for psychopathology in adulthood. Of note, the effects of ELS were preserved when additionally controlling for adulthood traumas and major life events in the past year (Heim et al., 2002), suggesting that stress sensitization in these women indeed was secondary to ELS.

These findings were replicated in other studies. For example, Rao et al. (2008) showed in a sample of adolescents with major depression that ELS was associated with markedly elevated responses to psychosocial laboratory stress. However, there are also studies that report decreased HPA axis reactivity in adults with histories of ELS (e.g.Carpenter et al., 2007; Carpenter, Shattuck, Tyrka, Geracioti, & Price, 2011). It must be noted that the latter studies were conducted in a nonclinical sample. It therefore appears that HPA axis hyperactivity as a consequence of ELS might be most pronounced in those subjects who went on to develop depression, while individuals who remain resilient are able to downregulate the HPA axis. It is, therefore, plausible that ELS in interaction with genetic risk for depression produces HPA axis hyperactivity. Another factor that might play a role is exhaustion of the system due to continued chronic stressors after ELS. Hence, a study by Goldman-Mellor and colleagues (2012) revealed that subjects who experienced ELS and suffered from recurrent psychological distresses over time showed blunted cortisol reactivity to a laboratory stress task. In contrast, subjects with ELS but no further recurrent distresses exhibited elevated baseline cortisol, prolonged cortisol responses and increased total cortisol production (Goldman-Mellor, Hamer, & Steptoe, 2012). Generally, studies in children have also provided mixed results in terms of the direction of dysregulation of the HPA axis after maltreatment (see Cicchetti & Toth, 2005). However,

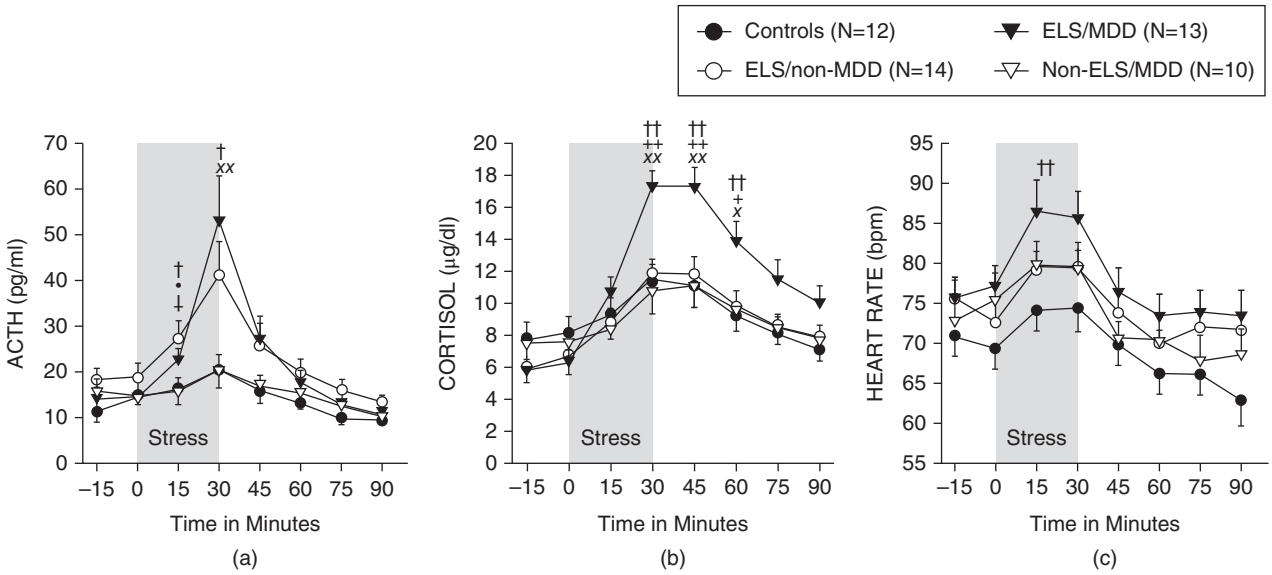


Figure 21.2 Sensitization to psychosocial laboratory stress in adult women with childhood abuse experience. *, $P<.05$ for controls vs ELS/non-MDD; †, $P<.05$ for controls vs ELS/MDD; ‡, $P<.05$ for ELS/non-MDD vs non-ELS/MDD; #, $P<.05$ for non-ELS/MDD vs ELS/MDD; +, $P<.05$ for ELS/non-MDD vs ELS/MDD; ††, $P<.01$ for controls vs ELS/MDD; ##, $P<.01$ for ELS/MDD vs non-ELS/MDD; ++, $P<.01$ for ELS/non-MDD vs ELS/MDD. *Source:* Adapted from Heim, C., Newport, D. J., Heit, S., Graham, Y. P., Wilcox, M., Bonsall, R., . . . Nemeroff, C. B. (2000), Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *Journal of the American Medical Association, 284*(5), p. 595.

these studies might be hampered by the fact that some of the children might still be living under adverse conditions. Taken together, additional studies are needed to identify the source of variability in the direction of HPA axis alterations after ELS in humans.

Pharmacological Challenge Tests of the HPA Axis

To identify changes in the dynamics of HPA axis regulation as a consequence of ELS, standard HPA axis challenge tests can be applied. Whereas psychosocial stress tests stimulate a stress response involving higher levels of cognitive and emotional processing, several neurotransmitter systems, and endogenous CRH release, the administration of a defined amount of synthetic CRH selectively stimulates ACTH release from the pituitary corticotrophs. Thus, the CRH stimulation test allows for an evaluation of the reactivity of the adenohypophysis to a defined amount of CRH. Changes in pituitary responsiveness to CRH stimulation may reflect CRH receptor changes on corticotrophs due to alterations in the activity of the PVN-median eminence CRH circuit. The administration of high doses of the biologically active $ACTH_{1-24}$ allows for the evaluation of the maximal responsiveness of the adrenal cortex (Heim & Ehlert, 1999).

In response to 1 g/kg ovine CRH stimulation, adult women with histories of ELS, who did not suffer from depression, exhibited increased ACTH responses, similar to their responses in the psychosocial stress test. In contrast, depressed women with and without histories of ELS exhibited blunted ACTH responses to CRH injection, which is a classic feature of major depression (Gold et al., 1984; Holsboer, von Bardeleben, Gerken, Stalla, & Muller, 1984). In response to 250 mg $ACTH_{1-24}$, women with histories of ELS, who did not suffer from depression, secreted less cortisol than controls and depressed women with or without ELS (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001). These findings can be interpreted as reflecting sensitization of the pituitary and counter-regulative adaptation of the adrenal gland as a consequence of ELS. This pattern might be a risk factor for the development of depression and HPA axis hyperactivity. Specifically, because cortisol has important regulatory effects on the central CRH and noradrenergic systems, it may be suggested that relative decreased availability of cortisol might facilitate disinhibition of central stress responses, when these women are exposed to further trauma or severe stress, eventually promoting the development of symptoms of depression through CRH effects in extra-hypothalamic circuits.

Such disinhibition of central stress response systems after ELS might be particularly expected if there were also changes in glucocorticoid-mediated feedback control of the

HPA axis. In other words, if receptors for glucocorticoids in the brain were relatively resistant, one would expect enhanced stress responses and risk for depressive behaviors. Therefore, consideration of glucocorticoid-mediated feedback under conditions of challenge might be particularly relevant to understand altered stress reactivity after ELS and its contribution to depression. The combined dexamethasone/CRH test was developed as a standardized test to assess the capability of the HPA axis to maintain feedback control under challenge. For this test, a high dose of dexamethasone is administered orally in the evening, which results in shutting down HPA axis; the next day, CRH is injected to simulate challenge. In healthy individuals, the HPA axis remains relatively contained in this test, reflecting functional negative feedback; however, in depressed patients, a characteristic escape of the HPA axis from suppression can be observed, reflecting impaired negative feedback inhibition of the HPA axis. The dexamethasone/CRH test is considered to be the most sensitive measure of HPA axis hyperactivity in depression (Heuser, Yassouridis, & Holsboer, 1994). The test further possesses sensitivity to detect familial risk in asymptomatic first-degree relatives of depressed patients (Holsboer, Lauer, Schreiber, & Krieg, 1995; Modell et al., 1998), serves as surrogate marker for treatment response (Ising et al., 2005), and varies with a polymorphism in the FKBP5 gene, a GR-regulating co-chaperone of hsp-90, which is also associated with recurrence of depression and antidepressant response (Binder et al., 2004). Our group sought to determine the effects of ELS on results in the dexamethasone/CRH test in adult men with and without current major depression. Men with ELS as a whole demonstrated markedly increased cortisol responses to dexamethasone/CRH administration when compared with men without ELS, reflecting escape of the HPA axis from inhibition. When stratifying groups by ELS and major depression, men with ELS and current major depression exhibited the highest degree of escape, whereas depressed men without ELS demonstrated normal HPA axis regulation. Indeed, increased response, or escape of the HPA axis from inhibition, was correlated with the severity of the abuse (Heim, Mletzko, Purselle, Musselman, & Nemeroff, 2008). These results suggest that ELS is associated with impaired glucocorticoid-mediated feedback control of the HPA axis during stimulated conditions in humans. The dexamethasone/CRH test appears to be sensitive to detect environmental risk secondary to ELS. Similar results have been reported for women with borderline personality disorder (Rinne et al., 2002), suggesting that escape after ELS occurs independent of sex. Of note, we also measured decreased GR sensitivity in mononuclear blood cells in individuals with ELS compared with healthy controls, further suggesting relative glucocorticoid resistance (Klengel et al., 2013). These results concur with reports that ELS in rodents and in humans is associated with reduced expression of hippocampal GR and with DNA methylation at a neuron-specific promoter site of the GR gene (McGowan et al., 2009; Weaver et al., 2004). These results further concur with findings of epigenetic changes in the FKBP5 gene after ELS in FKBP5 risk allele carriers, leading to increased FKBP5 expression, which is concordant with GR resistance (Klengel et al., 2013). Impaired glucocorticoid feedback due to GR resistance may plausibly contribute to increased stress reactivity and promote symptoms of depression (Pariante, 2004).

Central Corticotropin Releasing Hormone Activity

The findings of increased HPA axis responsiveness to psychosocial stress, blunted ACTH response to CRH challenge, and impaired glucocorticoid feedback as well as GR resistance in individuals with histories of ELS and current major depression are consistent with the notion that activation of the CNS CRH system should be increased after ELS in humans. To directly evaluate CNS CRH activity in humans, CRH concentrations can be measured in cerebrospinal fluid (CSF) obtained through lumbar puncture. Concentrations of CRH in CSF most likely reflect CRH activity in extra-hypothalamic circuits. Elevated CSF CRF concentrations have been repeatedly reported in patients with major depression (Hartline, Owens, & Nemeroff, 1996; Nemeroff et al., 1984; Widerlöv, Bissette, & Nemeroff, 1988). In post-mortem studies, increased CRH content or mRNA expression was found in the hypothalamic PVN, locus coeruleus and prefrontal cortex (Bissette, Klimek, Pan, Stockmeier, & Ordway, 2003; Merali et al., 2006; Raadsheer, Hoogendijk, Stam, Tilders, & Swaab, 1994; Raadsheer et al., 1995) of patients with major depression. Given the evidence from animal models, that CRH systems are hyperactive after ELS in rodents and nonhuman primates (Coplan et al., 1996; Plotsky et al., 2005). Carpenter et al. (2004) evaluated whether ELS contributes to CRH hyperactivity in depression in humans. These authors reported that levels of perceived preschool stress (around the age of 5 years) predicted CSF CRH concentrations, more so than a diagnosis of depression. Our group measured CSF CRH concentrations in women with and without histories of ELS. When classifying the women according to abuse type, women who had been physically abused demonstrated higher CSF CRH concentrations than women with no physical

abuse experience. Additional analyses showed that women who had experienced both sexual and physical abuse had particularly elevated CSF CRH concentrations compared with women with no abuse experience. Accordingly, CSF CRH concentrations were correlated with the severity and the duration of physical and sexual abuse in these women (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). It can be concluded that severe childhood abuse, in particular a combination of sexual and physical abuse, contributes to CNS CRH hyperactivity in adult women. Because of the widespread effects of CNS CRH systems in mediating endocrine, autonomic and behavioral responses to stress, it can be assumed that CNS CRH hyperactivity may contribute to stress vulnerability and depression risk after ELS in humans.

Oxytocin Activity

As noted already, the neuropeptide oxytocin has received considerable attention in preclinical and human research for its role in mediating social affiliation, mother–child attachment, social support, and trust (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005; Young & Wang, 2004). Oxytocin further has stress-protective effects and decreases amygdala reactivity in humans (Kirsch et al., 2005). Thus, the CNS oxytocin system may be profoundly impacted by disruption of the caretaker-child relationship during times of heightened plasticity, translating such experiences into stress vulnerability and disease risk. Early nurturing experiences induce persistent changes in the CNS oxytocin system in rodents and nonhuman primates (Francis et al., 2000; Winslow et al., 2003). Therefore, several studies have investigated potential changes in the CNS oxytocin system in humans as a function of ELS.

Indirect evidence for changes in central oxytocin function comes from a study by Seth Pollak and his group. Using a morphed face paradigm, in which children have to recognize and classify emotional expressions of ambiguous faces, maltreated children were less accurate in their emotion recognition and had a bias towards classifying ambiguous faces as angry (Pollak & Kistler, 2002). Although this study did not measure oxytocin levels, poor performance in similar tasks has been associated with oxytocin deficiency. Hence, a recent study in adults showed that intranasal oxytocin administration ameliorated the performance of women with histories of ELS in this task (Grimm et al., 2014).

Another study by Wismer Fries and colleagues (2005) measured urinary oxytocin excretion in children. Because it is unclear to what extent urinary oxytocin levels indeed do reflect CNS activity, this study used a behavioral paradigm consisting of a mother-child interaction task and compared increases in oxytocin excretion in response to the task between maltreated and nonmaltreated children. It can be reasonably assumed that the difference in the increase of oxytocin in response to this behavioral task reflects central oxytocin activation. The researchers observed that maltreated children activated their oxytocin system to a lesser degree in response to the task than nonmaltreated children, suggesting an early deficiency in the brain's oxytocin function after ELS (Wismer Fries, Ziegler, Kurian, Jacoris, & Pollak, 2005).

Measuring concentrations of oxytocin in CSF obtained by lumbar puncture is the only way to directly assess CNS oxytocin activity. Our group has measured CSF oxytocin concentrations in adult women with and without histories of ELS. Using validated cutoff scores for moderate-severe exposure across the five subscales for maltreatment (physical, sexual, emotional abuse; physical, emotional neglect) of the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003), we found a dose–response relationship between the number of maltreatment types that were met and the degree of decrease in CSF oxytocin levels. Emotional abuse was most predictive of decreased CSF oxytocin levels. There was an inverse relationship between CSF oxytocin concentrations and levels of anxiety in these women (Heim, Young, et al., 2009).

Taken together, these results support the hypothesis that ELS not only leads to hyperactivity of stress mediators such as CRH, but also interferes with the development of brain systems implicated in social attachment, which may then lead to decreased resilience against stress and anxiety. Indeed, the mechanism translating early social stress into vulnerability may not simply involve changes in stress-mediating systems, but a disturbed balance between stress-mediating and stress-protective neural systems.

Indicators of Inflammation after ELS

As noted before, the innate immune system can be activated by psychosocial stress, through autonomic inputs, leading to induction of NFκB and a proinflammatory cytokine response, which in turn impacts onto the brain, leading to further perpetuation of stress responses and neurostructural damage (Raison & Miller, 2006). The pattern of neurobiological changes after ELS, characterized by increased autonomic stress responsiveness and relative GR resistance, would be concordant with the presence of a state of inflammation after ELS. Of note, patients with depression exhibit marked increases in acute phase proteins, such as C-reactive (CRP) and in proinflammatory cytokines (Raison & Miller, 2006). Our group observed

that depressed adult men, many of whom reported high levels of ELS, exhibit markedly increased plasma levels of IL-6 in response to a psychosocial laboratory stressor, when compared with healthy controls. The increase in IL-6 after psychosocial stress was associated with increases in the induction of NFκB in these men (Pace et al., 2006). Of note, Carpenter and colleagues (2010) reported that ELS exposure was associated with increased IL-6 responses to psychosocial stress in a healthy adult sample.

Of particular relevance in elucidating the impact of ELS in inflammation are studies that have been conducted by Danese and colleagues in a longitudinal prospective birth cohort sample in Dunedin, New Zealand (Danese et al., 2008; Danese, Pariante, Caspi, Taylor, & Poulton, 2007). For this sample, which has been followed over 30 years, there is prospective information on maltreatment available. Danese and colleagues (2007) demonstrated that histories of child maltreatment were associated with pronounced systemic inflammation across the life span, as indicated by increased CRP levels above the clinical cutoff, increased fibrinogen levels, increased white blood cell counts, and an increased composite score of inflammation. The effect of ELS on inflammation was maintained when controlling for a large number of potential confounders, including lifestyle factors. A subsequent analysis by the same group revealed that elevated levels of systemic inflammation were particularly pronounced in those individuals with a history of maltreatment that also suffered from major depression (Danese et al., 2008). Another recent study reported elevated levels of adiponectin, an inflammation marker that is involved in modulating metabolic processes, in adults with histories of ELS (Lehto et al., 2012).

Such systemic inflammation appears to be present already in children exposed to maltreatment. Danese and McEwen (2012) showed in the Environmental Risk Study, conducted in the UK, that elevated levels of CRP were already measurable in maltreated children as young as 12 years of age. Similarly, children living in neighborhoods with high rates of crime and poverty exhibit increased CRP levels at an early age.

Taken together, available data suggest a strong link between ELS and inflammation. It is well conceivable that a chronic state of systemic inflammation starting in childhood can potently increase the risk for developing heart disease, stroke, metabolic problems, and other disorders related to inflammation across the life span. Effects of proinflammatory mediators on brain structure and function can plausibly contribute the development of depression and anxiety disorders after ELS. The role of neuroinflammation after ELS is an area that should be further investigated in future studies, as it might be a target for prevention.

Structural and Functional Brain Changes Following Early-Life Stress

Neuroendocrine and autonomic responses to psychological or emotional stress underlie a complex network of brain regions that influence the hypothalamus and brain stem nuclei that regulate outflow systems (Ulrich-Lai & Herman, 2009). This network includes the hippocampus, the amygdala and the prefrontal cortex as well as the anterior cingulate cortex (ACC). The fact that ELS is associated with hyperactivity of the CNS CRH system, resulting in exaggerated cortisol secretion upon additional stress, suggests that the primary lesion after ELS might be located at the neural systems level and may involve failure of these circuits to compensate or adapt to challenge, leading to maladaptive responses. The brain regions involved in the regulation of stress and emotion exhibit substantial developmental plasticity as a function of experience. In addition, these regions exhibit a high density of GR and are therefore particularly vulnerable to the effects of stress or excessive glucocorticoid release. Accordingly, patients with depression, PTSD, and other psychiatric disorders exhibit marked structural and functional changes in these circuits (Mayberg, 2003). Animal models have provided the causal evidence that ELS induces altered development of brain regions involved in stress processing and emotion regulation, and these changes converge into heightened physiological responsiveness to subsequent stress and depression- and anxiety-like behavior (Meaney, 2001). It is conceivable that ELS in humans might be associated with structural and functional brain changes, contributing to stress vulnerability and risk for disorders. In the following, we will provide an overview of this rapidly growing field of research.

Hippocampus

The hippocampus is an essential component in the neural network mediating stress responses. It exerts important inhibitory regulation of the HPA axis and plays a critical role in contextual aspects of fear conditioning. Moreover, the hippocampus is one of the most plastic regions within the CNS, with a high degree of synaptic plasticity and neurogenesis occurring in adulthood. The hippocampus has a high density of GR and is therefore particularly vulnerable to the effects of stress. A large number of experimental animal and human studies have shown that stress or prolonged exposure to glucocorticoids affect the

hippocampus, resulting in decreased neuronal excitability, dendritic atrophy and apoptosis particularly in the CA3 region, and decreased neurogenesis in the dentate gyrus (Lee, Jarome, Li, Kim, & Helmstetter, 2009). Therefore, the hippocampus has been the subject of intense inquiry in relation to stress, including ELS. In the following, we will provide an overview of studies that investigated the impact of ELS on the hippocampus in adult and in child samples.

Several studies consistently report a smaller hippocampal volume in adults with histories of ELS compared with adults with no such histories (Vermetten, Schmahl, Lindner, Loewenstein, & Bremner, 2006; Woon & Hedges, 2008). For example, adult survivors of severe childhood abuse had a 12% smaller left hippocampus volume compared with adults with no history of maltreatment (Bremner et al., 1997). Sexual abuse has also been seen associated with reduced left hippocampal volume (Stein, Koverola, Hanna, Torchia, & McClarty, 1997). In a recent study with a sample of 148 healthy participants, high CTQ scores were associated with reduced grey matter volume in the hippocampus (Dannlowski et al., 2012). Our group has investigated the contribution of ELS to hippocampal volume loss in major depression. By stratifying depressed women into those with and those without histories of ELS, we demonstrated that hippocampal volume reduction was limited to those depressed patients who were exposed to ELS, whereas depressed women without ELS exhibited normal hippocampal volume (Vythilingam et al., 2002). This result was in remarkable parallel to neuroendocrine findings and suggests that MDD in the context of ELS has a distinct pathophysiology with changes in stress-mediating systems that likely reflect risk to develop depression in response to stress (Heim et al., 2004). Accordingly, Frodl and colleagues (2010) report reduced left hippocampal volume in patients with major depression and a history of emotional neglect compared with those depressed patients who have not suffered from ELS (Frodl, Reinhold, Koutsouleris, Reiser, & Meisenzahl, 2010). To date, most of the studies measured whole hippocampal volume; however, different subfields within the hippocampus are known to differ in terms of their sensitivity to stress and their role in regulating the neuroendocrine stress response. Therefore, it is crucial to use high-resolution imaging methods to investigate region-specific effects of ELS. Notably, using high-resolution hippocampal imaging, Teicher and colleagues (2012) reported that childhood maltreatment was strongly associated with a reduction of more than 4% particularly in the CA3 region, the dentate gyrus and the left subiculum. Hence, volume loss as a function of the severity of ELS indeed occurred precisely in the subfields, which are particularly sensitive to stress and glucocorticoids (Teicher, Anderson, & Polcari, 2012).

Whereas it is a consistent finding that ELS is associated with smaller hippocampal volumes in adults, studies in children are rare and less clear in showing effects of ELS on the hippocampus (Tottenham & Sheridan, 2009). De Bellis and colleagues (2001) did not find adversity-related differences in hippocampal volume and no differences in volume changes over a period of two years in maltreated children (De Bellis, Hall, Boring, Frustaci, & Moritz, 2001). Lupien and colleagues (2011) compared children exposed to maternal depressive symptomatology since birth with control children raised by mothers without psychiatric symptomatology and could not detect changes in hippocampal volume. Whereas the majority of studies in child samples did not report any changes in hippocampal volume as a consequence of ELS, one longitudinal study in children, unfortunately conducted without a control group, found a link between the severity of ELS and a decrease of hippocampal volume over time (Carrion, Weems, & Reiss, 2007). A recent longitudinal study in 3–5-year-old children showed that stress levels early in life appeared to predict the left smaller hippocampal volume in childhood when the participants were between 7 and 12 years old (Pagliaccio et al., 2014). The most profound effects were detected in CA2/3 and CA4/dentate gyrus subfields. Moreover, genetic factors moderated this link. Interestingly, in contrast to the effects observed in adults, Tupler and De Bellis (2006) reported larger hippocampal volumes in a child population with PTSD following childhood abuse compared with healthy children.

To summarize, despite the numerous findings showing decreased hippocampal volume in adults reporting ELS, the evidence of differences in hippocampal volume in children caused by ELS is less consistent. These inconsistencies may be explained by the timing of the measurement. According to the neurotoxicity hypothesis one might argue that detrimental effects of ELS on the hippocampus may emerge over the course of life, indicating accumulating effects of repeated or prolonged overexposure to glucocorticoids or inflammatory mediators over time, which then lead to small hippocampal volume and risk for depression in adulthood (Lupien et al., 2009). To investigate the impact of ELS on morphometric development of the hippocampus over time, as well as the mediation of this impact by prolonged overexposure to glucocorticoids or inflammatory mediators, longitudinal neuroimaging studies, coupled with neurobiological assessments, starting in early childhood should be conducted.

Prefrontal Cortex and Cingulate Cortex

The prefrontal cortex (PFC) is of particular relevance in the study of the consequences of ELS. The PFC mediates executive functions and the regulation of goal-directed behavior and is further involved in the inhibition of impulses and emotional regulation. In particular, the medial PFC is relevant for emotional regulation, via connections with cingulate cortex and the amygdala. The PFC also exerts inhibitory actions via indirect pathways on the HPA axis (Ulrich-Lai & Herman, 2009). Small volumes of the PFC as well as reduced blood flow in medial PFC have been reported as features of major depression (Mayberg, 2003). It has further been suggested that reduced activation in the medial PFC during emotional challenge is a neural marker of depression risk (Goldapple et al., 2004). Similar findings have been reported for PTSD. In the following, we will discuss several studies that investigated the effects of ELS on the PFC.

A decreased volume of the PFC is a consistent finding in adults with histories of ELS. Tomoda and colleagues (2009) investigated the effects of harsh corporal punishment, which is a significant developmental stressor. They reported that harsh corporal punishment during childhood was associated with reduced gray matter volume in the left dorsolateral PFC and the right medial PFC later in life. Van Harmelen and colleagues (2010) reported that emotional maltreatment before the age of 16 was associated with decreased volume in left dorsal medial PFC when compared with a group composed of healthy controls and patients without a history of ELS. The anterior cingulate cortex, a frontal cortical region that is relevant to attention and emotional regulation, also seems to be reduced in volume after ELS in humans (Baker et al., 2012; Heim, Mayberg, Mletzko, Nemeroff, & Pruessner, 2013; Treadway et al., 2009).

Despite the consistent finding of decreased volume in prefrontal cortical regions relevant to emotion regulation in adults, findings in children are mixed. One study reports an association between ELS at age 7–10 years and a reduced frontal lobe asymmetry as well as decreased cerebral frontal volumes in these children (Richert, Carrion, Karchemskiy, & Reiss, 2006). Several studies in children investigated prefrontal structures in the context of PTSD. One study comparing children suffering from maltreatment-related PTSD to a healthy, nonmaltreated group did not find any differences in prefrontal volume (De Bellis et al., 1999). In contrast, in a later study, De Bellis and colleagues (2002) did report smaller prefrontal volume and white matter changes in the maltreated group. However, two recent studies also investigated PTSD and reported greater gray matter volume of the middle-inferior and ventral regions of the PFC related to PTSD in maltreated children (Carrion et al., 2009; Richert et al., 2006). Hanson and colleagues (2010) report significantly smaller volumes of the right orbital frontal cortex in children with histories of physical abuse in comparison to nonabused control children, which in turn predicted poorer social functioning.

To summarize, studies in adults consistently report decreased volumes in prefrontal cortical regions whereas studies in children show mixed findings. Factors that might account for this lack of consistency may include timing of ELS as well as developmental trajectories leading to structural damage over time.

Amygdala

In addition to changes in the hippocampus and the prefrontal cortex, research has also considered changes in the volume and reactivity of the amygdala associated with ELS. The amygdala is a small structure in the medial temporal lobe which plays a critical role in evaluating potentially threatening information, fear conditioning, emotional processing, and memory for emotional events (Phelps & LeDoux, 2005). The amygdala exerts stimulating effects on the HPA axis via indirect projections (Ulrich-Lai & Herman, 2009). It may be particularly vulnerable to the programming effects of early experience due to a high density of GR and a postnatal developmental trajectory characterized by growth and increasing connectivity until early adolescence (Uematsu et al., 2012). Animal studies have shown that psychological stressors, such as immobilization and the administration of stress hormones, lead to increased amygdala volume by stimulating dendritic arborization and the formation of new spines (Mitra, Jadhav, McEwen, Vyas, & Chattarji, 2005; Mitra & Sapolsky, 2008; Vyas, Pillai, & Chattarji, 2004). Patients with major depression demonstrate increased reactivity of the amygdala, whereas studies on volume changes in depression provided mixed results (Hamilton, Siemer, & Gotlib, 2008). Given these findings, it is of interest to evaluate structural and functional changes of the amygdala as a consequence of ELS in humans.

Studies investigating the effects of ELS on amygdala volume in humans have provided mixed findings. Of note, ELS was linked to reduced volume of the amygdala in patients with dissociative identity disorder or borderline personality disorder (Schmahl, Vermetten, Elzinga, & Douglas Bremner, 2003; Vermetten et al., 2006; Weniger, Lange, Sachsse, & Irle, 2009). Other studies have reported no differences in amygdala volume following ELS

(Andersen & Teicher, 2008; Bremner et al., 1997). Studies in children are equally inconsistent. According to Woon & Hedges (2008), children who developed PTSD secondary to childhood maltreatment did not differ from children without a history of maltreatment in terms of amygdala volume. However, some recent studies in children have reported findings concordant to studies in animals. For example, prolonged institutional rearing characterized by severe deprivation has been associated with greater amygdala volume in these children. Mehta and colleagues (2009) reported greater volume in 14 adopted adolescents who had experienced severe early deprivation in Romanian orphanages compared with a group of nondeprived, nonadopted UK controls. Tottenham and colleagues (2010) found similar changes in preadolescent children who had been adopted from an orphanage when older than 15 months when compared with nonadopted controls or to children adopted before the age of 15 months. The reported significant association between the age of adoption and volume increase in the amygdala suggests that early and extended exposure to institutional deprivation is likely to lead to an aberrant development of key structures in emotional regulation. Interestingly, increased amygdala volume as a consequence of ELS appears not to be reversible, which is in line with animal research (Lupien et al., 2009). Another study reported enlarged amygdala volume in children, who had been raised by chronically depressed mothers with sensitivity to the infant (Lupien et al., 2011). In the latter study, it was shown that amygdala volume predicted affective symptoms and aberrant emotional processing in these children.

Studies examining structural changes of the amygdala as a consequence of ELS are complemented by functional neuroimaging studies. Functional neuroimaging studies indicate that ELS is associated with hyperactivity of the amygdala in response to emotionally threatening stimuli (Dannlowski et al., 2012). This sensitization of the amygdala is also apparent in response to subliminally presented stimuli. Hence, Dannlowski and colleagues (2013) observed increased neural activation of the amygdala to subliminally presented sad facial expressions in a maltreated sample, indicating that ELS was strongly associated with detectable changes in amygdala function even at early subconscious stages of emotion processing. This limbic bias, which has been hypothesized to be a feature of major depression, was only present in depressed patients with a history of ELS. Hence, in a sample of unipolar depressed patients with and without a history of ELS, Grant and colleagues (2011) consistently found increased amygdala reactivity to aversive stimuli only in patients who had experienced abuse in childhood, whereas this dysfunctional pattern of limbic activation was absent in depressed patients without a history of ELS (Grant, Cannistraci, Hollon, Gore, & Shelton, 2011). A recent study by the same research group investigated the connectivity between the amygdala and prefrontal areas (Grant et al., 2014). Functional connectivity between the PFC and the amygdala is thought to underlie the cortical inhibition of amygdala output. In accordance with the aforementioned studies, ELS was associated with a failure of inhibition in the MDD group based on decreased connectivity between the medial PFC and the amygdala. Studies in children provide concordant findings. Tottenham and colleagues (2011) report increased bilateral amygdala activity in response to fearful faces in children with a history of institutional care. Maheu and colleagues (2010) report similar findings for institutionalized children. A recent study in children with and without depression reported that amygdala hyper-reactivity was associated with greater levels of life stress and trauma in these children, but was not generally related to psychopathology (Suzuki et al., 2014).

A seminal recent study by Burghy and colleagues (2012) used a prospective sample, following children from birth into young adulthood. Of note, impaired functional connectivity between prefrontal cortex and the amygdala in young adulthood was observed as a function of ELS and was best predicted by glucocorticoid levels of these children when they were 4.5 years old. This association was significant for girls but not for boys. These findings suggest the existence of sensitive periods and sex differences in the consequences of ELS, which will be discussed in more detail in the following section. In accordance with studies suggesting changes in functional connectivity between frontal cortical and limbic regions after ELS, studies using diffusion tensor imaging in children suggest reduced white matter integrity between frontal and temporal regions associated with early deprivation (Govindan, Behen, Helder, Makki, & Chugani, 2010).

Taken together, these findings provide convincing evidence that ELS is associated with increased reactivity of the amygdala in humans as well as reduced functional connectivity between the PFC and the amygdala, whereas results on structural changes of the amygdala after ELS are somewhat mixed. Increased reactivity of the amygdala and reduced connectivity likely indicate an aberrant neural circuitry with failure to compensate or adapt in response to challenge. Specifically, loss of top-down control of emotional responses may then lead to increased physiological stress responses and risk for affective disorders.

Corpus Callosum

Developmental programming by ELS also affects other brain regions, such as the corpus callosum (CC). The CC is the largest white matter structure in the brain that mediates communication between the two hemispheres. While nerve fiber connections of the CC are fully developed during the prenatal period, myelination continues across childhood and adolescence (Teicher et al., 2004), providing a basis to suggest that the CC is vulnerable to effects of ELS. The CC is relevant for hemispheric exchange of motor, sensory, and cognitive information between the brain hemispheres. Dysfunction of the CC has also been linked to alexithymia, which refers to emotional blunting and is often observed in trauma survivors. Few studies in adult samples focused on the association between the CC and ELS. Kitayama and colleagues (2007) reported a decreased volume in the posterior mid body of the CC in women who suffered from maltreatment-related PTSD. Using diffusion tensor imaging, Paul et al. (2008) found reduced neuronal integrity in the genu of the CC as a function of ELS, while total volume of the CC was unchanged.

Studies in children mostly focused on the morphometry of the CC and consistently found decreases in volume, which were most prominently shown in the middle and posterior part of the CC (De Bellis & Keshavan, 2003; Jackowski et al., 2008; Teicher et al., 2004). For example, Teicher and colleagues (2004) found that children who experienced abuse or neglect exhibited a 17% smaller total volume of the CC compared with controls who had never experienced any form of maltreatment and compared with children with psychiatric disorders without maltreatment exposure. Furthermore, preliminary evidence suggests that these effects depend on type of maltreatment and sex of the child.

Sensory Processing Areas

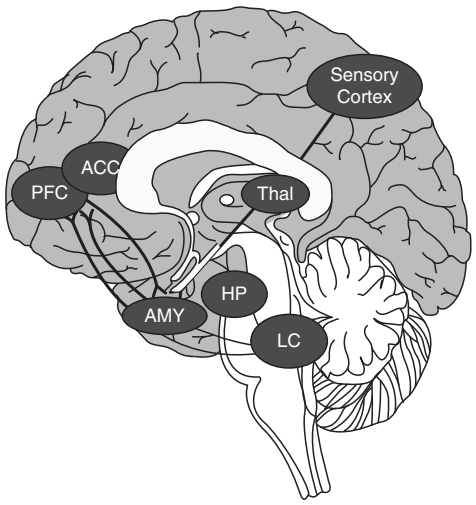
Recent studies also found experience-dependent alterations in sensory systems and pathways that process and convey the adverse experience. For example, exposure to parental verbal abuse has been shown to be specifically associated with alterations in the auditory cortex (Choi, Jeong, Rohan, Polcari, & Teicher, 2009; Tomoda et al., 2011). More specifically, Tomoda and colleagues (2011) reported a greater gray matter volume in the left superior temporal gyrus of verbally abused subjects. Besides this finding of aberrant auditory cortex development, a diffusion tensor imaging analysis revealed decreased fractional anisotropy in the arcuate fasciculus, reflecting reduced white matter tract integrity to be associated with parental verbal abuse. Interestingly, the arcuate fasciculus interconnects Wernike's and Broca's area, which play a key role in perception and processing of language. These findings suggest that the development of auditory association cortex as well as relevant pathways that process the adverse sensory inputs are likely to be modified in response to early exposure to emotionally abusive language.

Similar results were reported for witnessing domestic violence and alterations in the primary and secondary visual cortex. Tomoda and colleagues (2012) reported differences in the thickness of the lingual gyrus, occipital pole and V2 in individuals with a history of visually witnessing episodes of domestic violence. In addition, the same group of researchers also found a reduction in the integrity of the inferior longitudinal fasciculus interconnecting visual cortex to limbic system in adults who witnessed domestic violence during childhood (Tomoda, Polcari, Anderson, & Teicher, 2012).

Along the same lines, a recent study by our group (Heim et al., 2013) using whole mantle cortical thickness analysis found that exposure to childhood sexual abuse was specifically associated with pronounced cortical thinning of the somatosensory genital field, when controlling for all other forms of maltreatment, as measured using the CTQ. The effect was precisely localized in the coordinates that were identified as representing the female genitals using functional MRI studies (Michels, Mehnert, Boy, Schurch, & Kollias, 2010) Interestingly, emotional abuse was specifically associated with cortical thinning in the precuneus, a region that is relevant for self-awareness and self-evaluation, as well as thinning in the anterior cingulate cortex, which is relevant for emotional regulation.

Taken together, these findings suggest that experience-dependent plasticity leads to effects of ELS on sensory processing areas in a regionally highly specific manner, determined by the type of adverse experience. This suggests that certain forms of childhood abuse induce altered cortical representation of specifically those sensory and processing areas that are implicated in the adverse experience. We have suggested (Heim et al., 2013) that this specific cortical thinning in sensory and processing areas may represent the most adaptive and protective response of the developing brain that may shield the child living under these conditions from the abusive experience, similar to sensory gating. In later life, these neuroplastic changes may represent a direct biological substrate for behavioral disorders.

Taken together, a history of ELS is associated with marked structural and functional changes in brain regions that are critical to stress processing and emotional



Neural Changes after Early-Life Stress:

- Smaller hippocampus volume in adults
- Larger amygdala volume and reactivity
- Cortical thinning and/or volume loss in areas relevant for:
  - emotional processing and regulation (medial prefrontal cortex, anterior cingulate cortex)
  - sensory processing of the abuse
- Altered frontal-limbic connectivity (functional, structural)
- Smaller corpus callosum and decreased neural integrity
- Sensitized locus coeruleus in animal models

➛ ***Converging into stress sensitization and risk for emotional disorders***

Figure 21.3 Neural changes after early-life stress.

regulation (Figure 21.3). The hippocampus seems to be adversely affected in adults with history of ELS, but not in children, suggesting that hippocampal volume loss might occur over time as a function of glucocorticoid toxicity. In addition, children and adults show evidence for changes in frontal cortical regions as well as a hyper-reactive and hypertrophic amygdala. Changes in sensory processing areas implicated in the perception of the abusive experience may serve as a protective mechanism to shield the child living under abusive conditions. Finally, there is first evidence for deficient communication between various brain regions after ELS, as suggested by functional and structural connectivity studies. The concatenation of these findings suggests that ELS induces a dysfunction at the neural systems level, with failure of this network to compensate and adapt in response to challenge, which would converge into behavioral consequences and enhanced neuroendocrine and autonomic responses to stress. Longitudinal studies in children are needed to better understand the mechanisms involved in altering trajectories of brain development after ELS, which may allow insights into precise targets and time windows of plasticity that are amenable to intervention.

INDIVIDUAL DIFFERENCES IN THE EFFECTS OF EARLY-LIFE STRESS

The adverse consequences of ELS are highly variable across individuals. This outcome variability does not only apply to the specific disorder(s) an affected person might develop, but also to the fact that there is a high degree of resilience in many individuals exposed to ELS. Certainly, not all persons exposed to ELS will develop stress vulnerability and psychiatric or medical disorders. Indeed, a remarkable percentage of individuals exposed to substantial ELS remains resilient, even when exposed to additional stressors in adulthood. Therefore, it is important to consider factors that might contribute to such resilience. Understanding risk versus resilience factors in the consequences of ELS will allow us to develop diagnostic tests that identify cases at risk for disorders after ELS. If we understand mechanisms of resilience, we will be able to develop interventions to augment resilience in those individuals with ELS who are at risk for adverse outcomes. Several factors may contribute to the variability in the effects of ELS. These include timing of the ELS, sex/gender, genetic factors, and psychosocial factors. Timing of ELS is particularly relevant, as there might be defined developmental windows of plasticity during which a stressor may have a particularly strong or specific effect, depending on the developmental stage of brain regions at the time of exposure. In addition, sex/gender and genetic factors are dispositional factors that may interact with ELS in determining outcomes. Finally, psychosocial factors, such as availability of social support or personality traits, contribute to risk versus resilience after ELS. In the following, we will review the literature concerning individual variation in the outcomes of ELS.

Timing as a Critical Factor: Sensitive Periods for the Effects of Early-Life Stress?

Few clinical studies have revealed that there might be timing-dependent effects of ELS on depression risk.

For example, Maercker and colleagues (2004) reported that political traumatization before the age of 12 years was associated with risk for major depression in adulthood, whereas traumatization from 12 years throughout adolescence was associated with increased risk for PTSD (Maercker, Michael, Fehm, Becker, & Margraf, 2004). Similarly, a study by Agid et al. (1999) suggested that parental loss before 9 years of age was associated with higher depression risk compared with parental loss between 9 and 17 years of age. While these studies did not include biological measures, it is noteworthy that puberty starts around the age of 9 years and menarche is reached by around 12 years. Increasing sex steroid levels may have important implications for neural plasticity and endocrine stress responses (Blakemore, Burnett, & Dahl, 2010; Paus, Keshavan, & Giedd, 2008; Romeo & McEwen, 2006). Thus, research is needed that identifies and characterizes periods of sensitivity to the depression risk-inducing effects of ELS, by combining psychological and neurobiological outcome data.

Concept of Sensitive Periods

It is well known from developmental neuroscience that there are periods of increased plasticity of the brain throughout development. During such periods, experiences may have profound programming and organizing effects (for detailed discussion see Andersen & Teicher, 2008; Rice & Barone, 2000; Weiss & Wagner, 1998). Critical periods refer to time windows where expected experiences are necessary for a particular brain function to develop normally. Once the critical period is over and the experience was missing, the window of opportunity has closed. However, during such times of heightened plasticity, the brain may also be particularly sensitive to unexpected experience, opening a window for the destructive effects of negative/toxic experiences, or the beneficial effects of enriching experiences (see Weiss & Wagner, 1998). Thus, it has been suggested that sensitivity to the effects of ELS may depend on temporal and regional processes of neural development and function in brain regions that are relevant to emotional experience (see Andersen & Teicher, 2008; Andersen et al., 2008; Rice & Barone, 2000; Weiss & Wagner, 1998). To define sensitive periods for the effects of ELS in humans, it is therefore critical to consider developmental trajectories of these brain regions in humans.

Brain Maturation and Periods of Plasticity

Maturation rates and the extent of plasticity across development are highly variable for different brain regions, including those involved in the processing and regulation of stress and emotion (see, e.g., Dobbing & Sands, 1973; Lupien et al., 2009; Tau & Peterson, 2010). While the sequence of maturational events in brain development is similar across species, the time scales drastically differ (Rice & Barone, 2000); therefore, animal studies may have limited validity in elucidating sensitive periods for the effects of ELS in humans. Generally, in humans, there is extensive plasticity consisting of synaptic proliferation and a prolonged period of reduction of synapses and number of axons in the postnatal period. The surviving axons are covered with myelin to increase functional efficiency. Primary sensory and motor areas are myelinated by age 6; in limbic and cortical systems, myelination continues through adolescence into adulthood, perhaps providing the basis for emotional maturation (Benes, 1989). In terms of postnatal maturational refinement, there is high regional specificity: the hippocampus has the largest increase in volume during infant/toddler years and then steadily declines; the prefrontal cortex develops slower and demonstrates peaks in maturation and plasticity during adolescence, approximately between 8 and 15 years of age (Andersen & Teicher, 2008; Giedd et al., 2009; Lenroot & Giedd, 2006; Marsh, Gerber, & Peterson, 2008). In contrast, the female amygdala reaches its full volume early in life with no further volume increases observed between the ages of 4 and 18 years, whereas in boys amygdala growth is more prolonged and slower (Giedd et al., 1996). Such differences might give rise to sex differences in the neurobiological effects of ELS. Of note, with increasing maturation, structural and functional connectivity between brain regions increases. In rats, connectivity between the amygdala and prefrontal cortex continuously increases into early adulthood (Cunningham, Bhattacharyya, & Benes, 2002). In humans, frontal cortical input to control amygdala response to fear cues appears to increase from adolescence to adulthood (Yurgelun-Todd & Killgore, 2006). Adolescents show increased amygdala responses and decreased habituation to an emotional task, and failure to habituate to repeated stimuli is associated with less functional connectivity between ventral prefrontal cortex and amygdala (Yurgelun-Todd & Killgore, 2006). Adolescents compared with adults also use a differential prefrontal neural network to regulate autonomic response during laboratory stress (Strang, Pruessner, & Pollak, 2011). All of these brain regions are generally modified by early-life stress and have been implicated in depression risk (Mayberg, 2003) and control of neuroendocrine reactivity (Lupien et al., 2009). However, little is known regarding timing effects of ELS impacting on developmental trajectories of these brain regions and linking these effects to symptoms.

Role of Puberty

The processes contributing to brain plasticity around adolescence are modulated by gonadal hormones. Puberty starts around the age of 9 years in girls and somewhat later in boys. The hormonal changes that lead to the onset of puberty start as early as the age of 6 years. By the age of 12 years, most girls reach menarche. Estrogen and progesterone have marked effects on brain structure and function (McEwen, 2001). Gonadal hormones have been shown to influence CRH mRNA expression, HPA axis function, and synaptogenesis in the hippocampus (see McEwen, 2001). Of note, HPA axis responses during puberty are prolonged (Vazquez & Akil, 1993) and potentiated with repeated stressors (Girotti et al., 2006). Adolescents may be more vulnerable to the effects of glucocorticoids because of pronounced increases in GR expression in the PFC during this developmental stage (Pryce, 2008). The large degree of plasticity during puberty may reflect another sensitive window for the effects of adverse life events experienced in this development stage. In addition, the dynamic changes during puberty in stress response systems, brought about by the increases in sex steroids, might potentiate earlier programming of the HPA axis due to earlier life stress. For example, one might speculate that ELS programs glucocorticoid resistance and hence increased stress response that develops into a behavioral effect with full maturation and increased density of PFC GR during puberty. On the other hand, the high degree of plasticity during puberty may perhaps also open an opportunity for interventions to reverse effects or damage of insults during early life (see Romeo and McEwen, 2006). Hormonal changes associated with puberty are also related to brain development during adolescence, potentially giving rise to sex-specific effects of ELS. For example, estrogen levels are positively related to gray matter development in limbic regions specifically in female adolescents (for a review see Blakemore et al., 2010). Psychiatric disorders often manifest around puberty (Andersen & Teicher, 2008; Angold & Costello, 2006; Paus et al., 2008) and gonadal steroid effects on brain development, structure, and function may account for higher prevalence rates of depression in women compared with men (Young & Korszun, 2010). Taken together, complex interactions between neurodevelopmental stage, sex, gonadal steroid status, and HPA axis reactivity at the time of ELS exposure may contribute to the development of a vulnerable phenotype with risk for disorders, although the precise mechanisms are not well understood and require further study in humans.

Evidence for Sensitive Periods in the Effects of Early-Life Stress

Based on the before, it is conceivable that ELS experienced at different developmental stages may lead to differential neurobiological phenotypes with differential vulnerability to develop disorders across the life span, as a function of the relative plasticity of different brain regions and the effects of sex hormones. However, there are very few studies that have systematically evaluated neurobiological outcomes of ELS experienced at different developmental stages. Studies in rodents and nonhuman primates suggest that the direction of the effects of ELS on the CRH/HPA system depend on timing of the ELS (Coplan et al., 2006; van Oers, de Kloet, & Levine, 1998). Further of note are findings that early weaning of 21 day old rats causes faster myelination in the amygdala, decreased brain-derived neurotrophic factor protein levels in the hippocampus and prefrontal cortex, and reduced neurogenesis in the dentate gyrus (Kikusui & Mori, 2009). However, these studies cannot easily be generalized to humans.

There is limited evidence from human studies for age-dependent effects of ELS. Altered concentrations of dopamine–beta-hydroxylase, the rate limiting step in norepinephrine synthesis, were observed in children who were maltreated in the first 3 years of life, but not in children maltreated later in childhood (Rogeness & McClure, 1996). Differential effects of child abuse before versus after the age of 6 years on CSF CRH concentrations and cortisol response in the dexamethasone/CRH test were also reported (Heim, Mletzko, et al., 2008; Heim, Newport, et al., 2008). Carpenter et al. (2004) reported that preschool stress, but not later childhood stress, modulates adulthood CSF CRH levels. The same group reported that cortisol response to stress in adults decreases with increasing onset age of emotional abuse (Carpenter et al., 2009). Insight into sensitive periods in humans is also revealed through studies of previously institutionalized and adopted children. In a seminal work, Gunnar and colleagues (2007) report that adoption of previously institutionalized children who were adopted into families after the age of 24 months were more likely to develop behavioral problems when compared with children adopted into families before this specific age (Gunnar, van Dulmen, & International Adoption Project, 2007). Using an earlier age cut, Pollak and colleagues (2010) reported that previously institutionalized children who were adopted into families after 1 year of age had more neuropsychological difficulties than earlier adopted children. In a recent report, late compared with early adoption (based on median split) was associated with enlarged amygdala volume, emotional regulation difficulties, and increased anxiety in previously institutionalized children

(Tottenham et al., 2010). All of these studies point to potential sensitive periods for the effects of early-life stress on brain development and behavior, although earlier age at traumatization or deprivation might also reflect longer duration of stressful circumstances.

Of note, earlier stress may not be linearly linked to poorer outcomes, but there might be discrete periods of sensitivity based on regional brain plasticity at a given age. A seminal study by Andersen and colleagues (2008) was the first to provide important evidence for differential effects of ELS on regional brain volumes in 26 young adult women aged 18–22 years as a function of timing of sexual abuse experiences. Hippocampal volume was reduced in association with childhood sexual abuse experienced at ages 3–5 years and ages 11–13 years, whereas frontal cortex volume was attenuated in women with childhood sexual abuse experienced at ages 14–16 years. These results provided very important first support for the notion that timing of ELS is critical in inducing differential effects on brain development.

Pechtel and colleagues (2014) recently investigated sensitive periods in the effects of ELS on amygdala development. An increase in amygdala volume in young adulthood was most strongly associated with high levels of stress at the age of 10 and 11 years. Whereas the amygdala might be particularly sensitive to stress very early in life, as shown already, this finding points to the existence of another time window of vulnerability late in childhood (Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014). This is consistent with the developmental trajectory of the amygdala characterized by rapid initial growth followed by more sustained growth to peak volumes between 9 and 11 years when gradual pruning is taking over (Uematsu et al., 2012). Another recent study in young adults, using a prospective longitudinal design, suggested that changes in functional connectivity between the amygdala and prefrontal cortical regions as a function of ELS was best predicted by glucocorticoid levels at the age of 4.5 years, particularly in girls (Burghy et al., 2012).

Taken together, timing of exposure to ELS surely contributes to individual variability in the effects of ELS. Collapsing the assessment and quantification of ELS across childhood and adolescence (up to menarche or even up to the age of 18 years) as done in many retrospective studies, certainly fails to capture sensitive periods. The few existing studies that investigated timing of ELS in relation to neurobiological outcomes provide some evidence for sensitive periods for the effects of ELS in humans, although the time windows are not quite consistent within brain regions. Additional studies in larger samples are needed to study the effects of differential exposure ages on various neurobiological and clinical trajectories, ideally in longitudinal designs. Elucidation of these periods of plasticity will allow to define cases at risk for adverse outcomes and will allow for identifying time windows, during which given interventions might be maximally effective. For example, the effects of ELS in early childhood might be reversible during another plastic window in puberty.

Sex Differences in the Effects of Early-Life Stress

One important factor contributing to individual differences in the outcomes of ELS is sex or gender. The term ‘sex’ refers to biological differences between the sexes, whereas the term ‘gender’ describes differences that arise from different socialization or roles assigned to sexes. In the context of ELS, it is difficult to distinguish between sex and gender differences, as both biological dispositions related to sex as well as behaviors related to gender identity may contribute to outcomes of ELS. However, in the context of this chapter, we will discuss sex differences related to the neurobiology of ELS.

Sex differences in the outcomes of ELS may be related to 1) differences in the prevalence of ELS, or types of ELS, between girls and boys and 2) moderating effects of sex on the association of ELS with the risk for developing disorders later in life. In general, it must be noted that boys and girls overall have almost equal risk to be exposed to maltreatment according to the National Child Abuse and Neglect Data System. However, when differentiating between subtypes of maltreatment, boys may have a slightly higher risk to be exposed to physical abuse than girls (Edwards et al., 2003). On the other hand, girls are at higher risk to be exposed to sexual abuse than boys, according to data from the Child Welfare League of America. Hence, sex differences in the likelihood of being exposed to specific types of ELS may be one factor leading to differential risk of women and men for ELS-related disorders. It could be possible that higher rates of sexual abuse contribute to the well-known preponderance of women among patients suffering from depression and anxiety disorders (Gater et al., 1998; Kessler, 2003; Nolen-Hoeksema, 1987; Weissman & Klerman, 1977).

However, in addition to sex differences in the exposure to types of ELS, there are also moderating effects of sex in the response to ELS. Hence, sex interacts with ELS in predicting risk for various disorders. Specifically, it appears that women are at higher risk to develop depression and

anxiety disorders after ELS compared with men (Rind, Tromovitch, & Bauserman, 1998). For example, women with a history of ELS have a two-fold greater risk for developing PTSD than men with comparable experiences. Data from the National Comorbidity Survey confirm these results (Kessler, 2003). These data further suggest differential risk between men and women after ELS, with a higher risk for depression and anxiety disorders after ELS in women and a greater risk for substance use disorders after ELS in men.

Such sex differences in the strength of the association between ELS and risk for later disorders may be attributable to sex differences in the neurobiological responses to stress (see, e.g., Heim et al., 2008a; Heim et al., 2008b). Rodent studies suggest that females generally exhibit greater magnitude and duration of HPA axis responses to stress than males (Rhodes & Rubin, 1999), though findings in humans are not entirely consistent (Kudielka & Kirschbaum, 2005; Young, 1998). Sex differences in neuroendocrine stress responses have previously been attributed to direct effects of circulating estrogen on CRH neurons. For example, chronic estradiol treatment of ovariectomized rats enhances CRH mRNA expression in the PVN and increases ACTH/corticosterone responses to stress (Burgess & Handa, 1992; Swanson & Simmons, 1989). Short-term estradiol treatment of adult men induces increased ACTH, cortisol, and norepinephrine responses to psychosocial stress (Kirschbaum et al., 1996). Estrogen receptor mRNA has been localized in parvocellular CRH neurons of the PVN and there is evidence for an estrogen-responsive portion of the promoter region of the human CRH gene, which confers estrogen enhancement of CRH expression in CV-1 transfected cells (Vamvakopoulos & Chrousos, 1993). Sex steroids also interact with other neurotransmitter systems involved in the stress response, such as the serotonin system (Bethea, Mirkes, Su, & Michelson, 2002; Smith, Henderson, Abell, & Bethea, 2004). Progesterone has also been implicated in modulating these systems (Centeno et al., 2007).

However, sex differences in HPA axis responses to stress have now also been observed in humans, independent of acute gonadal steroid effects (Roca et al., 2005). Hence, other factors that might determine sex differences in the stress response therefore include genomic differences, organizational differences in brain structures or developmentally programmed effects of gonadal steroids (Kudielka & Kirschbaum, 2005; McEwen, 2001; Roca et al., 2005). Of note, sex steroids play a role in lifelong structural plasticity of several brain regions, including areas involved in stress responsiveness, i.e., the hippocampus and amygdala (McEwen, 2001). For example, it has been reported that estrogen levels in young women are correlated with gray matter volume in limbic regions (for an overview see Blakemore et al., 2010). Functional neuroimaging studies identified sex differences in the brain's response to fear stimuli (Schienle, Schafer, Stark, Walter, & Vaitl, 2005; Williams et al., 2005). Such processes may eventually converge into the basis of sex differences in the long-term neurobiological consequences of ELS that may translate into differential risk for psychopathology. Accordingly, female rhesus monkeys repeatedly separated from their mothers between 3 and 6 months of age exhibited increased cortisol responses to subsequent separation and flattened basal cortisol cycles at later ages; however, these changes were not observed in male macaques (Sanchez et al., 2005). Few studies in humans have systematically assessed sex differences in the neurobiological effects of ELS. Maltreated girls exhibit more dysregulation of the HPA axis than maltreated boys, even before puberty (Doom, Cicchetti, Rogosch, & Dackis, 2013). Of note is a recent longitudinal study that suggests that girls are more vulnerable than boys to exhibit impaired functional connectivity between PFC and limbic regions as a function of their cortisol levels at age 4.5 years (Burghy et al., 2012). A study by Buss and colleagues (2012) suggests that girls are more vulnerable to glucocorticoid levels of their mothers during mid gestation, with those girls exposed to high levels showing larger amygdala volumes and more affective symptoms at age 6–9 years; this association was not seen in boys. Scrutinizing the neurobiological basis of sex differences in the pathological effects of ELS will be an important area of future research. There is also emerging evidence for complex three-way interactions between sex, genotype, and ELS in predicting disease risk.

Gene–Environment Interaction in the Effects of Early-Life Stress

In addition to timing effects of ELS and sex differences, individual variation in genotype may interact with ELS to contribute to variability in clinical outcomes (see Heim & Binder, 2012, for review). Many of the disorders, for which ELS is a significant risk factor, have in part a heritable basis. For example, the overall heritability of major depression is estimated to be between 30 and 40%; however, this effect size also shows that environmental factors play a crucial role in this disorder. Of note, in a large meta-analysis of genome-wide association data for major

depression that included 5763 cases and 6901 controls, none of the tested polymorphisms reached genome-wide significance levels (Wray et al., 2012). These data suggest that major depression is likely not determined by main effect of genes, but rather by complex interactions of genes and environment, including ELS. While epidemiological and family data have long advocated the importance of gene–environment interactions in psychiatric disorders (Cadoret, Yates, Troughton, Woodworth, & Stewart, 1995; Kendler & Eaves, 1986), studies investigating these interactions on a molecular level have only been published since 2003. These studies have focused on candidate genes in neurobiological systems of known relevance to stress and emotion processing or neural plasticity. A rapidly growing number of studies have since documented an important role of gene–environment interactions in predicting the clinical outcomes of ELS. In addition to studying clinical outcomes, more recent studies have identified effects of gene–environment interactions on changes in neurobiological systems that mediate the link between ELS and a given clinical outcome, such as changes of the HPA axis or neural function, representing so-called intermediate phenotypes.

Serotonin Transporter Gene

The first study of a gene–environment interaction moderating the association between ELS and depression was published by Caspi and colleagues (2003). Using data from a prospective study of a representative birth cohort in Dunedin, New Zealand, it was shown that a common polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR), which is associated with altered transporter function, moderated the association between definite exposure to maltreatment and depression in adulthood. Specifically, carriers of one or two copies of the short allele (s/s or s/l) exhibited significantly more depressive symptoms, diagnosable depression, and suicide attempts in relation to ELS compared with individuals who were homozygous for the long allele (l/l). In the absence of ELS, this polymorphism had no effect on depression risk. Since the publication of this first finding, a surge of studies has attempted to replicate or extend the initial result. While the effect of the 5-HTTLPR in moderating the link between ELS and depression has been confirmed in a number of studies, including twin studies, there are also a number of negative studies that could not replicate the effect. While two early meta-analyses across studies suggested that the gene–environment interaction effect between 5-HTTLPR and ELS in the prediction of depression might not be valid (Munafo, Brown, & Hariri, 2008; Risch et al., 2009), a more recent meta-analysis of more available studies by Karg and colleagues (2011) confirmed a significant interaction effect between 5-HTTLPR allele status and ELS in the prediction of depression (Karg, Burmeister, Shedden, & Sen, 2011). Some of the inconsistencies across studies may be explained by the definition of the outcome variables. For instance, Uher and colleagues (2011) found that the interaction of 5-HTTLPR and ELS in the prediction of depression best predicts persistent depression, but not single episodes. Additional moderators, such as sex differences and ethnic background, also may contribute to further variability.

The 5-HTTLPR effect in moderating the link between ELS exposure and clinical outcome is not limited to the prediction of depression, but also impacts on other stress-related disorders and phenotypes, including PTSD, posttrauma suicide attempt, alcohol consumption, substance use, cigarette smoking, sleep disturbances, anxiety sensitivity, and impaired self-regulation of negative affect (see, e.g., Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Heim & Binder, 2012). Taken together, this would suggest that an interaction of 5-HTTLPR genotype and ELS moderates the susceptibility to a number of stress-related disorders, perhaps by determining the brain's response to stress or capacity for emotional regulation, particularly in circuits where serotonin serves as a transmitter to modulate these functions. Accordingly, neuroimaging studies have demonstrated an effect of the 5-HTTLPR genotype on amygdala reactivity as well as connectivity between the cingulate cortex and the amygdala (Hariri et al., 2005; Munafo et al., 2008; Pezawas et al., 2005). Interestingly, children carrying the s allele of the 5-HTTLPR show greater regional brain activation to sad movies compared with children carrying the long allele (Fortier et al., 2010). Hence, the reported decrease in function of the serotonin transporter in carriers of the s allele seems to lead to altered emotional brain activation pattern that might increase vulnerability to stress and the risk for a number of psychiatric disorders and medical diseases (Heim & Binder, 2012).

Corticotropin-Releasing Hormone Receptor Gene

In addition to the 5-HTTLPR, other genes involved in stress regulation have been studied as candidates in moderating the link between ELS and clinical outcomes. Given the importance of the CNS CRH system in mediating and integrating neuroendocrine, autonomic and behavioral responses to stress, and given the evidence that the CRH/HPA system is critically altered by ELS in animal models and human studies, variations in the gene that encodes for CRHR1, the receptor mediating

the stress-mediating effects of CRH, seem promising candidates for the investigation of gene–environment interactions in predicting the clinical outcomes of ELS.

In a first human study, our group demonstrated that polymorphisms in the CRHR1 gene interact with ELS, which was defined as sexual, physical, or emotional abuse, to predict adult depressive symptoms in an inner city African American sample of over 400 individuals (Bradley et al., 2008; Figure 21.4). We identified two protective CRHR1 haplotypes, which refer to a combination of polymorphisms. Individuals with high levels of ELS who were homozygous for the protective haplotypes had significantly less current depressive symptoms than abused individuals carrying other haplotype combinations. This finding has been replicated in additional cohorts with different ethnicities (Bradley et al., 2008; Polanczyk et al., 2009) as well as for a different type of ELS, namely physical neglect (Grabe et al., 2010); however, one study reported the effect of the CRHR1 haplotype in moderating depression risk after ELS only in African Americans, but not in European Americans (Kranzler et al., 2011).

It may be suggested that polymorphisms in the CRHR1 gene are associated with altered HPA axis responses to stress, which may then moderate the effects of ELS on HPA axis function. Accordingly, Tyrka and colleagues (2009) reported in healthy individuals that those exposed to ELS who carried the CRHR1 protective alleles showed a normal cortisol response to the dexamethasone/CRH test, whereas those individuals exposed to maltreatment who carried the risk alleles showed an escape from suppression in this test, indicating HPA axis hyperactivity. Notably, this effect of a genotypic variation in the CRHR1 receptor, that mediates CRH effects on the HPA axis, is not seen in the absence of ELS, indicating a gene–environment interaction at the neuroendocrine level. Our group (Heim, Bradley, et al., 2009) replicated and extended the aforementioned finding. We also observed an interaction effect between the CRHR1 protective haplotype and ELS in predicting cortisol responses to the dexamethasone/CRH test, with only risk allele carriers with ELS exhibiting escape from suppression. This effect was mainly present in male individuals who predominantly had experienced physical abuse, suggesting interactions between genes, sex, and type of abuse. Polymorphisms in the CRHR1 gene also interact in ELS to predict neuroticism (Deyoung et al., 2011). In nonhuman primates, it was shown that CRHR1 polymorphisms influence anxious temperament and metabolic activity in the hippocampus and amygdala. Taken together, the CRHR1 risk haplotype appears to be associated with increased CRHR1 signaling in neural circuits involved in stress and emotion processing, leading to a hyperactive HPA axis following exposure to ELS. However, the molecular mechanism for this effect is unknown (see Heim & Binder, 2012).

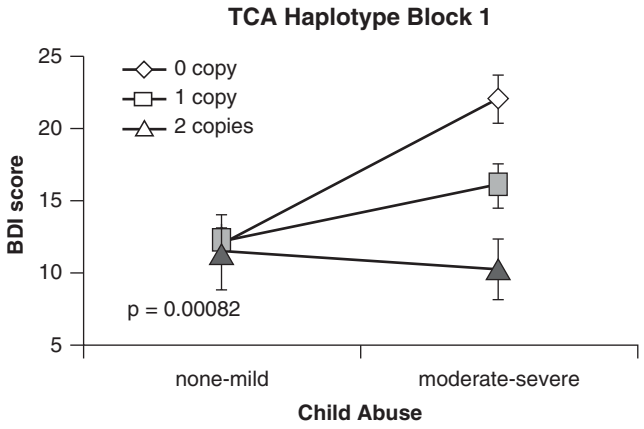


Figure 21.4 Example of a gene–environment interaction predicting depression risk after ELS. A protective TCA haplotype, formed by rs7209436, rs4792887, and rs110402, is associated with resilience against depression after ELS. *Source:* Adapted from R. G. Bradley, E. B. Binder, M. P. Epstein, Y, Tang, H. P. Nair, W. Liu, . . . K. J. Ressler, Influence of child abuse on adult depression: Moderation by the corticotropin-releasing hormone receptor gene, *Archives of General Psychiatry, 65*(2), 190–200, 2008.

Glucocorticoid Receptor and FK506 Binding Protein 5 Genes

A number of studies focus on candidate genes involved in feedback regulation of the CNS CRH system and the HPA axis. Given the well-established evidence that relative resistance of the GR contributes to HPA axis hyperactivity and risk for depression, especially after ELS exposure, several studies have investigated whether variations in the genes coding for GR as well as for co-chaperones of the GR, such as FK506 binding protein 5 (FKBP5), moderate the risk for developing depression or other affective disorders after ELS exposure.

In a longitudinal study of 906 elderly individuals, Bet and colleagues (2009) observed an interaction between GR polymorphisms 22/23EK and 9beta and ELS in predicting clinically relevant symptoms of depression. A larger number of studies have focused on the role of the FKBP5 gene in modulating the clinical outcomes of ELS. The FKBP5 gene codes for FKBP5, a co-chaperone of the GR, bound to hsp90, that fine-tunes GR sensitivity. Upon activation of the GR by cortisol, FKBP5 is removed from the hormone-receptor complex and replaced by FKBP4. The hormone-receptor complex develops affinity for the nucleus and trans-locates to the nucleus to bind to DNA.

Through binding to glucocorticoid response elements (GREs) in the FKBP5 gene, subsequent FKBP5 gene expression is increased, which binds to the GR and deactivates the GR. This mechanism represents an ultra-short feedback loop of GR activation and a molecular mechanism for increasing GR resistance (see Binder, 2009). A number of studies have shown that polymorphisms in the FKBP5 gene are associated with increased risk for depression and PTSD after ELS exposure (Binder et al., 2008; Luijk et al., 2010; Roy, Gorodetsky, Yuan, Goldman, & Enoch, 2010; Worthman, Kohrt, Ressler, & Binder, 2010; Xie et al., 2010; Zimmermann et al., 2009). It has been shown that polymorphisms in FKBP5 that are associated with increased risk for affective disorders after ELS disrupt the ultrashort negative feedback loop between FKBP5 and GR, leading to GR resistance and lack of feedback control of the HPA axis (Binder, 2009; Binder et al., 2008). Accordingly, FKBP5 risk allele carriers show a prolonged cortisol response to a psychosocial laboratory stressor (Ising et al., 2008). Taken together, these findings suggest that genetic variations interfering with feedback control of the stress response systems are associated with increased stress vulnerability and risk for developing psychiatric disorders after ELS. Compromised GR function as a result of gene–environment interactions may also plausibly contribute to inflammation and a range of physical diseases after ELS. Epigenetic mechanisms may be involved in the molecular mechanisms of gene–environment interactions regulating GR expression.

Other Candidate Genes

Other genes that have been studied as potential moderators of the link between ELS and clinical outcomes include genes involved in neuronal plasticity, such as brain-derived neurotrophic factor (BDNF), and stress protection, such as oxytocin receptor.

BDNF is a neurotrophin that is critically involved in neuronal plasticity, as it promotes the growth and differentiation of developing neurons in central and peripheral nervous systems. Synaptic atrophy and loss of dendrites in the hippocampus as a consequence of stress or glucocorticoid exposure is linked to reduced intracellular expression of BDNF. A common polymorphism in the BDNF gene (Val66Met) has been related to deficits in intracellular trafficking and the activity-dependent release of BDNF (Cardoner et al., 2013). Of note, Met allele carriers have a higher risk for depression after ELS compared with Val/Val allele carriers (Aguilera et al., 2009). In accordance with the role of BDNF as a neurotrophic factor, BDNF Met allele carriers, who were exposed to ELS, exhibited significantly less gray matter volume in the subgenual cingulate cortex compared with Met allele carriers without a history of ELS or Val/Val allele carriers. These findings are relevant given that the subgenual cingulate cortex plays a critical role in integrating emotional regulation between medial prefrontal cortex and limbic regions (Gerritsen et al., 2012).

As for the oxytocin receptor gene, it has been shown that carriers of the G/G alleles of the polymorphism rs53576 were overrepresented in a sample of patients with depression (Costa et al., 2009). The same polymorphism has been linked to modulating physiological stress reactivity (Rodrigues, Saslow, Garcia, John, & Keltner, 2009), making it an interesting candidate for investigating gene–environment interactions predicting clinical outcomes after ELS. Our group has shown that rs53576 in the oxytocin receptor gene interacts with ELS in the prediction of emotional dysregulation and attachment style later in life. Specifically, G/G allele carriers were at higher risk for developing emotional dysregulation difficulties compared with A/A and A/G allele carriers. Accordingly, Hostinar and colleagues (2014) found that maltreated children carrying the G/G allele genotype showed more internalizing symptoms than A/G or A/A allele carriers (Hostinar, Cicchetti, & Rogosch, 2014).

Of note, Bradley and colleagues (2014) reported that G/G allele carriers showed particular good health in the context of a supportive early family environment, suggesting that these genes are not *per se* risk genes, but rather reflect susceptibility to environmental influence, for better or worse. Hence, in the context of positive early environmental influences, these genes may confer plasticity leading to positive health outcomes and resilience (Bradley, Davis, Wingo, Mercer, & Ressler, 2013).

Further studies have investigated the potential importance of other genetic variants in moderating the effects of ELS. For example, the catechol-O-methyltransferase (COMT) gene interacts with ELS in predicting cognitive changes, emotion-elicited heart rate reactivity, and self-reported negativity, which are intermediate phenotypes for depression (Gatt et al., 2010b).

Defining the Environment

It should be noted that inconsistencies in results regarding gene–environment interactions may stem from different study designs that used different approaches to define the environmental exposure. For example, the original study by Bradley and colleagues (2008) identified a CRHR1 haplotype that moderates depression risk after ELS in a retrospective study of adults using the CTQ. Polanczyk

and colleagues (2009) were able to replicate this effect in another retrospective cohort in the UK using the CTQ, but failed to replicate the effect in the Dunedin cohort in New Zealand, which employed a mix of prospective and retrospective reports (not based on the CTQ). The authors speculate that the assessment method of ELS is critical in explaining inconsistencies. The CTQ may be more influenced by emotional memories and the CRHR1 haplotype might moderate recollection for traumatic events, which then might predict the development of emotional disorders. When we analyzed the same interaction effect of the CRHR1 gene and ELS exposure in the prediction of depression in an extended cohort of the original Bradley et al. (2008) sample, we observed that the interaction effect was carried by physical abuse, but not by sexual abuse (Heim, Bradley, et al., 2009). Because males experienced more physical abuse than females in our sample, this led to the appearance of a sex-gene-ELS interaction effect that suggested that CRHR1 moderated depression risk after ELS only in males. These examples illustrate the importance of precisely defining and measuring the exposure variables in gene–environment studies (Heim & Binder, 2012).

Multiple Genes and Environments

The rapidly increasing number of studies suggests that contributions to disorders related to ELS are more complex and go beyond single gene-single environment interactions (see Heim & Binder, 2012). As discussed previously, multiple studies have identified single candidate genes that moderated the link between ELS and depression or other disorders. These candidate genes were selected on the basis of their theoretical involvement in influencing stress responses and emotional regulation. Given the fact that multiple genes seem to play a role in predicting clinical outcomes after ELS, researchers have started to investigate several genes simultaneously, allowing for the elucidation of interactions between multiple genes and the environment in predicting clinical outcomes.

Several studies have now shown that there are complex interactions of multiple genes interacting with ELS in predicting clinical outcomes. Such interactions have been reported between 5-HTTLPR and polymorphisms in CRHR1, BDNF, and COMT in the prediction of depression (Aguilera et al., 2009; Conway, Hammen, Brennan, Lind, & Najman, 2010; Gatt, Nemeroff, et al., 2010; Gatt, Williams, et al., 2010; Kaufman et al., 2006; Ressler et al., 2010). For example, Ressler and colleagues (2010) reported that the 5-HTTLPR s allele appears to only increase risk for depression in carriers of CRHR1 risk haplotype. In addition, different types of environmental exposures can further moderate gene–environment interactions. For example, social support as well as general crime rate and unemployment rate have been shown to moderate the association between 5-HTTLPR and PTSD in victims of hurricane Kathrina (Kilpatrick et al., 2007; Koenen et al., 2009). In a sample of nearly 600 children, Cicchetti and Rogosch (2012) assessed polymorphisms in four genes, including 5-HTTLPR, CRHR1, dopamine receptor D4–521C/T, and oxytocin receptor, as well as maltreatment histories, and investigated gene–environment interaction effects in predicting resilient adaptive functioning in low-income children. Child maltreatment had a strong negative main effect on children's resilient functioning; however, no main effects for any of the genotypes were found. Gene–environment interactions were found for each of the assessed genotypes and child maltreatment in the prediction of resilient functioning. Across the four genes, a composite of the genotype had an effect on resilient functioning in nonmaltreated children, whereas genetic variation had a negligible effect on promoting resilience in maltreated children. It is likely that even more genes interact with even more environmental exposures to produce risk for a given disorder. Consequently, studying such multiple interactions will require large cohorts that provide sufficient power to detect effects (Heim & Binder, 2012).

Taken together, there is increasing and strong evidence for multiple gene-environment interactions in predicting clinical outcomes of ELS. It is noteworthy that main effects of genes are almost absent in the literature. Larger cohorts and consortia studies are needed to evaluate whether any of the candidate genes will remain a significant predictor when studying genome-wide effects on risk for disorders as a function of ELS. Such genome-wide association studies, that are hypothesis-free, may also identify novel genes that are important moderators of the link between ELS and a given disorder, leading to a novel understanding of the involved mechanisms.

Psychosocial Resilience Factors

In addition to the role of timing of ELS, sex differences, and individual genotypes in the prediction of clinical outcomes after ELS, several psychosocial factors and other environmental aspects moderate individual outcomes after ELS and can promote resilience. Oftentimes, ELS (i.e., maltreatment) occurs within the core family and the primary caregivers are the perpetrators. However, if available, an intact and positive bond between the child and one primary caregiver is probably the strongest psychosocial resilience factor (Wu et al., 2013). Furthermore, social

support from teachers and peers has been identified as a protective factor (Werner, 2012). Other factors that may augment resilience in the face of stress or trauma include positive affect and optimism (Folkman & Moskowitz, 2000), better overall physical health (Warner, Schwarzer, Schuz, Wurm, & Tesch-Romer, 2012), and higher IQ (Masten et al., 1999). In addition, the ability to reevaluate negative thoughts or situations, a skill also known as cognitive reappraisal, has been associated with resilience (Wu et al., 2013). With regard to coping, active coping styles such as behavioral and psychological strategies aiming at changing the quality or perception of the stressor are linked to greater adaptability and psychological resilience in comparison with avoidant coping styles characterized by emotional and behavioral withdrawal (Holahan & Moos, 1987). As mentioned before, a supportive social environment as well as support-seeking behavior is associated with resilient functioning even under circumstances of major adverse life events (Ozbay, Fitterling, Charney, & Southwick, 2008). Kaufman and colleagues (2006) reported that social support buffers the interaction effect of risk genes in combination with ELS on depression in maltreated children. More such studies are needed that investigate the influence of psychosocial resilience factors on clinical outcomes as a function of multiple interacting genetic and environmental risk factors, ideally in longitudinal designs.

Taken together, there is evidence that timing of ELS, sex differences, genetic makeup, and psychosocial resilience factors all contribute to individual variability in the clinical and neurobiological outcomes of ELS. Of note, gene–environment interactions may be subject to sensitive periods as well, as they may be relevant for developmental periods during which systems that use a particular neurotransmitter, such as serotonin, may be maximally plastic. Understanding the interplay and developmental trajectories of the effects of these various moderating factors may ultimately open novel strategies to develop predisease diagnostic tests that identify individuals with ELS who are at particular risk for developing a specific disorder or who might be responsive to a particular type of intervention. Understanding mechanisms of risk versus resilience after ELS will further identify modifiable targets for prevention and intervention of adverse clinical outcomes.

EPIGENETIC MECHANISMS OF THE EFFECTS OF EARLY-LIFE STRESS

As shown in the previous section, gene–environment interactions across a developmental trajectory with potential sensitive periods of plasticity produce neurobiological phenotypes with vulnerability to stress and risk for clinical disorders versus resilience. However, the molecular mechanisms that may underlie gene–environment interaction and their sensitivity to developmental timing are not well understood. In other words, how can social-emotional experiences between caretaker and child, such as maltreatment, interact with a stable DNA allele sequence to produce neurobiological changes that produces risk versus resilience to a range of disorders? In this context, epigenetic programming has been studied as a mechanism that may allow ELS to induce stable changes in gene regulation, leading to the long-term neurobiological consequences of ELS and risk for disorders. Such epigenetic programming may occur in dependence from risk allele status, thereby underlying gene–environment interactions in determining clinical outcomes (see Heim & Binder, 2012; Klengel et al., 2013).

Epigenetic programming refers to processes by which the environment regulates DNA transcriptional activity without altering the DNA sequence (Figure 21.5). Epigenetic changes are produced by DNA (de-) methylation, histone modifications, and noncoding RNAs (Jaenisch & Bird, 2003; Ptak & Petronis, 2010). Of these epigenetic processes, DNA (de-) methylation has been the most studied in relation to ELS. Specifically, DNA methylation refers to the addition of methyl groups to cytosines in cytosine-guanine (CpG) dinucleotides, which reduces the access of transcription factors to regulatory elements of the DNA, leading to transcriptional repression by decreasing the binding of specific transcriptional enhancers (Murgatroyd, Wu, Bockmuhl, & Spengler, 2010). Specific methyl CpG-binding domain (MBD) proteins bind to methylated DNA and interact with histone deactylases as well DNA methyltransferases to produce silencing of the gene and to stabilize DNA methylation status (Chen et al., 2003; Martinowich et al., 2003; Murgatroyd et al., 2009). Conversely, demethylation and removal of MBD proteins leads to increased gene activity (see Heim & Binder, 2012). Several studies in animal models and humans have now shown that ELS induces epigenetic alterations in stress-relevant genes that lead to changes in gene expression and, ultimately, a vulnerable neurobiological phenotype with increased risk for disorders.

In both rodents and humans, ELS has been associated with hypermethylation of DNA sequences in the gene encoding for the GR. In a rodent model, Weaver and colleagues (2004) observed increased DNA methylation in a neuron-specific promoter region of the GR gene in hippocampal tissue of offspring of mothers that exhibited

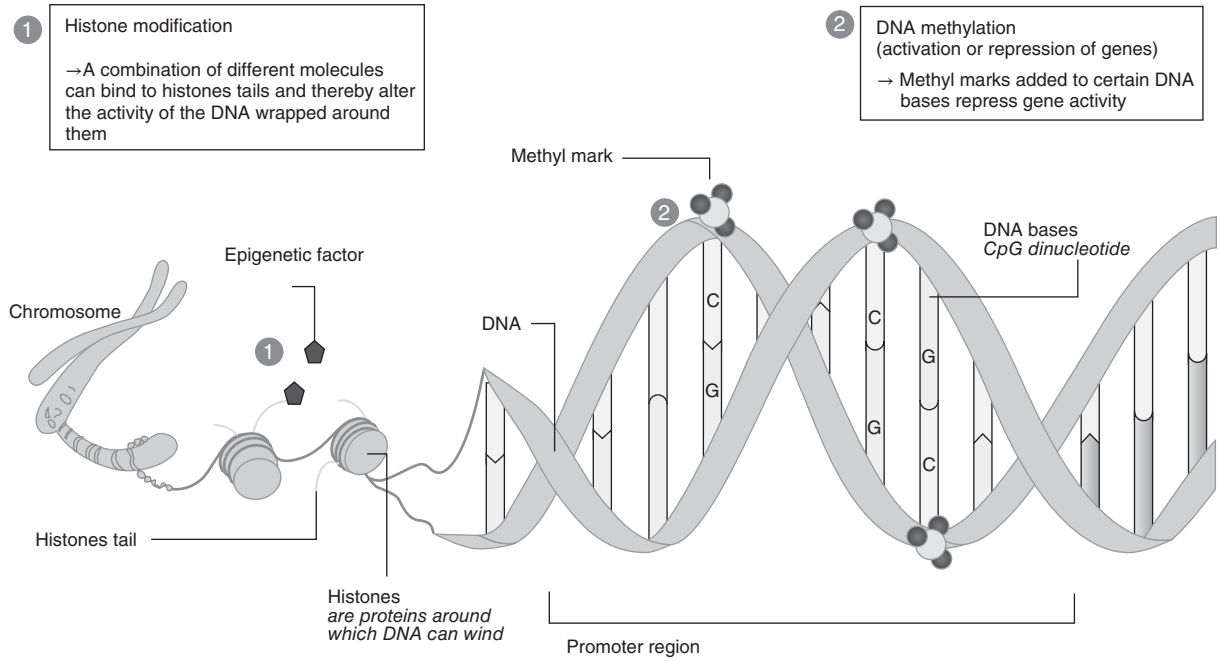


Figure 21.5 Principles of epigenetic programming. Two main epigenetic mechanisms involved in regulation of gene expression.

low maternal care behavior compared with offspring of mothers showing high maternal care behavior. This hypermethylation was associated with a decrease of NGFI-A transcription factor binding and decreased GR mRNA expression. In a postmortem study of suicide victims, reported histories of childhood abuse were associated with the same DNA hypermethylation in the GR gene in hippocampal tissue as well as decreases in NGFI-A binding and increases in GR mRNA expression (McGowan et al., 2009). Similar hypermethylation of the GR gene as a correlate of ELS was measured in leukocytes of healthy subjects (Tyrka, Price, Marsit, Walters, & Carpenter, 2012) as well as in patients with major depression or bipolar disorder (Perroud et al., 2014; Perroud et al., 2011). These findings of epigenetic silencing of the GR gene are in line with reports of long-term GR resistance and stress hormone system dysregulation following exposure to ELS.

Epigenetic changes have also been reported for other genes relevant to stress regulation in rodent models. Mice exposed to maternal separation exhibit hypomethylation of an enhancer region in the arginine vasopressin (AVP) locus, leading to increased binding of transcription factors and consequently an increase in AVP transcription and a lasting increase in AVP release (Murgatroyd et al., 2009). Similarly chronic social stress in adult animals has been shown to induce long-term hypomethylation in the promoter region of the gene encoding CRH, leading to an increase in CRH mRNA expression, but only in animals that display social avoidance (Elliott, Ezra-Nevo, Regev, Neufeld-Cohen, & Chen, 2010). Methylation changes have also been in the BDNF gene and were associated with altered BDNF mRNA expression in hippocampal and PFC tissue of rats exposed to stressed mothers who exhibited abusive behaviors (Roth, Lubin, Funk, & Sweatt, 2009). Whether these results translate to humans is unknown. Taken together, these results of epigenetic modification in CRH, AVP and BDNF genes are in line with dysregulation of the stress hormone system, neural changes, and risk for affective disorders after ELS.

These results focusing on methylation changes in single candidate genes were recently extended to investigate broader epigenetic changes. In rats exposed to low maternal care, altered methylation was reported for a larger region of the chromosome containing the GR gene, and within this larger region, the protocadherin gene family, which is implicated in synaptogenesis, showed the strongest association with exposure to low maternal care (McGowan et al., 2011). In humans, a genome-wide study of promoter methylation in hippocampal tissue of suicides revealed differential methylation of 362 genes in association with ELS, particularly genes involved in cellular or neural plasticity (Labonte et al., 2012). ELS-related differences in genome-wide methylation patterns are also seen in leukocytes from humans and are associated with changes

in gene expression (Mehta et al., 2013). Taken together, both, methylation and de-methylation of genes involved in regulating stress responses and neural plasticity have been reported as a consequence of ELS. The mechanism that underlies methylation changes might involve dissociation of MDB proteins from methylated DNA by phosphorylation, leading to removal of previously established DNA marks. Another potential mechanism involves glucocorticoid effects, as binding of GR to GREs in DNA leads to demethylation of CpGs around the GRE (see Heim & Binder, 2012).

A major advance in our understanding of the molecular mechanism mediating gene–environment interactions after ELS was recently provided by a seminal study by Klengel and colleagues that mapped a precise cascade of events that leads from ELS exposure to affective disorders via glucocorticoid-induced and genotype-directed epigenetic effects (Klengel et al., 2013). It was demonstrated in human leukocytes that a functional polymorphism altering chromatin interaction between the transcription start site and long range enhancers in the FKBP5 gene increases the risk of developing affective disorders in adulthood by allele-specific, ELS-dependent DNA demethylation in functional GREs of FKBP5. This demethylation was associated with increased stress-induced gene transcription and long-term dysregulation of the stress hormone system as well as a global impact on the function of immune cells and the structure of brain areas associated with stress regulation in risk allele carriers. Of note, FKBP5 demethylation in blood cells correlated with ELS, but not with current cortisol levels or adult trauma, suggesting that this epigenetic mark originated from childhood. To verify whether this finding that was obtained in peripheral leukocytes translates to neural cells and is indeed inducible by stress hormone elevations, in vitro experiments in human hippocampal progenitor cells were additionally performed. These experiments showed that a long-term demethylation of the same CpGs occurs after incubation of hippocampal progenitor cells with glucocorticoids, suggesting that human findings in leukocytes could extend to brain tissue and are dependent on GR activation. In addition, this demethylation was only seen in proliferating and differentiating neurons, but not in mature neurons, further evidencing that this epigenetic mark is a developmental event. Taken together, this study thus far provides the best evidence for a stress-induced molecular mechanism that translates ELS into risk for psychiatric disorders in genetically susceptible individuals. As the study clearly points to the existence of a sensitive period for this epigenetic effect, longitudinal studies in children are needed that map temporal trajectories of this molecular mechanism, which is essential for designing novel intervention strategies.

SUMMARY

We here provided a review of research concerning the relationship between exposure to adverse experiences during childhood and the risk for psychiatric disorders and medical diseases in later life. We have shown that ELS interacts with genetic factors to produce a neurobiological phenotype with changes in a connected circuitry of brain regions implicated in stress processing and emotion regulation. These changes likely lead to failure of this neural network to adapt or compensate in response to subsequent challenge, leading to exaggerated physiological responses to stress and failure of regulatory control, with impact on multiple organ systems and the immune system, as well as behavioral changes reminiscent of depression and anxiety disorders. The molecular mechanism that is at the core of the gene–environment interaction likely involves epigenetic programming of genes relevant to stress regulation with impact on gene expression, which ultimately underlies dysregulation of neurobiological stress systems and physiological and behavioral changes. Protective gene variants might not be susceptible to such programming. Psychosocial resilience factors and coping might buffer the effects of ELS through top-down regulation. There is reasonable foundation to believe that age at the time of ELS will critically interact with trajectories of brain regional development to produce variable outcomes (see Figure 21.6). These profound and stable changes induced by ELS are likely transmitted into the next generation.

FUTURE DIRECTIONS

While the here summarized research has provided major insights into the biological and molecular mechanisms that mediate the persistent effects of ELS on risk for a range of disorders, as well as the modification of this risk by gene–environment interactions, most human studies on the neurobiological effects of ELS are cross sectional or rely on retrospective self-reports of ELS in adult samples, not allowing for causal inferences. Cross sectional studies further do not allow for the identification of developmental trajectories of biological or behavioral changes over time, nor do they inform about sensitive periods for the effects of ELS. Available longitudinal studies in children were often started decades ago, and thus were not able

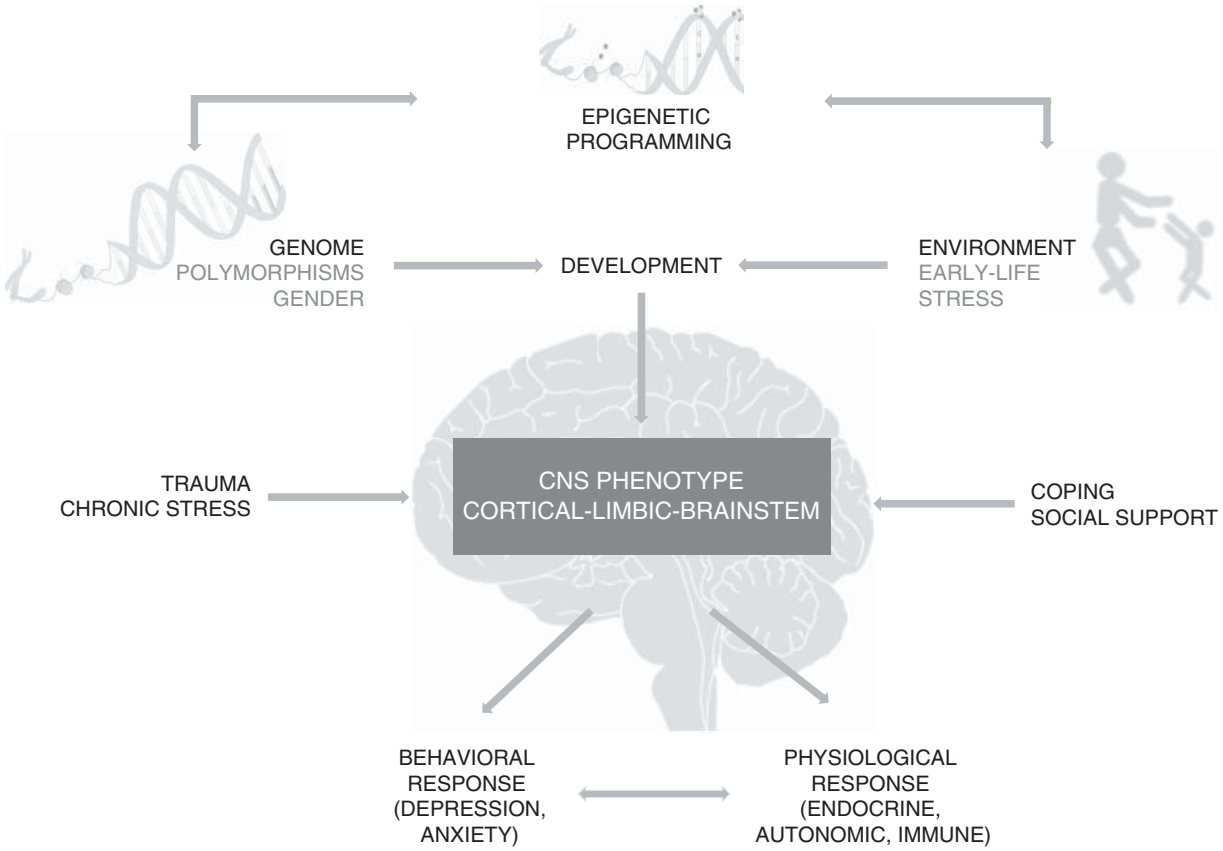


Figure 21.6 Vulnerability model. Genetic disposition and early-life stress interact via epigenetic programming to shape a vulnerable phenotype with changes in cortical–limbic–brainstem circuits. Upon additional stress or trauma exposure, maladaption in these circuits leads to increased endocrine–autonomic and behavioral–emotional responses. Social support and successful treatments may modify the stress responses system in different components. *Source:* Modified Ladd, C. O., Huot, R. L., Thrivikraman, K. V., Nemeroff, C. B., Meaney, M. J., & Plotsky, P. M. (2000). Long-term behavioral and neuroendocrine adaptations to adverse early experience. *Progress in Brain Research, 122*, 81–103.

to collect cutting-edge neurobiological or epigenetic data in the immediate aftermath of exposure to ELS or across development. Most studies, cross sectional or longitudinal, did not adopt a multisystem approach. Therefore, the implementation of longitudinal studies in children are urgently needed to understand the immediate processes of biological embedding of ELS over time, as well as their moderation by genotype, and that link these biological processes with symptom development. There is no doubt that ELS induces a fundamental change in stress systems at an early point in development, which programs these systems for life. Elucidating these immediate developmental events will provide insight into the early mechanisms that are responsible to produce this persistent and pronounced programming of stress systems and risk for stress-related disorders as well as its moderation by gene–environment interaction. In terms of gene–environment interactions after ELS and epigenetic embedding of ELS, genome-wide approaches will need to be applied, which will require large cohort studies.

TRANSLATIONAL IMPLICATIONS

There is a dire gap of translation between insights into the neurobiological and molecular mechanisms that link ELS exposure with long-term risk for clinical disorders and the use of this knowledge to develop new diagnostic markers and mechanism-based treatments. Understanding the precise mechanisms of biological embedding of ELS, as well as their moderation by genetic factors, will allow for the development of diagnostic markers that identify children at risk for developing psychopathological outcomes. In addition, such markers can identify children who might be susceptible to a specific intervention.

Precise knowledge of the mechanisms underlying the biological embedding of ELS will allow to develop completely novel and pathophysiology-based interventions that directly target these mechanisms to reverse or counteract biological changes after ELS and reduce or prevent disease risk. Understanding the temporal dynamics of biological embedding, including sensitive periods, may help to identify developmental time windows for specific interventions.

CONCLUSION

Taken together, the notion that ELS, in the context of genetic susceptibility, is a major risk factor for a range of disorders is widely accepted. Future research should elucidate the complex interplay of developmental trajectories, multiple genes, multiple environments, and molecular mechanisms in the relationship between ELS and clinical outcomes. Hopefully, such research will allow for designing novel and effective mechanism-based interventions that we can offer to children exposed to ELS, which might help reduce the adverse consequences of ELS and interrupt the transmission of ELS and its consequences across generations.

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CHAPTER 22

Psychophysiological Methods and Developmental Psychopathology

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Psychophysiological methods have been used throughout much of the history of modern psychopathology research. Measures of basal skin resistance were first used over 125 years ago in the laboratory of French neurologist Jean Charcot by Vigouroux (1879, 1888), who assessed differences in physiological arousal among various clinical groups. In 1904, Carl Jung reported a positive association between emotional responding to word stimuli and electrodermal reactivity (see Neumann & Blanton, 1970), foreshadowing later work linking skin conductance to state anxiety (e.g., Katkin, 1965). Soon thereafter, Eppinger and Hess (1910/1915) noted abnormally low resting heart rate among delinquents, a discovery that garnered considerable attention in the psychopathology literature for much of the next 100 years (see Lorber, 2004).

Psychophysiological research continues to burgeon in the 21st century. At present, two top-tier scientific journals (*Psychophysiology* and the *International Journal of Psychophysiology*) are devoted exclusively to measurement, assessment, and neurobiological mechanisms of psychophysiological phenomena. Many articles published in these journals address psychophysiological correlates of mental illness. Use of psychophysiological methods is also now common among those who publish in mainstream psychopathology journals.

Despite this popularity, psychophysiology has no universal definition. Although often considered a discipline in its own right (see, e.g., Berntson, Cacioppo, & Sarter, 2002), psychophysiology encompasses studies of phenomena that

[1]Color versions of Figure 22.9 is available at http://onlinelibrary.wiley.com/book/10.1002/9781119125556

cut across many areas of behavioral science, including health psychology (e.g., hypertension, insomnia; see Stoney & Lentino, 2000; Steptoe, 2007), forensic psychology (e.g., lie detection; see Iacono, 2007), social psychology (e.g., threat appraisal; see Tomaka, Blascovich, Kelsey, & Leitten, 1993), and psychopathology (e.g., delinquency, intentional self-injury, schizophrenia; see Beauchaine & Gatzke-Kopp, 2012; Edgar, Keller, Heller, & Miller, 2007; Levy, Sereno, Gooding, & O'Driscoll, 2010). These disciplines are characterized by different research questions, are born of different intellectual, philosophical, and research traditions, and often focus on different levels of analysis in terms of constructs (e.g., cognition, emotion, motivation), neurobiological systems (e.g., cortical, subcortical, peripheral), and social contexts (e.g., endogenous, exogenous, cultural). Nevertheless, psychophysiological methods are used quite fruitfully in each discipline.

Given this cross-disciplinary appeal, it is sometimes tempting to equate psychophysiology with a set of methods, such as electrocardiography, electroencephalography, and various brain imaging techniques, which can be used to identify biological bases of any human behavior. This conceptualization is potentially harmful, however, because it (1) encourages methods-driven training, research, and scholarship in which all psychological phenomena are studied in the same way and at the same level of analysis, depending on an individual's specific method of expertise (Sternberg, 2007), and (2) reinforces anachronistic reductionism in which 1:1 correspondences between psychological outcomes and physiological functions are assumed, which is rarely the case (see Berntson et al., 2002). Methods-driven research often impedes scientific progress, and is antithetical to modern multiple levels of analysis approaches to studying physiology-behavior-relations (e.g., Berntson & Cacioppo, 2004; Cicchetti, 2008). Thus, psychophysiological methods are best chosen based on specific research problems, and used in conjunction with other methods such as molecular genetics, behavior observation, self-reports, informant-reports, interviews, etc. (Beauchaine & Gatzke-Kopp, 2012; DeVries & Nelson, 2007; Sternberg, 2007). This is fully consistent with the developmental psychopathology perspective, outlined below.

In our view, psychophysiology is best defined as the study of (i.e., -ology) interactions between physiological systems (i.e., -physi-), and psychological states and traits (i.e., psycho-; see Fox, Hane, & Pérez-Edgar, 2006). Defined as such, psychophysiological methods can be especially useful in characterizing interactions between individual-level vulnerabilities and environmental risk factors in shaping maladaptive behavior. This is especially important for transactional models of psychopathology in which (1) specific biological vulnerabilities predispose individuals to mental illness, particularly in contexts of potentiating environmental risk; (2) vulnerabilities and risk factors span levels of analysis from genes, to intervening biological systems, to social contexts including families, neighborhoods, and cultures; and (3) causal influences on the development of psychopathology operate across these levels of analysis, sometimes changing in direction through both endogenous and exogenous mechanisms (see Beauchaine & Gatzke-Kopp, 2012; Mead, Beauchaine, & Shannon, 2010). Disentangling such processes is a primary objective of developmental psychopathology (Sroufe & Rutter, 1984).

THE DEVELOPMENTAL PSYCHOPATHOLOGY PERSPECTIVE

Until late in the twentieth century, formulations of psychopathology were dominated by questions of nature versus nurture. The more longstanding belief was that mental illness derived from dysfunction located within individuals. This assumption pervades much of written history, and dates to works by Hippocrates. Galen, extending Hippocrates' writings, attributed temperamental traits including psychopathology to imbalances in four bodily humors. According to Galen, emotional volatility resulted from excess yellow bile, whereas melancholia resulted from excess black bile.

Other historically influential accounts of psychopathology—most notably Freud's psychoanalytic theory—traced causes of mental illness to environmental experience. Freud attributed psychopathology to intrapsychic conflicts among the id, ego, and superego. According to Freud, both the ego and superego derived their relative strength or weakness almost entirely from early experience.

Questions of nature versus nurture were largely irresolvable until the mid- to late-20th century because modern methodological and technological advances, including behavioral genetics (especially statistical modeling of twin registries), molecular genetics, psychophysiological data acquisition and analysis, and the computational power each depended on were not yet developed fully (see Beauchaine & Gatzke-Kopp, 2013). Even before most of these advances unfolded, however, forward-thinking psychopathologists were offering more sophisticated etiological models of mental illness, beginning with the *reaction range* concept from quantitative behavioral genetics. According to this notion, heritability sets upper and

lower bounds on psychological adjustment, but reactions to the environment dictate where within those bounds an individual functions. The reaction range concept was followed quickly by related *diathesis–stress* conceptualizations of schizophrenia, which specify how expression of genetic liability depends upon exposure to environmental risk (Gottesman, 1963; Gottesman & Shields, 1966; Meehl, 1962). The diathesis–stress framework ushered in a slow transition away from strict endogenous models of psychopathology, which focused almost exclusively on pathophysiological processes within individuals, and away from strict exogenous models of psychopathology, which focused almost exclusively on early adverse experiences (Cicchetti, 1984). Psychopathology could now be construed as the end product of interactions between genetic vulnerabilities (diatheses) and environmental risk factors (stressors).

These advances in technology, methodology, and conceptualization of mental illness laid the groundwork for the emergence of developmental psychopathology—a new discipline that extended gene–environment interaction models by focusing on *processes,* or *transactions* through which biological vulnerabilities and contextual risk factors interact to affect psychological adjustment. As defined by Sroufe and Rutter (1984), developmental psychopathology encompasses, " . . . study of the origins and course of individual patterns of behavioral maladaptation, whatever the age of onset, whatever the causes, whatever the transformation in behavioral manifestations, and however complex the course of the developmental pattern may be" (p. 18). As this definition implies, developmental psychopathologists are concerned with specifying alternative pathways to psychopathology (see, e.g., Cicchetti & Rogosch, 1996), both multifinal (i.e., How do similar vulnerabilities eventuate in different manifestations of psychopathology?) and equifinal (i.e., How do different vulnerabilities eventuate in similar manifestations of psychopathology?). Such specification requires studies of (1) individual-level vulnerabilities across levels of analysis (e.g., genetic, neural, psychophysiological), (2) environmental risk factors (e.g., family, peer network, neighborhood, culture), (3) biological vulnerability–environmental risk interactions across time, and (4) developmental continuities and discontinuities in behavior (see Beauchaine & McNulty, 2013; Rutter & Sroufe, 2000). Developmental psychopathology research transcends traditional disciplinary boundaries, including child clinical psychology, child and adolescent psychiatry, behavioral neuroscience, behavioral genetics, psychiatric genetics, etc., and has produced increasingly sophisticated transactional models of psychopathology that are largely unique to the discipline (e.g., Beauchaine, Klein, Crowell, Derbidge, & Gatzke-Kopp, 2009; Beauchaine & McNulty, 2013; Cicchetti & Toth, 1998; Crowell, Beauchaine, & Linehan, 2009; Dawson, 2008).

WHY USE PSYCHOPHYSIOLOGICAL METHODS IN DEVELOPMENTAL PSYCHOPATHOLOGY RESEARCH?

Psychophysiological methods have proven invaluable in advancing the developmental psychopathology research agenda (see Beauchaine & Gatzke-Kopp, 2012; Fox et al., 2006), and will likely continue to do so in upcoming years. As described below, autonomic psychophysiology has helped specify which children are most vulnerable to developing both internalizing (e.g., anxiety, depression) and externalizing (e.g., delinquency, substance abuse) disorders in contexts of liability and risk. For example, low electrodermal responding among 8–12-year-olds confers vulnerability to conduct problems in contexts of paternal antisocial behavior, whereas high electrodermal responding confers protection (Shannon, Beauchaine, Brenner, Neuhaus, & Gatzke-Kopp, 2007). Furthermore, children who exhibit high baseline heart rate variability are either fully or partly protected from adverse outcomes associated with exposure to maternal depression (e.g., Blandon, Calkins, Keane, & O'Brien, 2008), paternal antisociality (e.g., Shannon et al., 2007), parental drinking (e.g., El-Sheikh, 2005), and marital conflict/divorce (e.g., El-Sheikh, Harger, & Whitson, 2001; Katz & Gottman, 1995). Such findings provide obvious advantages for identifying children who are most in need of prevention and intervention programs (see Beauchaine, Neuhaus, Brenner, & Gatzke-Kopp, 2008; Beauchaine et al., 2013).

Psychophysiological measures may also provide information about psychological reactivity that cannot be gleaned from behavioral observation alone. For example, although high-functioning 6–7-year-old children with autism do not differ from their peers in behavioral responding to reward tasks, they exhibit more electrodermal reactivity, suggesting greater state anxiety (Faja, Murias, Beauchaine, & Dawson, 2013).

Relatedly, psychophysiological reactivity may provide information about psychological processes among individuals who cannot or will not provide reliable self-reports, such as infants and toddlers (e.g., Moore et al., 2009; Porges, Doussard-Roosevelt, Portales, & Greenspan, 1998), children and adolescents on the autism spectrum (e.g., Laeng, Sirois, & Gredebäck, 2012), and individuals who are motivated to deceive, such as those who wish to escape detection for committed crimes (e.g., Iacono, 2007).

Physiological measures are also used to detect psychological reactivity to stimuli that are not processed consciously. For example, phobic individuals produce elevated SCRs in response to masked phobia-related images compared with masked neutral and masked nonphobia-related images (Öhman & Soares, 1994). This highlights the need to explore psychopathology at different levels of analysis, including those that are not contingent on self-awareness, to better understand attentional and cognitive processes associated with symptom expression. Following from these and other considerations, some have advocated using psychophysiological measures to complement, and in some cases supplant, behavioral observation and self-report. Perhaps the best such example is lie detection (see Iacono, 2007), which continues to evolve despite lingering problems with both sensitivity and specificity in applied settings (e.g., Ben-Shakhar & Elaad, 2003).

In addition, autonomic psychophysiology sometimes provides prospective information about vulnerability to later psychopathology. For example, developmental increases from early to late childhood in respiratory sinus arrhythmia (RSA)—the component of heart rate variability associated with parasympathetic nervous system (PNS) function (Beauchaine, 2001; Porges, 1995, 2007), predict strong emotion regulation skills in adolescence. In contrast, stasis in RSA across development predicts later emotion dysregulation, which confers vulnerability to a range of adverse outcomes (see Beauchaine, 2015a; 2015b; Vasilev, Crowell, Beauchiane, Mead, & Gatzke-Kopp, 2009). In fact, although attenuated RSA is not observed among disruptive preschool children (Crowell et al., 2006), low baseline RSA and excessive RSA reactivity to emotion evocation are observed consistently among disruptive middle schoolers and adolescents, who do not exhibit normative developmental increases in PNS tone (Beauchaine, Katkin, Strassberg, & Snarr, 2001; Pang & Beauchaine, 2013). Importantly, aberrant patterns of RSA reactivity and deficiencies in emotion regulation appear to co-develop over time specifically in contexts of family coercion (Beauchaine, Gatzke-Kopp, & Mead, 2007; Beauchaine & Zalewski, 2015). This provides one example of how longitudinal relations between physiological vulnerabilities and environmental risk factors are often interactive and at times bidirectional (Crowell et al., 2013; Ford, Fraleigh, Albert, & Connor, 2010). As reviewed above, characterizing transactions between individual-level vulnerabilities and contextual risk factors is a primary objective of developmental psychopathology research.

In addition, psychophysiological measures can provide information about central nervous system processes that either cannot be measured noninvasively, or require measurement techniques that cannot be implemented with young children (see, e.g., Beauchaine & Gatzke-Kopp, 2012; Clark, Hasser, Kunze, Katz, & Kline, 2011; Porges, 2005, 2007; Thayer & Lane, 2000). As detailed below, for example, attenuated sympathetic nervous system (SNS)-linked cardiac reactivity to incentives may serve as a proxy for midbrain dopamine responding (see, e.g., Brenner & Beauchaine, 2011)—a core neural substrate of trait impulsivity, which is often expressed very early in life as attention-deficit/hyperactivity disorder (ADHD; see Gatzke-Kopp & Beauchaine, 2007; Neuhaus & Beauchaine, 2013; Sagvolden, Johansen, Aase, & Russell, 2005). Using a psychophysiological proxy for midbrain dopamine activity in very young children allows us to make inferences about central nervous system processes that otherwise could not be assessed until late childhood, adolescence, or in some cases adulthood. For example, although positron emission tomography (PET), the most direct noninvasive measure of neural function available,[2] is often used to evaluate midbrain dopamine function among adults with ADHD (e.g., Volkow, Fowler, Wang, Ding, & Gatley, 2002; Volkow et al., 2009), it is rarely used with children or adolescents given safety concerns associated with ingesting radioactive tracers (i.e., radionuclides). Alternatively, functional neuroimaging (fMRI) can be used to evaluate neural function without radioactivity. Either way, imaging protocols are difficult for very young children with ADHD to tolerate. Thus, when valid psychophysiological proxies for central nervous system function exist, they provide opportunities for scientific discovery that might otherwise be unavailable. We return to this important point later.

Finally, psychophysiological methods can sometimes be used to identify neurobiological vulnerabilities to psychopathology that cut across traditional diagnostic boundaries. Continuing with the aforementioned example, attenuated SNS-linked cardiac reactivity to incentives is observed among preschool children with ADHD and oppositional defiant disorder (ODD; Beauchaine et al., 2013; Crowell et al., 2006), middle schoolers with ADHD and conduct disorder (CD; Beauchaine et al., 2001), adolescents who are delinquent and aggressive (Beauchaine, Hong, & Marsh, 2008), and adolescents who

[2]PET provides the most direct index of neural function because radionuclides are designed to bind with specific receptors or transporters (in this case, dopamine transporters/receptors). In contrast, functional neuroimaging quantifies blood oxygen level, a less direct measure of neural function that is not specific to any particular neurotransmitter.

engage in later substance use (Brenner & Beauchaine, 2011). According to the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (*DSM-5;* American Psychiatric Association, 2013), this list comprises no fewer than four assumedly distinct psychiatric syndromes (ADHD, ODD, CD, substance use disorder), despite evidence of shared etiology at genetic, psychophysiological, and neural levels of analysis (for reviews see Beauchaine & Gatzke-Kopp, 2012; Beauchaine & McNulty, 2013; Beauchaine, Shader, & Hinshaw, 2015; Gizer, Otto, & Ellingson, 2015). A major criticism of the *DSM* is its strict adherence to syndromal (i.e., symptom-based) diagnosis, even when neurobiological indicators suggest shared pathophysiologies (Beauchaine, Klein, Erickson, & Norris, 2013; Beauchaine & Marsh, 2006). In turn, when pathophysiology is ignored, etiological pathways to psychopathology are obscured (Preskorn & Baker, 2002), with adverse consequences for diagnosis, and for development of effective prevention and intervention programs (see Beauchaine, Neuhaus et al., 2008). This was a core contributing factor to the National Institute of Mental Health (NIMH) embarking on development of a new diagnostic system, the Research Domain Criteria (RDoC; Insel et al., 2010; Sanislow et al., 2010). The RDoC—a currently evolving dimensional approach to diagnosis—is based on *both* identifiable neurobiological processes and observable behavior (NIMH, 2015).[3]

DEFINITIONS, ASSUMPTIONS, AND TENETS OF PSYCHOPHYSIOLOGICAL RESEARCH

We now turn to general definitions, assumptions, and tenets of psychophysiological research. In recent years, many who would not have used psychophysiological measures in the past have begun doing so given hardware that is more affordable and readily implemented, and software that is largely automated. Although these advances make psychophysiological data collection more accessible and less labor-intensive, modern systems are also easier to use by those who do not have formal training in psychophysiology, and who may not be familiar with certain principles, assumptions, and limitations of the psychophysiological approach. Accordingly, below we outline a number of issues that should be considered when planning, executing, and interpreting psychophysiological experiments. We then turn our attention to uses of specific psychophysiological measures, before discussing various data analytic considerations.

Like any branch of science, psychophysiology has its own conceptual underpinnings and terminological conventions. Some of these are specific to particular methods (e.g., electro-cardiography, pupilometry), whereas others are more general, and should therefore be familiar to most anyone who conducts psychophysiological research. Thus, we provide discussion of several important terms and concepts below. We note however, that the scope of such issues is broad enough that several full-length texts have been devoted exclusively to psychophysiology (e.g., Andreassi, 2007; Cacioppo, Tassinary, & Berntson, 2007; Schmidt & Segalowitz, 2008; Stern, Ray, & Quigley, 2001). Readers are referred to these sources for more comprehensive coverage.

Tonic Versus Phasic Measures and Establishing Appropriate Baselines

By definition, tonic psychophysiological *activity* is assessed at rest, whereas phasic psychophysiological *reactivity* is computed as change from rest. Ideally, tonic measures are collected at the end of a movement- and stimulus-free quiet baseline condition, which must be long enough for an individual to achieve a wakeful resting state (Obrist, 1981). Such true baselines minimize effects of both exogenous (e.g., exposure to stressors before arrival at the lab, current lab conditions) and endogenous (e.g., individual differences in state anxiety) sources of error variance on estimates of both tonic and phasic psychophysiological function. This can be especially important in psychopathology research. For example, failure to collect true baseline heart rate from anxious participants may result in overestimates of tonic heart rate, which in turn translate into underestimates of phasic heart rate reactivity to stressors. This is likely to result in a Type II error (see Hastrup, 1986).

Quiet periods lasting 10–20 min or more may be required to achieve a true resting baseline (see Hastrup, 1986;

[3]This discussion may raise questions in some readers' minds about the distinction between biomarkers and endophenotypes, and the relative values of each in psychopathology research. Although space constraints preclude full consideration of these issues, biomarkers are usually defined by psychopathologists as endogenous, measurable characteristics that mark either risk for or manifestation of psychiatric illness. According to this definition, biomarkers need not be specific to any particular disorder as currently defined in the *DSM*. In contrast, endophenotypes are usually defined more restrictively, including specificity to a particular psychiatric disorder. As these definitions imply, psychophysiological variables can be biomarkers and/or endophenotypes. Interested readers are referred elsewhere for more comprehensive discussions (Beauchaine, 2009a; Gottesman & Gould, 2003; Gould & Gottesman, 2006).

Jennings, Kamarck, Stewart, Eddy, & Johnson, 1992). This has led some, especially those who conduct psychophysiological research with children, to use alternative conditions, such as vanilla baselines, when collecting tonic measures. With this approach, participants either watch a quiet, age-appropriate video (e.g., Sulik, Eisenberg, Silva, Spinrad, & Kupfer, 2013), or engage in minimally demanding tasks, such as color detection (Jennings et al., 1992). In developmental psychopathology research, use of vanilla baselines usually follows from one of two assumptions: (1) that young children, regardless of their level of functioning, cannot tolerate true baselines; or (2) that children with a particular trait being studied (e.g., impulsivity, emotion dysregulation), cannot tolerate true baselines (see, e.g., Gavin & Davies, 2008).

Although these assumptions should not be discounted, use of vanilla baselines may be quite problematic for some psychophysiological measures, such as heart rate and RSA. As will be discussed, RSA indexes ebbing and flowing of heart rate across the respiratory cycle. Low tonic RSA and excessive RSA reactivity to evocative stimuli are associated with emotion dysregulation—a hallmark of both internalizing and externalizing psychopathology (see below; Beauchaine, 2015a; 2015b; Beauchaine et al., 2007). Notably, however, even moderate levels of attention deployment, such as those elicited by vanilla baselines, reduce RSA somewhat among normal controls, but not among those with attention problems (see Beauchaine, 2001). In fact, RSA reactivity to lab tasks varies as a function of individual differences in both impulsivity and attention (e.g., Beauchaine et al., 2001). Thus, vanilla baselines may produce attention-induced confounds in comparisons of tonic and phasic responding between certain groups, such as externalizing males and controls.

Fortunately, even though 10–20-minute baselines are often preferred (Jennings et al., 1992), shorter intervals can be effective. In our own work, we regularly use 5 min resting baselines with children as young as age 4 years who have ADHD (see Beauchaine et al., 2013; Crowell et al., 2006). Our baselines consist of having children sit by themselves in a quiet room, facing a white wall, with no auditory or visual stimulation. Given the novelty of this situation, even preschool children with ADHD are able to sit almost movement-free for this length of time. Stillness is of course essential given the functional role of the ANS in supporting metabolic demands (see, e.g., Bush, Alkon, Obradović, Stamperdahl, & Boyce, 2011).

A final point regarding tonic versus phasic responding concerns consistent and specific use of terminology, which facilitates effective communication in any discipline. As noted already, tonic measures, by definition, are collected at baseline, whereas phasic measures, by definition, reflect change from baseline, regardless of the eliciting source of psychophysiological reactivity. When phasic measures are referred to as tonic measures, considerable confusion may result. For example, following publication of a highly influential paper on emotion regulation titled "Vagal Tone and the Physiological Regulation of Emotion (Porges, Doussard-Roosevelt, & Maiti, 1994), many subsequent papers appeared in the developmental and developmental psychopathology literatures in which the term vagal tone was used to refer broadly to any measure of RSA, whether tonic or phasic. As we have noted elsewhere (Beauchaine, 2001; 2015b), this is problematic for several reasons. For the discussion at hand, it is sufficient to state that tonic and phasic measures of RSA often have different external correlates and may reflect different physiological functions and should therefore be distinguished from one another for precise communication and indexing purposes.

Misinterpreting Baseline Measures

Failure to distinguish between tonic and phasic responding can also result in confusion regarding the neural underpinnings of, and individual differences in, baseline psychophysiological measures. For example, phasic changes in cardiac pre-ejection period (PEP), a systolic time interval spanning left ventricular depolarization and ejection of blood into the aorta (see below), are determined almost exclusively by SNS reactivity (Sherwood, Allen, Obrist, & Langer, 1986). In contrast, tonic PEP is determined by a host of additional factors, including preload, afterload, peripheral resistance, biomechanics, and pathophysiological processes (see, e.g., Sherwood et al., 1990). Accordingly, group differences between those with and without psychopathology in baseline PEP (e.g., Beauchaine et al., 2001) cannot be interpreted as deriving from sympathetic neural function. *At a minimum, any such conclusion requires assessment of phasic PEP reactivity*. This conclusion generalizes to most if not all psychophysiological processes. Nevertheless, it is quite common in the developmental and developmental psychopathology literatures to equate individual and group differences in baseline measures of autonomic activity with specific neural processes—a practice that is often unwarranted and potentially misleading.

Even phasic PEP responses, although initiated by the SNS, may be moderated by nonneural influences such as loading effects (see, e.g., Obrist, Light, James, & Strogatz, 1987). For this reason and others, we cannot assume

either (1) linear correspondences between neural reactivity and PEP change within individuals, or (2) equivalency in associations between neural reactivity and phasic PEP change across individuals. For example, a 10 ms change in PEP may correspond with more β-adrenergic neural reactivity in a person high in afterload than in a person low in afterload. Although this adds error variance to our measures, we are still on much stronger footing when making inferences about the neural underpinnings of phasic PEP reactivity than we are in making inferences about the autonomic underpinnings of tonic PEP. This conclusion also generalizes to most if not all psychophysiological processes.

The Law of Initial Values and Psychophysiological Reactivity

According to the law of initial values (LIV), relative magnitudes of phasic psychophysiological responding depend in part on preceding levels of tonic activity (Wilder, 1931, 1957). Wilder first articulated the LIV after noticing that changes in blood pressure following administration of both SNS agonists (e.g., adrenaline) and PNS antagonists (e.g., atropine)—both of which increase blood pressure—were smaller among those who exhibited higher resting values.

Debate over causes of the LIV has existed for years (see Furedy & Scher, 1989). Although LIV effects undoubtedly result in part from biomechanics (e.g., effects of maximum stroke volume on cardiac output), neural mechanisms (e.g., effects of the minimum refractory period on maximum heart rate), and their interactions, additional factors, including statistical artifacts, also play a role (see Berntson, Uchino, & Cacioppo, 1994). Furthermore, similar phenomena—often referred to as ceiling and floor effects—are common in other areas of research. For example, therapeutic gains among those in randomized clinical trials are often highly dependent on levels of baseline function (see, e.g., Vickers & Altman, 2001). Thus, across different areas of research, baseline values and subsequent change scores tend to covary negatively.

This covariation must be considered when we interpret both within-individual and between-groups psychophysiological research findings (Furedy & Scher, 1989). For example, if valid resting baselines are not obtained within individuals, subsequent change scores (baseline minus stimulus) will underestimate true psychophysiological reactivity. In between-groups research, unaccounted for differences at baseline may obscure important group differences in reactivity. As reviewed below, baseline differences in psychophysiological responding are observed between control participants and those with a host of psychiatric conditions. Since group differences in phasic responding are in part dependent on any such baseline differences, psychophysiological reactivity should not be evaluated without considering baseline responding.

Constructs Versus Measures

In psychology and most other branches of science, a *measure* is a quantifiable, directly observable variable. Measures are often referred to as *manifest indicators* in the psychometrics literature. In contrast, a *construct* is an unobservable, *latent variable* that must be inferred from manifest indicators (see, e.g., Nunnally & Bernstein, 1994). Almost all psychiatric diagnoses (e.g., depression, ADHD) represent latent variables (constructs), which are inferred from imperfect manifest indicators (measures) of clinical state (see Meehl, 1995). Importantly, measures may be specified at any of several levels of analysis, including genetic, hormonal, neural, behavioral, self-report, etc.

The distinction between constructs and measures, although often ignored in psychophysiology research, is no less important than it is in studies of psychopathology (see Strube & Newman, 2007). Vagal tone, for example, defined as resting parasympathetic efference from the brainstem to the heart (see Porges, 1995), is a *construct*. It is not observable directly, and can only be estimated noninvasively from indirect *measures* such as heart rate change following pharmacologic blockade, and quantification of RSA (see Berntson et al., 1997). In fact, RSA is only an accurate measure of vagal tone in specific contexts that include a valid resting baseline and tight respiratory control (see below; Grossman, 1992; Grossman, Karemaker, & Wieling, 1991; Ritz, 2009). The terms vagal tone (a construct) and RSA (a measure) should therefore not be used interchangeably, as they often are in the developmental and developmental psychopathology literatures. Although this particular example may seem harmless, it has produced considerable confusion in the literature about possible neural underpinnings of individual differences in RSA. More egregious examples of conflating constructs with measures also appear in the literature. In particular, low RSA is often equated with emotion dysregulation, when it is better construed as a biomarker of emotional lability. Emotion dysregulation itself is a psychological construct that can only be assessed with multiple measures collected across levels of analysis (e.g., self-report, behavior observation, informant report; see Cole, Hall, & Hajal, 2013).

Developmental Considerations

Finally, developmental changes in tonic and phasic psychophysiological responding are quite common, and occur through various mechanisms, including increased body size and associated alterations in cardiodynamics (e.g., Smulyan et al., 1998), age-related variation in physical fitness (e.g., Tulppo, Mäkikallio, Seppänen, Laukkanen, & Huikuri, 1998), maturation of frontal brain structures implicated in self-regulation and autonomic function (e.g., Gogtay et al., 2004), migration of neural control over behavior to different neural networks across development (Beauchaine & McNulty, 2013; Geier & Luna, 2009), age-dependent physiological changes (e.g., arterial hardening with older age; Mitchell et al., 2004), and psychological maturation (e.g., improved control over attention; e.g., Karatekin, 2004). Given this wide range of developmental effects, failure to model age is likely to introduce confounds and unwanted error variance into psychophysiological studies. Perhaps more importantly, understanding maturational effects and maturational failures is of direct interest to developmental psychopathologists (see Beauchaine & McNulty, 2013). Since no single longitudinal trajectory characterizes all autonomic constructs, we include descriptions addressing normative development in each section below. First, however, we provide a brief description of the autonomic nervous system (ANS).

THE AUTONOMIC NERVOUS SYSTEM

The ANS is a subdivision of the vertebrate nervous system that controls involuntary actions of body organs and certain tissues, including glands, extrastriatal muscles, and vasculature (see, e.g., Robertson, Biaggioni, Burnstock, & Low, 2004). Actions of the ANS are primarily reflexive, and occur in response to changing demands from the internal (visceral) and external environments. Under conditions of impending danger, for example, inhibitory parasympathetic effects on cardiac output are withdrawn and excitatory sympathetic effects are enhanced, which provides for rapid increases in blood flow and mobilization of energy to respond to the threat. Following escape or removal of threat, these responses are reversed, returning the ANS to its longer-term function of maintaining physiological homeostasis.

Based on both anatomical and functional distinctions, the ANS is typically parsed into sympathetic, parasympathetic, and enteric subdivisions, (Jänig, 2006). As alluded to already, a primary function of the SNS is to mobilize metabolic resources to cope with real or perceived threat. During fight-or-flight responding, the SNS (1) increases contractile force of the atria and ventricles, increasing blood flow and availability of oxygen to large muscle groups throughout the body; (2) elicits peripheral vasoconstriction, reducing blood supply to the extremities; (3) promotes bronchial dilation, improving respiratory efficiency; and (4) stimulates eccrine sweat gland secretion, improving grip of the palms and soles of the feet, among other effects.

The PNS also plays an important role in fight-or-flight responding through acute withdrawal of its inhibitory effects on dually innervated organs including the heart. This allows the SNS to exert excitatory effects unopposed. During periods of rest, however, the PNS serves primarily restorative functions by decreasing heart rate and contractility of the atria, promoting digestion, eliciting vasodilation, and stimulating bronchial contraction. Although the SNS and PNS often act in opposition to one another, they may also operate in coactive, coinhibitory, and uncoupled states, with important implications for health outcomes, including several that are linked to psychopathology, as described below (see Beauchaine, 2001, Beauchaine et al., 2007; Berntson, Cacioppo, & Quigley, 1991, 1993; Berntson, Cacioppo, Quigley, & Fabro, 1994; Berntson, Cacioppo, Binkley et al., 1994; Ondicova & Mravec, 2010; Thayer & Lane, 2000).

The third division of the ANS, the enteric nervous system (ENS), comprises an intrinsic, mesh-like network of neurons in the gastrointestinal tract. The ENS controls digestive processes and communicates with the CNS indirectly through sympathetic and parasympathetic innervation, but unlike the SNS and PNS, can also function independently of the CNS (Goyal & Hirano, 1996). In sections to follow, we focus exclusively on the SNS and PNS. Readers interested in learning more about the functions and neurodevelopment of the ENS are referred elsewhere (Gershon, 2008; Sasselli, Pachnis, & Burns, 2012).

The SNS and PNS are comprised of two populations of autonomic motor neurons, including (1) preganglionic neurons originating in the spinal cord or brain stem, and (2) postganglionic neurons synapsing with preganglionic neurons outside the CNS, which innervate target organs/tissues directly (see, e.g., Cramer & Darby, 2005). Cell bodies of preganglionic neurons in the SNS are located in the intermediate zone of thoracic and lumbar regions of the spinal cord, and form cholinergic synapses with postganglionic neurons located in chain formations on either side of or in front of the spinal cord (termed paravertebral ganglia and prevertebral ganglia, respectively). Synapses created

by postganglionic neurons and target organs/tissues are primarily noradrenergic, with some exceptions, including sweat glands, which are cholinergic (see below). Cell bodies of preganglionic PNS neurons are located in the sacral region of the spinal cord or the brainstem, where they exit through cranial nerves III, VII, IX, and X. The vagus (cranial nerve X) in particular subserves core regulatory functions, as described below, in its role mediating efferent and afferent neural traffic between target organs and CNS structures located in the medulla oblongata. Similar to the SNS, pre-postganglionic PNS synapses are cholinergic. Parasympathetic postganglionic neurons typically form cholinergic synapses with target organs and tissues, but sometimes use other neurotransmitters, including nitric oxide and vasoactive intestinal polypeptide. In both ANS branches, sensory neurons that originate from target organs provide feedback to the CNS, which modulates activity of autonomic motor ganglia. In fact, at least 80% of vagus neurons are afferent (i.e., originating in target organs and terminating in the CNS; see, e.g., Berthoud & Neuhuber, 2000). Combined, ganglia and sensory neurons provide infrastructure for motor and sensory communication between target organs/tissues and the CNS.

The ANS acts in concert with both the somatic nervous system (i.e., the skeletomotor system), which controls voluntary body movements, and neuroendocrine pathways, which regulate hormone release, to effect commands from the central nervous system (CNS). Coordination between the CNS and these peripheral systems enables organisms to respond to their external environments without compromising the integrity of internal body systems. For example, the ANS and the neuroendocrine system both contribute to the acute physiological stress response (PSR), a set of physiological and behavioral changes that occur following perception of psychological or physical threat. Neurophysiologically, the PSR is comprised of two primary components: (1) a quick-acting monoaminergic CNS response, which is initiated by the amygdala and serves to raise arousal and vigilance; and (2) short- and longer-lasting sympathetic and neuroendocrine responses involving systemic release of catecholamines and glucocorticoids (Rodrigues, LeDoux, & Sapolsky, 2009). During acute stress, epinephrine and norepinephrine are released from sympathetic nerve endings in the adrenal medulla, initiating a near-immediate response to threat, including accelerated breathing and heart rate (Carrasco & Van de Kar, 2003). In contrast, glucocorticoid release is regulated by a neural network including the paraventricular nucleus (PVN) of the hypothalamus, the pituitary gland, and the adrenal glands (i.e., the hypothalamic-pituitary-adrenal [HPA] axis). Primarily indirect limbic activation prompts secretion of corticotrophin-releasing hormone (CRH) in medial parvocellular neurons of the PVN, which then signals secretion of the adrenocorticotropic hormone (ACTH) in the anterior pituitary gland, which in turn stimulates release of glucocorticoids (primarily cortisol in humans) from the adrenal cortex (Jankord & Herman, 2008). Although autonomic reactivity and HPA axis responding are intricately co-regulated by the CNS, we do not discuss the structure or function of the HPA axis further, since it is covered in other chapters of this volume.

Importantly, CNS structures in the brainstem and elsewhere exert top-down effects on autonomic outflow, which accounts in part for effects of psychological factors such as subjective feelings of distress on autonomic function (de Morree, Szabó, Rutten, & Kop, 2013). Subcortical regions, including the paraventricular nucleus (PVN) and other nuclei of the hypothalamus, the periaqueductal gray of the midbrain, the central nucleus in the amygdala, the bed nucleus of the stria terminalis in the basal forebrain, and cortical regions, including the anterior cingulate, insular, and ventromedial prefrontal cortices, are implicated in coordination of autonomic, neuroendocrine, and somatomotor responses (e.g., Busnardo, Tavares, Resstel, Elias, & Correa, 2010; Dong & Swanson, 2006; Sullivan & Gratton, 1999). These regions either contain source nuclei that descend to SNS and/or PNS-specific structures in the brainstem or spinal cord (e.g., the nucleus ambiguus, the PVN via the dorsal longitudinal fasciculus) or provide input to regions that modulate autonomic neuronal activity (e.g., the septal nuclei, hippocampal, and amygdalar influences on the PVN via the medial forebrain bundle and other pathways). Although much remains to be learned about mechanisms that underlie neural influences on ANS functioning, psychological factors, such as stress, motivation, mood, and affective states, induce reliable changes in ANS activity and reactivity. Accordingly, measuring baseline ANS activity and ANS reactivity to certain experimental manipulations may inform our understanding of neural processes implicated in normal and pathological functioning. We now turn our attention to specific ANS constructs, how these are measured, and how inferences about psychopathology and its development may sometimes be gleaned from assessing ANS responding at baseline and in response to carefully chosen stimulus conditions.

CARDIOVASCULAR PSYCHOPHYSIOLOGY

Cardiovascular measures have a long history of use in psychopathology research. Although at one time most of this research was restricted to evaluation of heart rate (HR)

and HR reactivity, several additional cardiac variables are now routinely assessed. Some of these provide unique information that cannot be gleaned from measuring HR alone. Below we discuss some of these measures, beginning with HR itself.

Heart Rate

As noted already, HR has been used for decades to evaluate effects of various psychological phenomena—including those elicited by both endogenous states and exogenous stimuli—on autonomic function. Heart rate is easy to capture, and can be used in within-subjects, between-groups, and mixed experimental designs. Each cardiac cycle is characterized by rhythmic contractions and relaxations of the myocardium, which are induced by periodic patterns of electrical activity. Associated voltage changes are recorded with an electrocardiogram (ECG) to determine HR, which is typically measured in beats/min. The QRS complex, depicted in Figure 22.1, quantifies rapid depolarization of the left and right ventricles. The latency between peaks of the QRS complex (termed the R-R interval) can be digitized to the nearest ms (i.e., 1kHz., the current standard for most cardiac psychophysiology applications; see Berntson et al., 1997; Sherwood et al., 1990), and time series of contiguous R-R intervals can then be used to derive HR. Heart rate and related measures, such as heart period, are often used to index baseline cardiac function and event-related cardiac responses. In some contexts, measurement of heart period, or interbeat interval (IBI), offers advantages over HR, since heart period is related more linearly to autonomic control of the heart (Berntson, Cacioppo, & Quigley, 1995). In fact, use of HR may overestimate autonomic interactions on cardiac function, which can distort relations between psychological processes and autonomic functioning (Quigley & Berntson, 1996). Perhaps given its intuitive appeal, however, HR remains a more popular measure among many of those interested in physiology-behavior relations (see, e.g., Lorber, 2004).

Although the temporal sequence of electrical events underlying myocardial contraction is independent of neural and hormonal influences, both HR and the contractile force of heartbeats are determined by dynamic interactions among the SNS, the PNS, hormonal control, and several additional influences, including cardiovascular reflexes (e.g., the dive reflex), peripheral resistance, mean arterial pressure, and pathophysiological processes (for a more comprehensive account, see Berntson, Quigley, & Lozano, 2007). Acceleratory SNS activation is effected through β-1 adrenergic receptors located on the sinoatrial (SA) node. Since SNS innervation is excitatory, increased β-adrenergic activity produces HR increases (termed tachycardia), and stronger contractile force. In contrast, inhibitory PNS innervation is effected through the vagus nerve via cholinergic mechanisms, which slow HR (termed bradycardia). Heart rate is also affected by endogenous and exogenous factors that alter CNS and autonomic functioning, such as physical activity, psychological stress, medication use, etc. (see, e.g., Cacioppo, Uchino, & Berntson, 1994; Novak et al., 1993; Palatini, Benetos, & Julius, 2006).

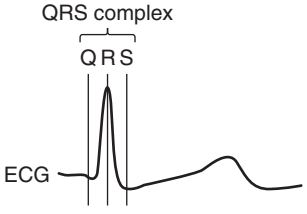


Figure 22.1 The QRS complex, as derived from a Lead III electrocardiogram (ECG).

Given this wide range of influences on cardiac function, determining specific sources of individual differences in HR and HR change is impossible without using measures that parse SNS, PNS, and other effects (see Berntson, Cacioppo, Quigley, & Fabro, 1994; Cacioppo et al., 1994). This is illustrated in the long history of research on autonomic function among aggressive and delinquent males. Collectively, these individuals exhibit low resting HR compared with their nonaggressive peers, a phenomenon described in the literature for over a century. For many decades, this low resting HR was attributed to excessive inhibitory vagal (PNS) efference to the heart, as outlined in the *vagatonia* hypothesis (Eppinger & Hess, 1910/1915). However, research conducted in our lab and others in which concurrent effects of SNS and PNS activation are evaluated indicates that males who engage in clinical levels of externalizing conduct exhibit *attenuated* PNS cardiac control, and that low resting HR likely results from deficient excitatory SNS effects (e.g., Beauchaine et al., 2001; Crowell et al., 2006; Mezzacappa et al., 1996). This demonstrates the value of parsing HR into its constituent autonomic components if we wish to better understand neural correlates of psychological phenomena including psychopathology (see Beauchaine, 2012; Beauchaine et al., 2007; El-Sheikh et al., 2009). We return to this point in later sections.

Autonomic Space

The decades-long assumption that low resting HR among externalizing males results from excessive PNS activation followed from what is often called the accentuated antagonism hypothesis of cardiovascular control. According to this hypothesis, which derived largely from research on

anesthetized dogs (e.g., Levy & Zieske, 1969), the SNS and PNS function reciprocally, with increased activity in one branch accompanied by decreased activity in the other. It is now widely recognized, however, that accentuated antagonism is an oversimplification, and that effects of the SNS and PNS on dually innervated organs such as the heart can be coupled or uncoupled based on environmental demands, psychological states and traits, and pathophysiological effects (Berntson, Cacioppo, & Quigley, 1991, 1993; Berntson, Cacioppo, Quigley, & Fabro, 1994; Berntson, Cacioppo, Binkley et al., 1994). Thus, ANS determinants of HR must be represented in two-dimensional autonomic space (see Figure 22.2), and HR cannot be used to surmise relative levels of SNS or PNS activation (see also Beauchaine, 2012; Paton, Boscan, Pickering, & Nalivaiko, 2005). As outlined below, the doctrine of autonomic space has major implications for developmental psychopathology research in which psychophysiological measures are used (see Beauchaine, 2001, 2009; Beauchaine et al., 2001; Boyce et al., 2001; Bubier & Drabick, 2008; El-Sheikh et al., 2009; Wolff, Wadsworth, Wilhelm, & Mauss, 2012).

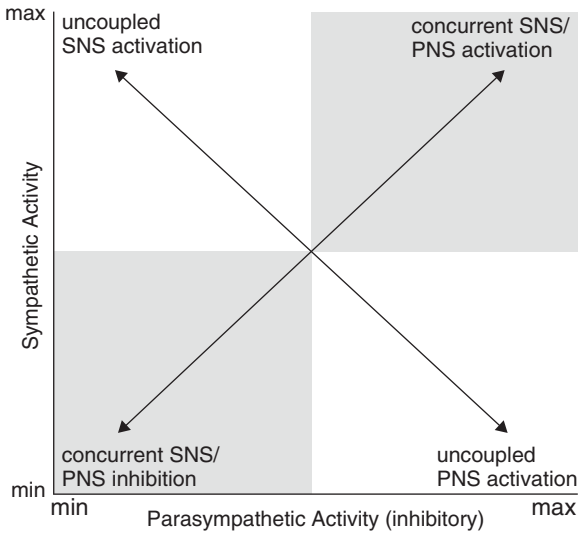


Figure 22.2 Two dimensions of autonomic space, with excitatory SNS activation represented on the y axis and inhibitory PNS activation represented on the x axis. Heart rate may be determined by coactive sympathetic and parasympathetic activity (concurrent SNS/PNS activation or concurrent SNS/PNS inhibition), or by uncoupled sympathetic/parasympathetic activity (SNS activation and PNS inhibition; SNS inhibition and PNS activation). As indicated in text, low resting HR among externalizing males appears to result from concurrent SNS and PNS inhibition (bottom left quadrant). *Source:* Adapted from Berntson, Cacioppo, Quigley, and Fabro (1994), Autonomic space and psychophysiological response. *Psychophysiology, 31*, 44–61

Links to Psychopathology

Despite these caveats, HR and HR change have long been used to render objective inferences about constructs such as overarousal among those high in trait anxiety (e.g., Rogeness, Cepeda, Macedo, Fischer, & Harris, 1990), biological vulnerability to antisocial personality disorder (e.g., Raine, Lencz, Bihrle, LaCasse, & Colletti, 2000), underarousal among externalizing children, adolescents, and adults (e.g., Dietrich et al., 2007), and sex differences in neurobiological risk for conduct problems (e.g., Beauchaine, Hong et al., 2008). As early as preschool, low resting heart rate is associated with aggressive behavior (Zahn-Waxler, Cole, Welsh, & Fox, 1995). In fact, low resting HR is the most replicable psychophysiological marker of externalizing behavior problems among males of all ages (Lorber, 2004; Raine, 2002). More recent work, however, reveals that SNS and PNS components of HR often correlate with different behavioral traits and affective states (see Beauchaine, 2001; Demaree & Everhart, 2004; Dietrich et al., 2007; Rogeness et al., 1990), even among those with externalizing disorders (Beauchaine et al., 2001, 2007; Beauchaine & Gatzke-Kopp, 2012).

Developmental Considerations

Median resting heart rate (HR) is 127 bts/min at birth, peaks at 145 bts/min at one month of age, and decreases to 113 beats/min by age 2 years (Fleming et al., 2011). Thereafter, HR declines at a more gradual yet steady rate to a median of 70 bts/min by age 18. Among healthy adults up to age 68, no further changes in resting HR or average ambulatory HR are observed (e.g., Kostis et al., 1982). However, both HR and HR reactivity are affected by cardiovascular conditions that are more prevalent in older age (e.g., Perret-Guillaume, Joly, & Benetos, 2009).

Reduced HR reactivity to psychosocial stressors is also observed across childhood (Matthews, Salomon, Kenyon, & Allen, 2002) and into old age (Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004). Furthermore, decreases in maximum HR during exercise are observed even among healthy aging individuals (e.g., Kostis et al., 1982). These developmental effects on HR and HR reactivity must be modeled explicitly if we wish to link trajectories in HR to psychological outcomes and reduce unwanted error variance in our longitudinal models (Burt & Obradović, 2013).

Choosing Appropriate Stimulus Conditions

As outlined previously, baseline HR should be acquired in a quiet, neutral setting after participants have acclimated

to the laboratory environment, and are relaxed and inactive (i.e., a true baseline). Multiple baseline recordings from different testing sessions are sometimes used to assess stability over time, or to reduce session-specific error variance by averaging (see Jennings et al., 1992).

As with any psychophysiological measure, HR reactivity is assessed by subtracting task-related HR from baseline HR. For some research questions, HR change in anticipation of threat or during study participation itself may be of interest (Burt & Obradović, 2013). However, it is more common in developmental research to evaluate HR reactivity to tasks that either elicit targeted emotions (e.g., empathy, exuberance), or induce attention deployment (e.g. Critchley et al., 2005; Lansink & Richards, 1997). Although no firm guidelines on stimulus duration exist, research with infants indicates that HR reactivity to 75 db acoustic stimuli follows an inverted U function across 2, 6, 10, 18, and 30 s stimulus durations, with maximum HR reactivity observed to stimuli of 10 s duration (Clifton, Graham, & Hatton, 1968).

Differences in HR reactivity following induction of specific emotions are subtle, but may nevertheless discriminate between emotions characterized by positive versus negative valence. For example, HR reactivity induced by negative emotional states lasts longer than HR reactivity induced by positive emotional states (Brosschot & Thayer, 2003). Moreover, larger HR responses are observed during presentation of sad and angry facial expressions than during presentations of happy facial expressions (Critchley et al., 2005). Such findings suggest that HR responses should not be collapsed across different types of emotion induction, unless the emotions are similar in valence.

Cardiac Pre-ejection Period

As noted already, cardiac PEP is a systolic time interval that spans the onset of left ventricular depolarization and ejection of blood into the aorta. Electrophysiologically, PEP is bounded by the ECG Q-wave, and the impedance-cardiographic (ICG) B-wave (Figure 22.3). Developed by the National Aeronautics and Space Administration (NASA) to evaluate cardiac function noninvasively (see Miller & Horvath, 1978), ICG captures systolic time intervals (e.g., PEP, left ventricular ejection time) and related cardiodynamic events (e.g., stroke volume, cardiac output) by measuring changes in impedance across the thorax (Sherwood et al., 1986). Since blood conducts electricity, changes in blood flow through the aorta can be estimated from the ICG signal via corresponding changes in thoracic impedance.

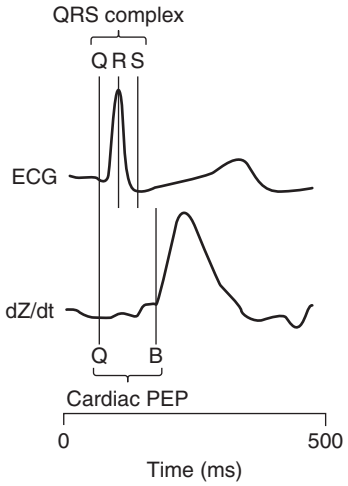


Figure 22.3 Electrocardiographic (top) and impedance cardiographic (bottom) recordings of one cardiac cycle. Time elapsed between the Q-wave of the QRS complex (top) and the B-wave of the ICG recording (bottom) represents cardiac pre-ejection period [PEP]). *Source:* Adapted from Sherwood Allen, Fahrenberg, Kelsey, Lovallo, and van Doornen (1990), Methodological guidelines for impedance cardiography. *Psychophysiology, 27*, 1–23.

Although resting PEP is determined by a variety of neural and mechanical factors and therefore suffers from interpretability concerns associated with almost all biomechanical processes, min-to-min evoked changes in PEP are determined almost exclusively by sympathetic (β-adrenergic) influences. Excitatory input from the SNS increases contractile force of the heart, elevates cardiac output, and produces shortened PEP latencies (Sherwood et al., 1986; see also Schächinger, Weinbacher, Kiss, Ritz, & Langewitz, 2001). However, because β-adrenergic effects on the heart operate through a second messenger system (adenylate cyclase), SNS-initiated changes in cardiac output following exogenous (e.g., threat) and endogenous (e.g., subjective distress) stimuli are delayed by about 20–30 s. Thus, unlike PNS influences, outlined below, SNS influences do not exert beat-to-beat control over cardiac reactivity. Cardiac PEP therefore provides less temporal resolution than some other measures of autonomic function described in this chapter. Nevertheless, it remains a valuable biomarker of certain emotional and motivational states, given appropriate stimulus conditions (see Beauchaine & Gatzke-Kopp, 2012; Brenner & Beauchaine, 2011; Brenner, Beauchaine, & Sylvers, 2005).

Most early work linking PEP reactivity to psychological states examined effects of stress on autonomic function. Some psychologically stressful laboratory conditions, particularly active coping tasks including public speaking and performance of mental arithmetic while being observed

by others, elicit PEP shortening, which indicates increased SNS activation (e.g., Berntson, Cacioppo, Binkley et al., 1994; Kelsey, Soderlund, & Arthur, 2004). Such stimulus conditions induce fear and anxiety, which mobilize the SNS to prepare for appropriate behavioral action (see Beauchaine, 2001; Brenner et al., 2005). A considerable body of research has also examined relations among PEP reactivity in the lab, PEP reactivity to everyday events, and cardiovascular health in different clinical groups (e.g., Nyklíček, Vorselaars, & Denollet, 2011).

Links to Psychopathology

Given its value as an index of SNS reactivity, and clear links between autonomic function and behavior problems among children, adolescents, and adults (e.g., Beauchaine, 2001; Beauchaine et al., 2001; Boyce et al., 2001), PEP has become a focal dependent variable in developmental psychopathology research (see Beauchaine & Gatzke-Kopp, 2012; Brenner & Beauchaine, 2011; Bubier & Drabick, 2008). We have used PEP reactivity with preschoolers (e.g., Beauchaine et al., 2013), middle-schoolers (e.g., Beauchaine et al., 2007), adolescents (Beauchaine et al., 2001), and young adults (Brenner et al., 2005) to evaluate reward-related processing and its associations with externalizing behavior disorders. As noted previously, under carefully selected stimulus conditions, PEP reactivity to monetary incentives serves as a peripheral biomarker of mesolimbic dopamine responding and associated individual differences in approach motivation (see Beauchaine & McNulty, 2013; Brenner et al., 2005; Brenner & Beauchaine, 2011). This assertion—that PEP reactivity *specifically* to incentives marks midbrain dopamine responding—follows from strong theoretical considerations and empirical associations. First, approach behaviors, which characterize reward-related processes, require energy mobilization, a function subserved by the SNS to meet metabolic demands. Second, changes in cardiac output required for behavioral approach are mediated by SNS-induced increases in the contractile force of the left ventricle (Sherwood et al., 1986). Third, dopamine modulates sympathetic function (Mannelli et al., 1999) and direct infusions of dopamine agonists into midbrain structures produce SNS-mediated increases in cardiac output (van den Buuse, 1998) that are similar to those observed when normal controls participate in reward tasks (see Brenner et al., 2005; Richter & Gendolla, 2009).

Compared with controls, males with ADHD, ODD, CD, and antisocial personality traits exhibit either diminished PEP reactivity to monetary incentives, or no PEP reactivity at all (for a review see Beauchaine & Gatzke-Kopp, 2012). This PEP nonreactivity parallels consistent neuroimaging results showing attenuated mesolimbic reactivity to reward among externalizing males (see, e.g., Durston, 2003; Rubia, 2011), and provides prospective prediction of substance use initiation and escalation among middle-schoolers (Brenner & Beauchaine, 2011).

The consistency of such findings has led our group and others to propose that deficient midbrain dopamine responding to reward—reflected in PEP under-reactivity during monetary incentive tasks—is a principal mechanism of behavioral impulsivity, a trait common to all externalizing conditions (see Beauchaine et al., 2009; Gatzke-Kopp, 2011; Gatzke-Kopp & Beauchaine, 2007; Sagvolden et al., 2005). Thus, consistent with sensation-seeking and central/autonomic underarousal theories (e.g., Castellanos-Ryan, Rubia, & Conrod, 2011; Gatzke-Kopp, Raine, Loeber, Stouthamer-Loeber, & Steinhauer, 2004), we have argued that those who exhibit impulse control problems engage in unrestrained reward-seeking behaviors to upregulate a chronically irritable/aversive mood state, the affective consequence of persistently low midbrain dopamine responding (see, e.g., Ashby, Isen, & Turken, 1999; Laakso et al., 2003).

The use of PEP to evaluate reward-related processing among externalizing preschoolers, middle-schoolers, adolescents, and adults exemplifies several of the advantages of psychophysiological research outlined previously. First, it provides for inexpensive, noninvasive estimation of central nervous system function. Many other noninvasive techniques such as functional neuroimaging and to a lesser extent EEG are costly, which limits their use and causes researchers to recruit small samples with low statistical power. Although several of our studies have involved neuroimaging (e.g., Gatzke-Kopp et al., 2009; Sauder, Beauchaine, Gatzke-Kopp, Shannon, & Aylward, 2012; Sauder, Derbidge, & Beauchaine, 2013; Shannon, Sauder, Beauchaine, & Gatzke-Kopp, 2009), by using cardiac psychophysiology we have extended our work on reward processing to larger externalizing samples, and to a broader age range than we could have otherwise assessed. In fact, it is difficult to imagine conducting neuroimaging studies with preschoolers, yet autonomic psychophysiology has enabled us to identify vulnerability among children as young as age four (Beauchaine et al., 2013; Crowell et al., 2006). In turn, early identification of vulnerability is of utmost importance if we wish to prevent progression along the externalizing spectrum as affected children mature (see Beauchaine, Hinshaw, & Pang, 2010; Beauchaine & McNulty, 2013; Beauchaine, Neuhaus et al., 2008).

Developmental Considerations

In our own work with typically developing individuals, we have found resting PEP values of 71.5 ms among preschoolers (mean age = 4.5 years), 99.3 ms among middle schoolers (mean age = 10.0 years), and 113.3 ms among young adults (age range = 18–24 years; see Brenner et al., 2005; Crowell et al., 2006; Marsh, Beauchaine, & Williams, 2008). Thus, resting PEP increases monotonically as a function of age through early adulthood, after which age-related changes are negligible (Uchino, Uno, Holt-Lunstad, & Flinders, 1999). Although developmental increases in resting PEP are also observed among externalizing samples, these individuals exhibit lengthened PEPs compared with controls at all ages.

Developmental trajectories in PEP reactivity are more difficult to ascertain, since different research labs have used different stimuli to evoke PEP responses. However, research using reward tasks in particular show no consistent differences across preschool, middle childhood, adolescence, and early adulthood (Beauchaine et al., 2001; Beauchaine, Hong et al., 2008; Brenner et al., 2005; Marsh et al., 2008). In contrast, Quigley and Stifter (2006) reported greater PEP reactivity among young adults than among preschoolers in response to a series of reaction time, emotion evocation, and interview tasks. This illustrates once again the importance of considering stimulus conditions in planning and interpreting psychophysiological experiments. Indeed, PEP reactivity appears to depend on a number of factors unrelated to chronological age, including task type and demographic variables, including sex and race (Matthews et al., 2002).

Choosing Appropriate Stimulus Conditions

It is important to reemphasize that the validity of peripheral markers of CNS processes is highly dependent on the choice of appropriate stimulus conditions. As we have described elsewhere (Brenner & Beauchaine, 2011), PEP reactivity should not be considered a marker of central dopamine responding under conditions other than reward. Although active coping tasks also induce PEP shortening (e.g., Kelsey et al., 2004), they do so through brain systems that subserve fear and anxiety—not behavioral approach (see, e.g., Pribram & McGuinness, 1975). Pre-ejection period reactivity during mental arithmetic therefore cannot be considered a marker of central dopamine responding. This illustrates why stimulus conditions must be considered carefully when formulating tasks designed to elicit specific patterns of neural activity if one wishes to interpret peripheral psychophysiological measures validly (see also Fortunato, Gatzke-Kopp, & Ram, 2013).

Because the ICG signal is sensitive to movement artifacts, respiratory artifacts, and other sources of noise, extracting a valid index of PEP requires that the ECG Q-wave and the ICG B-wave be ensemble averaged across multiple heart beats (see Kelsey & Guethlein, 1990; Sherwood et al., 1990). Similar to techniques used in event-related potential studies described elsewhere in this volume, ensemble averaging filters out noise contained in single heartbeats, and sums signal common across heartbeats. The minimum accepted duration for ensemble averaging is about 20 s, which captures roughly 25 cardiac cycles at normal adult HRs. Importantly, however, since SNS effects on cardiovascular function operate through a second messenger system, maximum PEP reactivity may lag up to 20 s poststimulus presentation. As a result, stimulus epochs should be considerably longer, and the first 20 s should be discarded for an accurate estimate of SNS reactivity.

Heart Rate Variability

Heart rate variability (HRV) refers to beat-to-beat changes in the time (ms) between successive R-R intervals derived from ECG recordings. This variability is determined by a number of factors, including diurnal influences, baroreceptor activation, tonic and phasic influences of the SNS and PNS, nonneural effects, and pathophysiological processes (see Beauchaine, 2001; Berntson et al., 1997; Porges, 1995; Ritz, 2009). The most basic measures of HRV include standard deviation of, coefficient of variance of, and mean successive difference in R-R intervals (see Allen, Chambers, & Towers, 2007; Berntson et al., 1997). These measures correlate highly with one another, and under certain conditions (see below), with vagal efference to the heart as determined by pharmacologic blockade (see Allen et al., 2007; Grossman, Van Beek, & Wientjes, 1990; Hayano et al., 1991). Associations with PNS activity/reactivity are a primary motivation for capturing HRV in psychopathology research, given consistent empirical links between deficient PNS responding and emotion dysregulation, which characterizes many clinical disorders (see Beauchaine, 2001; Beauchaine et al., 2007; Chambers & Allen, 2007; Dennis, Buss, & Hastings, 2012; Friedman, 2007; Obradović & Boyce, 2012; Rottenberg, 2007).

As reviewed previously, the SA node is innervated by both inhibitory PNS fibers from the vagus nerve and excitatory SNS fibers from thoracic spinal nerves. Thus, although SNS and PNS influences are primary determinants of HR and HRV, basic measures of HRV cannot be used to quantify parasympathetic contributions to

cardiac function, as is sometimes supposed (see Berntson, Cacioppo, & Quigley, 1991, 1993; Berntson, Cacioppo, Quigley, & Fabro, 1994; Berntson, Cacioppo, Binkley et al., 1994; Levy, 1988). Rather, to infer vagal activity/reactivity, more sophisticated processing of the ECG signal is required. This processing quantifies respiratory sinus arrhythmia (RSA), or the degree of ebbing and flowing of HR associated specifically with respiration (see Berntson et al., 1997; Porges, 1995). Inhibitory PNS efference slows HR during exhalation, whereas PNS withdrawal speeds HR during inhalation. This respiration-related periodicity in HR defines RSA, which is measured using either frequency domain or time domain methods (see Allen et al., 2007; Katona & Jih, 1975; McCabe, Yongue, Ackles, & Porges, 1985; Santucci et al., 2008; Thayer, Hansen, & Johnsen, 2010).

Frequency domain methods quantify the amount, or power of HRV within specific frequency bands, or windows (see Grossman, 1992). The most commonly used technique for capturing HRV in the frequency domain is spectral analysis, which decomposes the R-R time series into different components using fast-Fourier transformations or autoregressive techniques (see Akselrod et al., 1981; Beauchaine, 2001; Hayano et al., 1991; Thayer, 2002). Fast-Fourier transformations convert time-dependent phenomena into a spectral density function across all frequencies. The spectral density function can then be subdivided into specific frequency bands of interest (Figure 22.4). For example, depending on experiment-specific considerations, total spectral power in HRV might be subdivided into low frequency variability (below 0.04 Hz), mid frequency variability (0.04–0.15 Hz), and high frequency variability (above 0.15 Hz) components. At normal adult breathing rates, this high frequency component yields an estimate of RSA.

Provided that the high frequency band is defined to match the breathing rate of participants—a process called windowing—the estimate of RSA quantifies vagal efference to the heart (see Grossman, 1992; Grossman et al., 1991; Ritz, 2009). Yet breathing rates vary substantially both within and between individuals and samples. This can be especially problematic when ages of participants are dispersed widely, since children breathe at much higher frequencies than adults (see below). One approach used to deal with this problem is to have all participants breathe at the same rate, a process referred to as paced breathing. However, this method is artificial, is impractical for use with very young children, and cannot be used in naturalistic settings that require ambulatory assessment. Many researchers have therefore turned to autoregressive

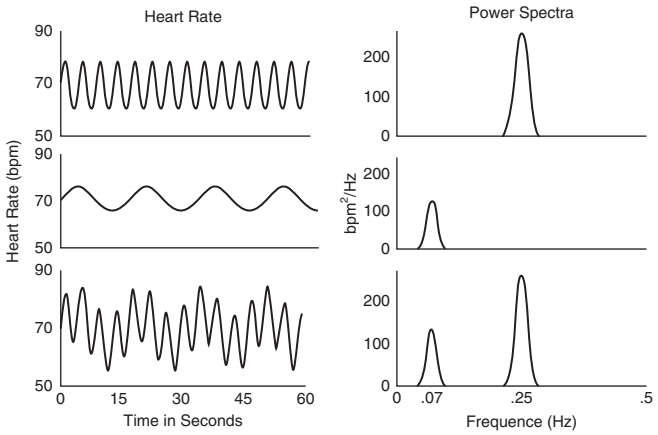


Figure 22.4 Fictitious heart rate signal (left) and associated power spectra (right). The top panels represent pure high-frequency variability (0.25 Hz), which is associated with RSA at normal breathing rates. The middle panels represent low-frequency variability (0.07 Hz), which arises from parasympathetic, sympathetic, and nonneural origin. The bottom panels represent the high- and low-frequency combined signal. Actual heart rate signals include spectral power at additional frequencies. *Source:* Adapted from Beauchaine (2001), Vagal tone, development, and Gray's motivational theory: Toward an integrated model of autonomic nervous system functioning in psychopathology. *Development and Psychopathology, 13*, 183–214.

techniques to circumvent the windowing problem (see Thayer, 2002; Thayer et al., 2010). These methods apply true components analysis to the IBI time series to determine empirically the appropriate breathing frequency for each participant (see Kay & Marple, 1981).

Certain time domain methods can also be used to address the windowing problem. Time domain methods estimate RSA directly from the IBI time series. Although basic metrics such as standard deviation of IBIs are necessarily computed in the time domain, these include all HRV—not only that associated with respiration (see Task Force of the European Society of Cardiology and the American Society of Pacing and Electrophysiology, 1996). Thus, time domain methods must also be chosen carefully if one wishes to extract high frequency HRV associated with respiration. One popular approach is the peak-to-valley method, in which differences between the shortest IBI during inhalation and the longest IBI during exhalation are averaged (Grossman, 1992; Grossman & Svebak, 1987; Grossman, Van Beek, & Wientjes, 1990). When using this approach, respiration data must be collected along with the IBI time series.

Much of the debate concerning control for respiration rate and/or tidal volume when estimating RSA concerns construct validity. Although it has long been assumed that

RSA indexes vagal efference to the heart (see Beauchaine, 2001), under certain conditions this may not be the case unless proper methods are used and/or controls are used (Grossman & Taylor, 2007; Ritz, 2009). It was also once thought that sympathetic influences on cardiac function predominate at low- to mid-frequency bands (Hayano et al., 1991), and that the low/high frequency ratio reflected autonomic balance between the SNS and PNS (e.g., Eckberg, 1997). However, more recent studies demonstrate quite clearly that considerable PNS influence exists in the low and mid frequencies (see Reyes del Paso, Langewitz, Mulder, van Roon, & Duschek, 2013). Thus, low frequency spectral power cannot be used to estimate SNS effects on the heart, and should not be substituted for PEP, which is well validated.

Links to Psychopathology

Although alternative measures of RSA do not correlate perfectly with one another, and do not always index vagal efference to the heart (construct validity), they may nevertheless serve as reliable markers of clinical state (predictive validity). Across many different measurement methods, low baseline RSA and excessive RSA reactivity (i.e., withdrawal) to emotion evocation are associated with internalizing and externalizing symptoms of psychopathology (see Beauchaine, 2001; 2012; 2015a; 2015b; Beauchaine & Thayer, in press; Porges, 2007; Vasilev et al., 2009), and with specific psychopathological conditions and traits, including anxiety (e.g., Hastings, Sullivan et al., 2008; Thayer, Friedman, & Borkovec, 1996), attention problems (see Rash & Aguirre-Camacho, 2012), autism (Neuhaus, Bernier, & Beauchaine, 2014; Patriquin, Scarpa, Friedman, & Porges; 2013), callousness (de Wied, van Boxtel, Matthys, & Meeus, 2012), conduct disorder (Beauchaine et al., 2001, 2007; Mezzacappa et al., 1996), depression (e.g., Rottenberg, 2007; Rottenberg, Salomon, Gross, & Gotlib, 2005; Rottenberg, Wilhelm, Gross, & Gotlib, 2002), nonsuicidal self-injury (Crowell et al., 2005), panic disorder (e.g., Asmundson & Stein, 1994), phobias (e.g., Ahs, Sollers, Furmark, Fredrikson, & Thayer, 2009), and trait hostility (Sloan et al., 1994), among others. Furthermore, concurrent internalizing and externalizing symptoms predict greater RSA withdrawal to emotion evocation than either internalizing or externalizing symptoms alone (Calkins, Graziano, & Keane, 2007; Pang & Beauchaine, 2013). In Figure 22.5 we present data on RSA reactivity to negative emotion induction collected from adolescent girls who engage in nonsuicidal self-injury (Crowell et al., 2005). Interestingly, this finding violates the law of initial values, since self-injuring adolescents

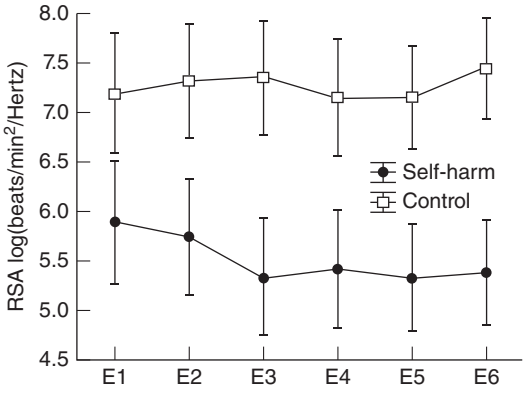


Figure 22.5 Respiratory sinus arrhythmia values (log[beats/min^2/Hz]) for control adolescent girls (open squares) and girls who engage in self harm (closed circles), across six 30 s epochs of negative mood induction during which participants watched a film clip of a young boy with his dying father. A significant main effect of group, and a significant Group × Epoch interaction were found, indicating lower RSA among those who engaged in self-harm, and progressively more RSA withdrawal across epochs for the self harm group, but not for controls. *Source:* From Crowell, Beauchaine, McCauley, Smith, Stevens, and Sylvers (2005), Psychological, autonomic, and serotonergic correlates of parasuicidal behavior in adolescent girls. *Development and Psychopathology, 17*, 1105–1127.

exhibited both lower RSA at baseline and more RSA reactivity to mood induction. Similar findings have emerged for many of the clinical conditions outlined previously.

All of these conditions are characterized by emotion dysregulation—the inability to effectively modulate affective states (see, e.g., Cole et al., 2013). As a result, one or more negative emotions (e.g., sadness, anxiety, rage) are experienced either too intensely or too enduringly to be adaptive (see Beauchaine et al., 2007). Although low baseline RSA and excessive RSA reactivity to emotion evocation mark this core emotion dysregulatory component of psychopathology (Beauchaine, 2001; 2015a; 2015b), specific manifestations (e.g., internalizing versus externalizing) are determined by interactions between emotion dysregulation, dysfunction in other neurobiological systems, and social determinants, some of which are discussed below (see Beauchaine et al., 2001; 2007; Beauchaine & Gatzke-Kopp, 2012; Chambers & Allen, 2007; El-Sheikh et al., 2009; Mead et al., 2010; Porges, 2007).

In contrast to consistent links between low baseline RSA, excessive RSA reactivity, and emotion dysregulation, high baseline RSA and moderate RSA withdrawal during attention demanding tasks are adaptive, and reflect strong regulatory capacity (e.g., Marcovitch et al., 2010; Richards, 1987). Children who exhibit high baseline RSA and either very little RSA withdrawal, or increased RSA to

emotion evocation, which is likely indicative of attention deployment (see Suess, Porges, & Plude, 1994), are either fully or partially protected from adverse outcomes often associated with exposure to maternal depression (e.g., Blandon et al., 2008), paternal antisociality (e.g., Shannon et al., 2007), parental drinking (e.g., El-Sheikh, 2005), and marital conflict/divorce (e.g., El-Sheikh et al., 2001; Katz & Gottman, 1995). Furthermore, studies of normative samples indicate consistent associations between resting RSA and several aspects of adaptive functioning in infancy, childhood, adolescence, and adulthood, including temperamental complaisance (Huffman et al., 1998), social competence, (e.g., Eisenberg et al., 2008) behavior regulation during social challenge tasks (e.g., Hastings, Nuselovici et al., 2008), attachment security (Diamond, Fagundes, & Butterworth, 2012), positive social interactions with partners (Diamond, Hicks, & Otter-Henderson, 2011), and empathy toward others who are in distress (e.g., Eisenberg et al., 1996; Liew et al., 2011). Thus, high baseline RSA and moderate RSA reactivity to emotionally evocative stimuli mark positive social adjustment and resilience in contexts of stress and adversity (see Beauchaine 2001).

Inconsistencies in the Developmental Versus Clinical Literatures?

A major objective of developmental psychopathology research is to juxtapose findings obtained from normative samples with findings obtained from clinical samples in efforts to (1) further our understanding of typical and atypical development, and (2) identify mechanisms through which certain individual differences, though not disordered themselves, render some children more vulnerable to developing psychopathology as they mature (see Beauchaine & McNulty, 2013; Cicchetti, 1984, 2006; Cicchetti & Rogosch, 1996; Sroufe, 1997; Sroufe & Rutter, 1984). By conducting these group comparisons across multiple levels of analysis (e.g., genetic, neural, autonomic, social), we seek to discover etiological and pathophysiological processes, specification of which is sometimes a precondition for effective intervention (e.g., Beauchaine & Gatzke-Kopp, 2012; Beauchaine, Neuhaus et al., 2008; Cicchetti, 2008; Cicchetti & Blender, 2004; Cicchetti & Dawson, 2002). Accordingly, when seemingly different neurodevelopmental processes characterize typical and atypical samples, understanding those differences should be a research priority.

In apparent contrast with findings described previously in which children, adolescents, and adults with clinical levels of conduct problems, delinquency, and related externalizing comportment exhibit excessive RSA withdrawal to emotion evocation (e.g., Beauchaine, Hong et al. 2008; Beauchaine et al., 2001, 2007; de Wied et al., 2012; Mezzacappa et al., 1996), in both normative and high risk samples, symptoms of externalizing behavior are often associated with either *less* RSA withdrawal during lab tasks, or no RSA withdrawal (e.g., Dietrich et al., 2007; Obradović, Bush, Stamperdahl, Adler, & Boyce, 2010). For example, Fortunato et al. (2013) reported less RSA reactivity during positive film clips among at-risk preschoolers who scored high on externalizing symptoms, and Hinnant and El-Sheikh (2009) reported a positive correspondence between externalizing symptoms and increases in RSA during problem solving among children in middle childhood. The consistency of divergent findings in clinical versus normative/high risk samples suggests that the discrepancy is not arbitrary, and cannot be explained away by failures to replicate (see Beauchaine, 2009b).

There are several possible explanations for these discrepant findings. One possibility is that different mechanisms of RSA-behavior relations exist at the extreme of externalizing scores than at the mode of the distribution. Even in high risk samples, few children meet clinical criteria for conduct problems. Thus, within such samples, most of the variance in correlations between RSA reactivity and externalizing behavior is determined by those who score <1 standard deviation above the mean on externalizing, where 84% of observed scores lie. In contrast, most of the clinical samples described previously either met criteria for conduct disorder or scored above the 95th percentile on conduct problems, aggression, delinquency, and so forth. If relations between RSA and externalizing behavior are different at extreme scores, any such difference will be swamped in normative samples by individual variation among those who score closer to the mean (see Beauchaine, 2009b). Notably, however, any such explanation requires specification of alternative mechanisms of RSA–behavior relations among normative versus clinical samples, for which there is no evidence to date.

A second, related explanation concerns the meaning of externalizing symptoms at different points of a normal distribution. Individual differences in externalizing scores are dispersed across the entire range of normal to extreme, and low to intermediate scores do not reflect problem behavior. As alluded to already, most of those who comprise both normative and high risk samples score within normal ranges of externalizing conduct. It makes little sense to suggest that an individual who scores $T = 60$ on the Child Behavior Checklist (Achenbach, & Edelbrock, 1991)—or one standard deviation above the population mean—is

exhibiting problematic behavior. On the contrary, externalizing scores in this range, which are by definition normal, are likely to reflect temperamental exuberance, positive affectivity, social competence, and adaptive engagement with the environment (see Degnan et al., 2011). These are the very traits that modest RSA withdrawal to emotion evocation and attention demanding tasks has been associated with in numerous studies, as described previously (Marcovitch et al., 2010; Richards, 1987; Suess et al., 1994). Thus, measures designed to assess psychopathology may not capture problematic behavior when used among individuals who score within normal ranges. Apparent associations between behavior problems and low RSA reactivity to behavioral challenge among normal and high risk samples may therefore be misinterpretaion.

A third possible explanation concerns differences in definitions of RSA used by developmentalists versus psychopathologists. In our work with clinical samples of adolescents, for example, we typically define (i.e., window) RSA as all spectral power > 0.15Hz (e.g., Beauchaine et al., 2001; Beauchaine, Hong et al., 2008; Crowell et al., 2005; Vasilev et al., 2009). This captures respiratory frequencies at and above 9 breaths per min. In contrast, it is common practice among those who work with developmentally normative and at-risk samples to set age-dependent upper limits when windowing RSA (e.g., Dietrich et al., 2007; Kennedy, Rubin, Hastings, & Maisel, 2004; Leary & Katz, 2004). Although appropriate windowing is important if one wishes to index vagal efference to the heart, upper limits can filter out variance in RSA from participants who breathe especially fast. Importantly, these individuals may be particularly vulnerable to developing psychopathology.

Finally, differences in stimulus conditions used by developmentalists versus psychopathologists must be considered. A core theme of this chapter is that the functions and CNS origins of psychophysiological responses cannot be inferred without considering the context within which the psychophysiological responses are evoked (see Beauchaine, 2012; Beauchaine & Gatzke-Kopp, 2012; Brenner & Beauchaine, 2011). Given its incredible complexity, the human brain is capable of far more variegated responding than the ANS. Yet because the ANS is the final common pathway between CNS responding and behavior, what may appear to be identical ANS response patterns are often initiated by very different neural systems and psychological reactions. As noted already, for example, although considerable evidence suggests that PEP reactivity to incentives marks midbrain dopamine responding, PEP reactivity to threat is driven by different neural systems. Thus, we cannot interpret PEP reactivity as an index of any single CNS process. Rather, as a marker of SNS reactivity, PEP shortening could reflect appetitive responding, fear, or stress reactivity, depending on stimulus conditions.

The same tenet applies to interpretations of RSA reactivity. Links between externalizing behavior and RSA reactivity have been evaluated across many stimulus conditions, including emotion evocation (e.g., Beauchaine et al., 2001), attention allocation (e.g., Suess et al., 1994), executive function (e.g., Marcovitch et al., 2010), and positive mood induction (e.g., Fortunato et al., 2013). In general, *externalizing behaviors are associated with excessive RSA withdrawal specifically during emotion evocation—not during other types of tasks*. This reflects the emotional lability/dysregulation component of conduct problems and related externalizing conditions (see Beauchaine et al., 2007, 2009; Beauchaine & Gatzke-Kopp, 2012). In contrast, *externalizing behaviors are associated with either less RSA withdrawal or increases in RSA during attention demanding, executive function, and problem solving tasks* (e.g., Dietrich et al., 2007; Hinnant & El-Sheikh, 2009; Obradović et al., 2010). This likely reflects attentional difficulties among these individuals (see also Beauchaine, 2001; Rash & Aguirre-Camacho, 2012).

Developmental Considerations

Among healthy individuals, time domain measures of baseline HRV increase linearly throughout infancy, childhood, and adolescence (e.g., Massin & von Bernuth, 1997; Silvetti, Drago, & Ragonese, 2001). For example, Silvetti et al. (2001) reported resting standard deviation of R-R interval values of 87, 133, 155, and 201 for 1–5-year-old, 6–10-year-old, 11–15-year-old, and 16–20-year-old females, respectively. Although slopes were not equivalent across sexes, a linear increase in HRV was also observed among males in the same age groupings (113, 154, 183, and 187), Linear increases in time domain measures of HRV should not be surprising given their dependence on respiratory frequency, which decreases substantially from childhood to adulthood (e.g., Fleming et al., 2011).

Frequency domain measures of RSA also increase with age, yet direct comparisons across broad time intervals are difficult given alternative metrics used to quantify spectral power by different labs and software programs (e.g., ln[beats/min^2/Hz] versus ms^2). Using the ln(beats/min^2/Hz) metric, we have reported resting RSA values of 6.73 among typically developing preschoolers (mean age = 4.5 years), and 7.20 among typically developing middle schoolers (mean age = 13.2 years; see Beauchaine et al., 2001; Crowell et al., 2006). After young adulthood, gradual

decreases in RSA are observed across the life span, although such decreases are moderated by physical fitness (Byrne, Fleg, Vaitkevicius, Wright, & Porges, 1996).

As noted previously, it is also important to define windows appropriately when estimating high frequency spectral power, which is used to extract RSA. To date, many researchers have used windows that are appropriate for infants or very young children across all age ranges in both cross sectional and longitudinal studies, which results in greater and greater misspecification of RSA as individuals mature. As alluded to before, accurate assessment of RSA depends on appropriate specification of respiration rate, which varies considerably across development (see Wallis, Healy, Undy, & Maconochie, 2005). In Table 22.1 we present expected respiration rates (at the 2–1/2 percentile, which captures most individuals) for children, ages 4–16 years. These values can be used to adjust windows when calculating RSA in the frequency domain.

Developmental changes in RSA reactivity are also difficult to evaluate given different stimulus conditions applied across labs and age groups. However, during emotion evocation tasks, we have found RSA reactivity values of −0.89 ln(beats/min^2/Hz) among typically developing preschoolers (mean age = 4.6), 0.02 ln(beats/min^2/Hz) among typically developing middle schoolers (mean age = 10.3), and −0.18 ln(beats/min^2/Hz) among typically developing adolescents (mean age = 13.2; Beauchaine et al., 2001; Crowell et al., 2006; Pang & Beauchaine, 2013). These data suggest that healthy control children become better able to regulate their physiological reactions to emotion evocation as they mature. In contrast, children with behavior problems become more reactive (see Pang & Beauchaine, 2013). Finally, older adults exhibit greater RSA reactivity to acute psychological stress than younger adults (Uchino et al., 1999).

TABLE 22.1 Respiration Rates (2–1/2 percentile) in Beats/Minute and Corresponding Hertz (cycles per second) for Appropriate Windowing of Frequency Domain Metrics of RSA

Age in years	Respiration rate[1] (beats/min)	Hertz
4	20	.33
5	19	.32
6	18	.30
7	17	.28
8	17	.28
9	16	.27
10	15	.25
11	14	.23
12	14	.23
13	13	.22
14	12	.20
15	12	.20
16	11	.18
adult	9	.15

[1]Respiration rates evaluated among 1,109 children, as reported by Wallis et al. (2005)

Choosing Appropriate Stimulus Conditions

In developmental and developmental psychopathology research with infants and children, RSA is often used as a peripheral index of attention allocation, emotion regulation, and social affiliative capacity (see, e.g., Beauchaine, 2001; Patriquin et al., 2013; Porges et al., 1994; Richards, 1985; Suess, et al., 1994). Linking RSA reactivity to these different constructs is fully appropriate when stimulus conditions are designed to evoke a matching psychological state. For example, to infer that RSA reactivity marks individual differences in empathic responding, RSA should be measured during an empathy-eliciting task (see, e.g., Liew et al., 2011). As we note earlier and elsewhere (Beauchaine, 2012), however, far too little attention has been paid to choosing appropriate stimulus conditions in psychophysiological research with children. This problem is especially evident in studies of RSA, where inferences are often extrapolated about psychological constructs (e.g., emotion regulation) from RSA reactivity collected during stimulus conditions that evoke psychological states that are only partly related.

In addition, even though the PNS exerts beat-to-beat control over HR, RSA cannot be measured on a second-to-second basis. Rather, to meet minimum assumptions of spectral analysis and related frequency domain techniques, at least 10 waveforms (respiratory cycles) must be subjected to fast-Fourier analysis (preferably more; see, e.g., Berntson et al., 1997). Thus, in research conducted with infants, who exhibit respiratory frequencies as high as 60 breaths/min, minimum epoch lengths as short as 15 s might be acceptable. In contrast, in research conducted with adults, who exhibit respiratory frequencies as low as 12 breaths/min, minimum epoch lengths may need to be 1 min or longer. Notably, however, stable estimates of RSA can also be extracted by averaging somewhat shorter epochs, an approach that may be advantageous when evaluating PNS reactivity. In our own research, we routinely examine trends in RSA reactivity during 3 min film clips by estimating spectral densities in successive 30 s epochs (e.g., Beauchaine et al., 2001; Crowell et al., 2005, 2006).

Finally, as with any psychophysiological measure, participant movement should be controlled carefully, since movement induces artifacts and increases measurement error by changing metabolic demands (see, e.g., Bush et al., 2011). Notably, however, minimal motor activity,

such as that involving hand movements to complete tasks, do not affect RSA or heart period appreciably (Porges et al., 2007).

ELECTRODERMAL ACTIVITY AND REACTIVITY

The term electrodermal activity (EDA) refers to both tonic and phasic responding of eccrine sweat glands, located primarily on the palms of the hands and soles of the feet, and innervated cholinergically by the SNS (see Uno, 1977; Vetrugno, Liguori, Cortelli, & Montagna, 2003). Eccrine sweat glands respond more strongly to emotion evocation than apocrine sweat glands, which more densely populate other parts of the body (Dawson, Schell, & Filion, 2007; Van Dooren, De Vries, & Janssen, 2012). Thus, assessing eccrine sweat gland activity and reactivity provides useful information about individual differences in emotional reactivity, and induction of certain psychological states, described below.

As noted already, measures of EDA were first used over 125 years ago by the French neurologist Jean Charcot, who discovered that tonic skin resistance differentiated between certain clinical populations (Vigouroux, 1879, 1888), and that phasic changes in skin resistance were evoked by sensory and psychological stimuli (Féré, 1888). Following from this early work, for many decades psychophysiologists continued to quantify EDA as *resistance* to current flow. This is accomplished by applying a small, constant current across the surface of the skin and measuring resistance to that current, usually in units of kilohm (kΩ) or megohm (MΩ). Since sweat conducts electricity, high skin resistance is associated with low sweat gland activity.

Although EDA has remained popular among psychophysiologists given its sensitivity to a wide range of experimental stimuli, its low cost, and its specificity as an index of SNS reactivity (see Uno, 1977; Vetrugno et al., 2003), it is no longer measured in units of skin resistance. Rather, contemporary measures of EDA index skin *conductance* by capturing current flow across the surface of the skin while voltage is held constant. Skin conductance is typically indexed in microsiemens (μS; $[1/\Omega] \times 10^{-6}$). Greater skin conductance results from increased sweat gland activity, and thus provides a more direct, linear index of eccrine sweat gland activity (Lykken & Venables, 1971). Changes in skin conductance that are not linked to any particular environmental stimulus or event are often referred to as nonspecific fluctuations (NSFs). In contrast, event-related skin changes in skin conductance (i.e., those that immediately follow a stimulus) are often called electrodermal responses (EDRs) or skin conductance responses (SCRs). Such event-related SCRs are elicited by a wide range of environmental stimuli of both positive and negative valence/hedonic value (see Dawson et al., 2007).

Recording EDA requires electrodes, electrode gels/pastes containing a conductive medium, signal conditioners/amplifiers, and appropriate software. The EDA signal can be collected in one of three ways, including (1) exosomatic recording using direct current (DC), (2) exosomatic recording using alternating current (AC), and (3) endosomatic recording (for a detailed discussion, see Boucsein et al., 2012). Across techniques, the EDR signal is very sensitive to measurement artifacts, which may arise from a number of influences (e.g., extraneous noise, signal drift across long testing sessions, hydration artifacts, etc.).

When using exosomatic recording with DC current, two silver–silver chloride (Ag/AgCl) electrodes are placed on either the distal phalanges or the thenar and hyper thenar eminences of the nondominant hand. This enables participants to use their dominant hand in experimental protocols without inducing movement artifacts into the EDR signal. Electrolyte gel or a sodium or potassium chloride paste is placed between the electrodes and the skin, and a small resistor is placed in series. A minute electrical current (e.g., 0.5 V) is then run between the electrodes. Exosomatic DC recording is the most commonly used method in psychophysiology research given the relative ease with which signals can be amplified and recorded.

One drawback to DC recording is electrode polarization, which results in voltage that runs counter to the applied voltage at the electrode-metal surface. Polarized electrodes reduce current flow, thereby inducing measurement error, which must be accounted for in quantifying EDA, particularly when tonic measures are computed. Unfortunately, polarization is not readily quantified, and may be induced nonlinearly as a function of applied voltage (Schaefer & Boucsein, 2000). However, some preventative measures can be taken to diminish polarization. For example, use of nonpolarizing (i.e., sintered) electrodes slows, but does not eliminate current flow reductions. Fowles et al. (1981) also recommend reversal of the DC current flow every 10–15 min during a single recording session to reduce polarization. Finally, polarization of electrodes can be eliminated almost entirely by use of AC rather than DC recording (since alternating current cyclically reverses polarity). Nevertheless, traditional DC recording remains more common in EDA research.

When using the third approach, endosomatic recording, no voltage or current is applied. Rather, a single electrode

is positioned on the palmar surface of the hand or sole of the foot and a reference electrode is placed on an inactive site, such as the forearm. Changes in potential are then compared at the active versus reference site. Although advantages of endosomatic EDA recording include its unobstrusiveness and its utility in identifying phasic responses, signals are not readily interpretable (see below), limiting its use in psychophysiological research.

The term EDA is used broadly to refer to tonic levels of skin conductance, and EDR is used to refer to phasic changes in skin conductance. These terms replace galvanic skin response and galvanic skin reflex, respectively, which are now considered to be anachronistic for two reasons (Boucsein, 1992). First, they imply erroneously that the skin-electrode interface behaves like a galvanic cell (a type of battery that generates current through chemical reactions). This does not reflect the exosomatic recording techniques that dominate the field today. Second, the term galvanic skin reflex suggests that responses cannot be elicited by cognitive or emotional processes since such responses are not reflexive. Accordingly, EDA and EDR are now preferred.

Whereas tonic activity captures basal skin conductance level (SCL), phasic reactivity captures moment-to-moment changes in skin conductance that occur either in response to identifiable stimuli (EDRs/SCRs), or in response to unidentifiable stimuli/internal events (nonspecific fluctuations [NSFs]). As this discussion implies, SCRs and NSFs are superimposed on SCL, and must therefore be decomposed mathematically from SCL when analyzing EDA data (see, e.g., Boucsein et al., 2012; Dawson et al., 2007). For exosomatic recordings, such transformations can be modeled offline using the EDA time course, which begins with 1–3 s nonresponse latency following stimulus onset (if a stimulus is presented), followed by a 1–3 s rise in skin conductance level, then a gradual decline/recovery period that may exceed 10 s (Figure 22.6; Dawson et al., 2007). For endosomatic recordings, the signal contains negative or positive responses that can follow mono-, bi-, and triphasic waveforms, and is thus subject to difficulties in terms of quantifying and interpreting the EDR signal (Christie, 1981).

Psychophysiologists are often interested in measuring the relative magnitude of SCRs, or the number of EDRs in a given time interval, since both capture SNS orienting and reactivity. In event-related designs, greater SCR amplitudes are observed when participants attribute more significance or self-relevance to a stimulus (Janes, 1982). In contrast, habituation can be quantified by reductions in EDR amplitudes across subsequent presentations of a stimulus (Martin & Rust, 1976). In addition, a number of other metrics may be of interest, including SCR latency (the time interval between stimulus presentation and an SCR), rise time (the time interval between stimulus presentation and peak SCR), recovery time (the time interval between peak SCR and full recovery of SCL amplitude),

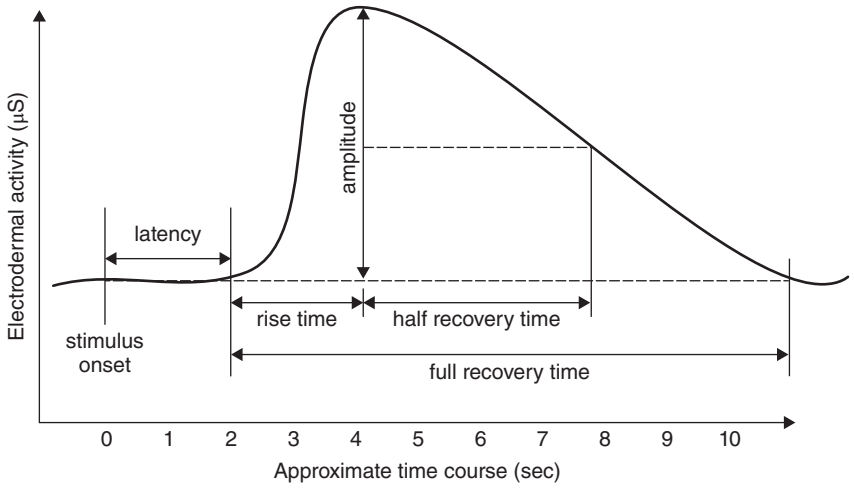


Figure 22.6 Prototypical post-stimulus skin conductance response (SCR). Note the 2–3 s latency period, followed by a steep rise in skin conductance and a much slower recovery to baseline. Both event-related SCRs and nonspecific fluctuations (NSFs) in skin conductance are superimposed on tonic skin conductance level (SCL), and are subject to sensitization and habituation effects. Although the time course of SCRs is often similar to that depicted here, considerable variability is observed, with lower amplitude responses exhibiting shorter recovery times, and higher amplitude responses exhibiting longer recovery times.

half-recovery time (the time interval between peak SCR and 50% recovery of SCL amplitude), number of trials to habituation, and stimulus-specific and nonspecific responding (see Dawson et al., 2007).

Although these measures are highly correlated with one another, some may index particular aspects of psychological functioning better than others. For example, following presentation of stimuli with high subjective significance, recovery time may be slowed more than amplitude is increased (Janes, 1982). In addition, although rise time and recovery time are correlated (Lockhart, 1972), rise time is associated with cardiac acceleration, whereas recovery time is not (Venables, Gartshore, & O'Riordan, 1980). For some populations, differences in responding across metrics may also have clinical implications. For example, antisocial males who exhibit better autonomic conditioning and faster EDR half-recovery time during midadolescence are partially protected from engaging in crime as adults (Raine, Venables, & Williams, 1996).

Links to Psychopathology

EDRs are elicited by a wide range of stimuli, including those that are cognitively demanding, novel, and evocative emotionally (Blanchette & Richards, 2012; Dindo & Fowles, 2008; Gao, Raine, Venables, Dawson, & Mednick, 2010a). Certain personality traits are also associated with individual differences in EDA (e.g., Yoshino, Kimura, Yoshida, Takahashi, & Nomura, 2005), and under appropriate stimulus conditions, patterns of EDA/EDR are associated with psychological vulnerabilities to psychopathology, including trait anxiety, impulsivity, and punishment insensitivity (see Beauchaine, 2001). For example, those high in trait anxiety exhibit greater EDA than controls (Katkin, 1965), and anxious individuals with alexithymia (difficulty identifying and expressing emotions) exhibit greater EDR amplitudes and slower recovery times to novelty than patients low in alexithymia (Rabavilas, 1987).

In contrast, males who are aggressive, and those with externalizing spectrum disorders including ADHD, CD, ASPD, and psychopathy—many of whom experience very little trait anxiety—exhibit attenuated EDA/EDR to a wide range of stimuli (see, e.g., Beauchaine et al., 2001, 2008; Chattopadhyay, Cooke, Toone, & Lader, 1980; Crowell et al., 2006; Giesen & Rollison, 1980; Hare, Frazelle, & Cox, 1978; Lorber, 2004). Such findings are observed in preschoolers, middle-schoolers, adolescents, and adults, and likely reflect a core neurobiological vulnerability to externalizing behavior. Satterfield and Dawson (1971) found that hyperactive children exhibit lower mean SCL, smaller stimulus-specific EDRs, and fewer and smaller NSFs than controls when listening to acoustic stimuli. When administered dopamine agonists, SCL and nonspecific EDRs become similar to those observed in typically developing children.

Children with ADHD also exhibit deficient SCRs during extinction of previously rewarded behaviors (Iaboni, Douglas, & Ditto, 1997), and boys with comorbid ADHD and CD show dampened EDRs, fewer NSFs, and habituate faster to experimental stimuli than controls (Beauchaine et al., 2001, 2008; Herpertz et al., 2001). This pattern of findings is similar to that observed among adults with antisocial personalities (e.g., Raine et al., 2000), and appears to reflect deficient inhibitory control over behavior (Beauchaine et al., 2015). Furthermore, lesions to the ventromedial prefrontal cortex (vmPFC) and the anterior cingulate gyrus—both of which are hypofunctional among psychopaths (Blair, 2008)—result in attenuated SCRs among adults (Tranel & Damasio, 1994). Finally, children and adolescents who exhibit diminished EDRs during fear conditioning are at risk for developing aggression as they mature (e.g., Fung Raine, Loeber, Lynam & Steinhauer, 2005; Gao, Raine, Venables, Dawson, & Mednick, 2010b). Taken together, consistent findings of hyper EDA/EDR among those high in trait anxiety and hypo EDA/EDR among those who are impulsive, aggressive, and low in trait anxiety indicate that EDA serves as reliable biomarker of vulnerability to both internalizing and externalizing spectrum conditions.

Abnormalities in EDA are also observed among those with schizophrenia, and among children with autism spectrum disorder (ASD). In fact, 40–50% of individuals with schizophrenia are classified as electrodermal nonresponders to innocuous but moderately intense stimuli that induce orienting responses in most participants (Bernstein, 1987). In contrast, 6–7-year-old children with ASD and normal intellectual functioning exhibit higher amplitude SCRs to reward feedback (Faja et al., 2013), but are less responsive to visual target stimuli compared to controls (van Engeland, Roelofs, Verbaten, & Slangen, 1991). However, consistent with the notion that autonomic measures usually capture individual differences in traits that cut across disorders, and rarely identify specific disorders as defined by our current diagnostic system (see above), SCR response amplitudes among those with ASD are correlated with internalizing symptoms, and with repetitive behaviors, particularly rituals and need for sameness.

In turn, repetitive behaviors have long been linked to high levels of anxiety in ASD populations, especially among high-functioning individuals (e.g., Gillott, Furniss, & Walter, 2001; Rodgers, Riby, Janes, Connolly, & McConachie, 2012). Thus, as in other populations, greater EDR is associated with anxiety among those with autism, and is not specific to the disorder.

Developmental Considerations

Although developmental changes are not observed in either SCL or NSFs from middle childhood through adulthood, evidence suggests greater EDA among preschoolers. For example, higher initial SCL and more NSFs are observed among 5-year-olds compared to 10-, 15-, 20-, and 25-year-olds (Venables & Mitchell, 1996). Other research groups have also reported stabilization of SCL beginning around age 6 (El-Sheikh, 2007; see also Shields, 1983).

The orienting response can be detected with electrodermal measures among children as young as age 3 months (Ingram & Fitzgerald, 1974). However, mature orienting (see below) does not appear until about age 3 years (Gao, Raine, Dawson, Venables, & Mednick, 2007; Tuvblad et al., 2012). Habituation effects emerge around age 4 years, and continue to increase into childhood (Gao et al., 2007). Like other psychophysiological responses, electrodermal orienting diminishes among older adults, yet habituation remains stable (Plouffe & Stelmack, 1984).

Evoked changes in EDA (i.e., EDRs) in response to external stimuli emerge in infancy around age 30 weeks (Storm, 2001), and are observed thereafter in children, adolescents, and adults (e.g., Cole, Zahn-Waxler, Fox, Usher, & Welsh, 1996; Fabes et al., 1994; McManis, Bradley, Berg, Cuthbert, & Lang, 2001). Such EDRs are observed to a wide range of stimuli, regardless of stimulus valence. Similar to findings associated with orienting, older adults (ages 70–80 years) show attenuated EDRs, especially to negative stimuli (Gavazzeni, Wiens, & Fischer, 2008).

Choosing Appropriate Stimulus Conditions

Perhaps more than any other psychophysiological measure, SCRs are evoked by a wide range of stimuli across sensory modalities (e.g., visual, auditory, tactile). Phasic SCRs are often used to quantify the *orienting response*, a coordinated set of actions across multiple physiological systems in response to novelty and/or changing environmental conditions. Orienting facilitates intake of information and preparedness for action through SNS activation and PNS withdrawal, among other mechanisms (see, e.g., Barry, MacDonald, De Blasio, Steiner, 2013; Porges, 1995). Skin conductance responses have long been used to assess both individual differences in orienting (e.g., Berggren, Öhman, & Fredrikson, 1977; Neary & Zuckerman, 1976), and effectiveness of experimental manipulations in inducing orienting (e.g., Dimberg & Öhman, 1983; McCarthy & Waters, 1997). Orienting responses are often evaluated using aversive auditory stimuli. Children with anxiety disorders produce larger EDRs to loud, abrupt sounds than controls, which reflects hypersensitivity to threat (Bakker, Tijssen, van der Meer, Koelman, & Boer, 2009). In contrast, many of those who are vulnerable to or affected by schizophrenia are under-responsive to orienting stimuli (e.g., Dawson & Nuechterlein, 1984; Gruzelier & Venables, 1972).

Skin conductance response amplitudes are also used to quantify *habituation*, or the tendency of physiological systems to decrease reactivity to a stimulus following repeated exposures (see, e.g., Lykken, Iacono, Haroian, Mc Gue, & Bouchard, 1988). Rates of habituation vary as a function of stimulus saliency (e.g., Öhman, Eriksson, Fredriksson, Hugdahl, & Olofsson, 1974), and faster habituation to punishment/extinction is often observed among impulsive individuals. For example, boys with comorbid ADHD and CD exhibit more rapid habituation to both orienting and aversive stimuli than controls (Herpertz et al., 2001), and less SCR reactivity to punishment/extinction (e.g., Iaboni et al., 1997).

Given the sensitivity of EDR to such a wide range of stimuli, careful attention must be given to experimental design and interpretation of results. Important considerations include the type of stimuli presented (including sensory modality and subjective significance of stimuli), presentation schedule (including sequencing and time intervals between and during stimulus presentations), number and order of different categories of stimuli in a single experiment (Boucsein et al., 2012), and instructions to participants. For example, participants who are instructed to ignore tones exhibit smaller amplitude SCRs and habituate faster than those who are told to attend to stimuli (Iacono & Lykken, 1983).

In general, since EDR is observed to such a wide range of stimuli, skin conductance is of limited value in distinguishing between emotions (see Johnsen, Thayer, & Hugdahl, 1995). Although some have reported differences in SCRs across certain emotions (e.g., higher amplitudes for anger and happiness than for fear, disgust, sadness, and surprise), such findings are not well replicated, and most emotions are indistinguishable using skin conductance alone (see Collet, Vernet-Maury, Delhomme, & Dittmar, 1997). Similar problems arise in research designed to

disentangle affective responses from potentially related but partly distinct processes such as orienting, attention, and goal-directed responses (Bradley, 2009). For example, stimuli of subjective significance elicit SCRs independent of associated emotional arousal level among adults (Dindo & Fowles, 2008), and independent of stimulus novelty and complexity in both normal children and children with psychopathology (van Engeland et al., 1991). Accordingly, manipulating the subjective significance of stimuli may render psychophysiological measures more sensitive to cognitive aspects of psychopathological phenomena, such as ruminative aspects of anxiety, than simply presenting stimuli that are novel or emotionally charged.

Psychological and physiological factors that are specific to participants themselves are also reflected in EDR, which may complicate interpretability. Such variables include skin hydration levels (Bundy & Mangan, 1979), individual differences in tonic electrodermal activity (Benedek & Kaernbach, 2010), age (Barontini, Lazzari, Levin, Armando, & Basso, 1997), medication/drug use (specifically substances with anticholingergic properties; e.g., Green, Nuechterlein, & Satz, 1989), and race (El-Sheikh, Keiley, & Hinnant, 2010; Janes, Worland, & Stern, 1976). For example, research shows consistently lower EDA among African Americans that among Whites. If race effects are not accounted for in psychophysiological research, incorrect conclusions may be drawn about EDA-behavior relations, especially if group comparisons are conducted across subsamples with different race distributions.

Characteristics of the physical environment during EDA recording should also be controlled to reduce their influence on eccrine secretion. For example, ambient temperature and humidity should be maintained and comfortable levels that do not induce hydration artifacts. Furthermore, given the sensitivity of EDA to both internal and external stimuli, preventative measures should be taken to diminish confounds and extraneous stimulation (e.g., noise). First, as outlined above, researchers should collect true resting baselines, even among children, to capture tonic SCL after habituation to the lab environment has occurred. Only then can reactivity to subsequent stimuli be assessed precisely. Many who conduct research with children use vanilla baselines in which soothing or mildly entertaining stimuli are presented (e.g., Jennings et al., 1992), under the assumption that children are either incapable of or will be disturbed by being left alone for 5–10 min—the minimum we recommend for obtaining a true baseline. However, in our own work with children as young as age 4 years—even those with severe ADHD—we have not found obtaining true baselines to be problematic (see, e.g., Beauchaine et al., 2013; Crowell et al., 2006). In addition, Boucsein et al. (2012) recommend affixing electrodes to the skin at a minimum of 5–10 min before recording to allow for better electrode-skin contact, and to provide time for the corneum to hydrate to similar levels across participants.

VULNERABILITY TO PSYCHOPATHOLOGY IN MULTIDIMENSIONAL AUTONOMIC SPACE

Thus far we have discussed only bivariate relations between vulnerability to psychopathology and psychophysiological responding. Well-replicated findings linking low resting heart rate to delinquency and aggression, blunted PEP reactivity during reward to externalizing spectrum disorders, electrodermal responding to trait and state anxiety, and RSA reactivity during mood induction to emotion dysregulation, are all examples of such bivariate associations. A growing body of research, however, has also examined vulnerability to psychopathology across multiple trait dimensions, using psychophysiological variables as biomarkers (see, e.g., Beauchaine et al., 2001; Beauchaine, Hong et al., 2008; Bubier & Drabick, 2008; Crowell et al., 2005, 2006; El-Sheikh et al., 2009; Gray, 1970; Shannon et al., 2007; Tranel, 1983). Extending research on psychopathology to multiple levels of analysis, including neurobiological systems implicated in behavior, mood, and emotion regulation, has important implications for our understanding of psychiatric comorbidity, resilience in the face of vulnerability, and both moderating and interactive effects of different neural systems on psychiatric adjustment (e.g., Beauchaine & McNulty, 2013; Beauchaine & Thayer, in press; Beauchaine et al., 2007; Cicchetti, 2008). Indeed, concurrent compromises in neurobiological systems underlying both appetitive and aversive responding are associated with worse behavioral outcomes than compromises in either system alone (e.g., Sauder et al., 2012). Understanding such interactive effects requires multidimensional models of psychopathology.

Two-Dimensional Models of Personality

Contemporary multidimensional models of psychopathology almost all include, at a minimum, separate axes for appetitive (e.g., behavioral activation, impulsivity, novelty seeking) and aversive (e.g., behavioral inhibition, trait anxiety, harm avoidance) behaviors (see Cloninger, Svrakic, & Przybeck, 1993; Gray, 1987; Gray & McNaughton, 2000;

McNaughton & Corr, 2004). These models follow from recognition that (1) those who fall at extremes along dimensions of approach behavior and avoidance behavior often suffer from functionally impairing levels of impulsivity and anxiety, respectively, and (2) individual differences in approach and avoidance motivation must be represented by separate axes since their neural underpinnings are structurally and functionally distinct (see, e.g., Gray & McNaughton, 2000).

The first two-dimensional model of personality, which was later modified to describe vulnerability to psychopathology, was published by Eysenck (1947; Eysenck & Eysenck, 1969). Eysenck's model included orthogonal dimensions of extraversion and neuroticism, which were later rotated by Gray (1970) to describe individual differences in motivated behavior, based on relative sensitivities of two phylogenetically old neural systems: the dopaminergically mediated mesolimbic (behavioral approach) system (BAS), which evolved to subserve appetitive func-tions, and the serotonergically mediated septo-hippocampal (behavioral inhibition) system (BIS), which evolved to subserve aversive functions (see Beauchaine, 2001; Fowles, 1980, 1988; Gray, 1987). Eysenck's two-dimensional model of personality and Gray's rotation appear in Figure 22.7.

In a highly influential Presidential Address to the Society for Psychophysiological Research, Fowles (1980) reviewed evidence that behavioral approach system activity could be indexed by HR acceleration to incentives, and behavioral inhibition system activity could be indexed by EDRs to mild punishment. He then noted that psychopaths demonstrate normal HR reactivity, behavioral approach, and active avoidance of threat, suggesting a functional BAS, but deficient EDR, passive avoidance learning, and extinction of previously rewarded behaviors, suggesting a dysfunctional BIS. Fowles (1988) later extended this motivational account of psychopathology to anxiety disorders, depression, mania, drug abuse, and schizophrenia.

After publication of Fowles' (1980, 1988) papers, Gray's (1970, 1987) reinforcement sensitivity (BIS/BAS) became a predominant organizing framework in psychophysiological research on psychopathology, including depression (e.g., Davidson, 2003; McFarland, Shankman, Tenke, Bruder, & Klein, 2006), anxiety (e.g., Colder & O'Connor, 2004) externalizing spectrum disorders (e.g., Beauchaine et al., 2001; Crowell et al., 2006), criminal offending, (e.g., Arnett & Newman, 2000), and schizophrenia (e.g., Scholten, van Honk, Aleman, & Kahn, 2006). At present, however, the popularity of reinforcement sensitivity theory in psychopathology research appears to be waning. Although this is likely stems from several factors, which we do not have space to review here (for discussions, see Brenner et al., 2005; Poythress et al., 2008), an especially important consideration is that strictly motivational models of psychopathology do not account for emotion dysregulation, which (1) characterizes many if not most forms of mental illness, (2) is mediated by different neural structures than either approach or avoidance tendencies, (3) tends to emerge later in development than individual differences in approach and avoidance behaviors, and (4) is less heritable than either approach or avoidance tendencies (see Beauchaine, 2001; 2015a; 2015b; Beauchaine & Gatzke-Kopp, 2012; Beauchaine & Thayer, in press; Beauchaine et al., 2007). Any multidimensional autonomic model of psychopathology should therefore include a peripheral index of emotion regulation/dysregulation.

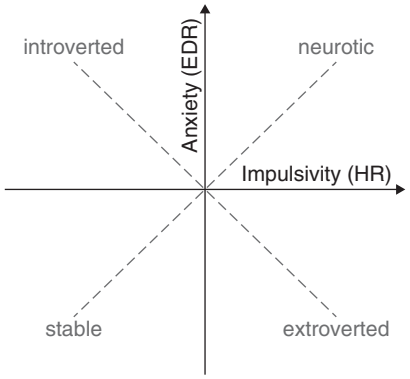


Figure 22.7 Gray's (1970, 1987) rotation (solid axes) of Eysenck and Eysenck's (1969) two-dimensional model of personality (hashed axes). Gray linked Eysenck's behavioral facets of personality to individual differences in susceptibility to reward cues (impulsivity) and punishment cues (anxiety). In doing so, he proposed specific neurobiological systems responsible for processing reward and removal of punishment (the behavioral approach system [BAS]) versus punishment and frustrative nonreward (the behavioral inhibition system [BIS]). Fowles (1980) noted that BAS activation could be indexed psychophysiologically by heart rate (HR) reactivity to incentives, whereas BIS activation could be indexed by electrodermal reactivity (EDR) to extinction/mild punishment. See text for further details. *Sources:* Adapted from Gray (1970), The psychophysiological basis of introversion-extraversion, *Behaviour Research and Therapy, 8*, 249–266; Gray (1987), Perspectives on anxiety and impulsivity: A commentary, *Journal of Research in Personality, 21*, 493–509; Eysenck & Eysenck (1969), *The structure and measurement of personality,* London, UK: Routledge & Kegan Paul; and Fowles (1980), The three arousal model: Implications of Gray's two-factor learning theory for heart rate, electrodermal activity, and psychopathy, *Psychophysiology, 17*, 87–104.

Vulnerability to Psychopathology in Three-Dimensional Autonomic Space

To address these concerns, we characterize vulnerability to psychopathology in three-dimensional autonomic space (Figure 22.8). Consistent with traditional motivational models, one of our axes represents trait impulsivity, assessed psychophysiologically as PEP reactivity to incentives, and a second represents trait anxiety, assessed psychophysiologically as EDR (either baseline NSFs or SCRs to mild punishment). However, we also include a third dimension, which represents emotion dysregulation, assessed psychophysiologically as RSA reactivity to emotion evocation (see Beauchaine, 2001; 2015a; 2015b). We have used this three-dimensional model as an organizing framework in our work on ANS-behavior relations among preschoolers with ADHD and ODD (e.g., Beauchaine et al., 2013; Crowell et al., 2006), middle schoolers with CD and depression (e.g., Marsh et al., 2008; Shannon et al., 2007; Vasilev et al., 2009), and adolescents who engage in self-harm (e.g., Crowell et al., 2005, 2013). Adding an emotion regulation dimension to traditional motivational models of psychopathology is important because many individuals who exhibit motivational vulnerability (i.e., high trait impulsivity or high trait anxiety) are protected from psychopathology if they have strong emotion regulation skills. For example, trait impulsivity, expressed early in life as ADHD, may only develop into more severe externalizing conduct if a child fails to develop strong emotion regulation capabilities, as reflected psychophysiologically in RSA (see Beauchaine et al., 2007; Beauchaine & McNulty, 2013).

OTHER PERIPHERAL MEASURES

Although cardiovascular and electrodermal measures are the most popular psychophysiological techniques in developmental, child psychopathology, and developmental psychopathology research, other methods can also be useful in addressing vulnerability–behavior relations, and other research questions discussed above. We now turn our attention to some of these alternative methods.

Startle and Prepulse Inhibition

The startle reflex is an ANS-mediated response that is elicited by abrupt presentations of intense stimuli. A variety of stimuli in auditory, tactile, vestibular, visual, and

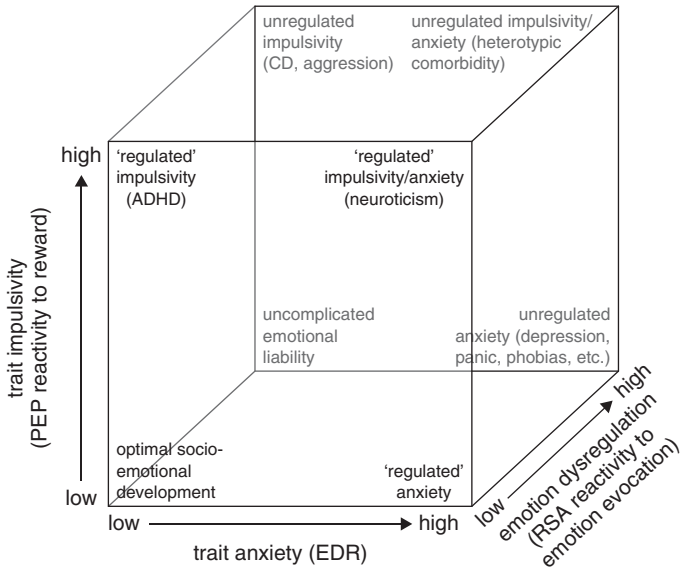


Figure 22.8 Three-dimensional representation of motivational and emotion regulational vulnerabilities to psychopathology. Trait impulsivity, assessed psychophysiologically as PEP reactivity to incentives, is depicted on the y axis. Trait anxiety, assessed psychophysiologically as EDR to extinction/punishment, is depicted on the x axis. Emotion dysregulation, assessed psychophysiologically as RSA reactivity to emotion evocation, is depicted on the z axis. Vulnerability to internalizing disorders is especially high when trait anxiety and emotion dysregulation co-occur, and vulnerability to externalizing disorders is especially high when trait impulsivity and emotion dysregulation co-occur. In contrast, vulnerability to internalizing and externalizing disorders may be offset by strong emotion regulation (see text). ADHD = attention-deficit/hyperactivity disorder. CD = conduct disorder. Heterotypic comorbidity = co-occurrence of internalizing and externalizing disorders.

olfactory modalities generate and/or contribute to startle responses among humans and other mammals (Cook, Davis, Hawk, Spence, & Gautier, 1992; Paschall & Davis, 2002; Yeomans, Li, Scott, & Frankland, 2002). Startle reflexes are produced by skeletomuscular contractions, which generate sudden, bilateral movements. These movements are most observable in the neck and shoulders, and in the eyeblink response. Other physiological changes, such as increases in blood pressure and heart rate, accompany the startle response (Holand, Girard, Laude, Meyer-Bisch, & Elghozi, 1999), and serve to prepare the body for defensive action. Startle responses are typically quantified by measuring skeletomuscular contractions following stimulus presentations. In humans, reflexive eyeblinks, generated by the orbicularis oculi muscle, are measured using electromyography (EMG; Berg & Balaban, 1999). Metrics of interest include signal magnitude (peak minus baseline), onset latency (interval to onset of response), and signal latency (interval between stimulus onset and peak response).

Startle modulation, that is, startle potentiation or inhibition, is quantified as the difference between startle elicited by a stimulus with and without the modulating stimulus/stimuli. Both the startle stimulus itself and modulating stimuli can be tested with varying intensities. Startle can be potentiated by pairing a startle-inducing stimulus, such as a loud sound, with aversive stimuli that either affect the senses directly (e.g., whiplash) or are psychological in nature (e.g., aversive visual stimuli). In contrast, startle can be diminished when an intense stimulus is presented immediately after a comparably weaker, nonstartling stimulus. The term prepulse inhibition (PPI), refers to this decrease in startle and is used to index *sensorimotor gating*, or the degree to which central inhibitory mechanisms regulate reflexive startle responses. The prepulse stimulus can be presented in the same or different sensory modality as the pulse, or startle stimulus.

Neural circuitry underlying acoustic startle is well characterized from animal research. Loud acoustic stimuli are initially processed by cochlear root neurons (CRNs) in the auditory nerve, which project to neurons in the nucleus reticularis pontis caudalis (PnC) that then synapse onto spinal motoneurons (Lee, López, Meloni, & Davis, 1996). Lesioning the CRNs or PnC eliminates the startle reflex, whereas lesions to other nearby structures, such as the ventrolateral lemniscus, suggest that these regions may be involved, but are not essential (Lee et al., 1996). The neural circuitry underlying PPI is more complex than the primary startle circuit described above. Brain areas implicated in PPI include limbic regions (e.g., hippocampus, basolateral amygdala, nucleus accumbens), the striato-pallidal circuit, thalamic and pontine nuclei, and the superior and inferior colliculi (Swerdlow, Geyer, & Braff, 2001).

Interest in startle responding derives in part from its sensitivity to modulatory effects of affective and attentional processes. Reflexive startle responses are exaggerated (i.e., potentiated) by aversive emotional cues (particularly fear-inducing stimuli), and suppressed by pleasant and otherwise appetitive stimuli (see Lang, Bradley, & Cuthbert, 1990). Potentiation and suppression of startle are effected through modulation of the PnC by the amygdala, which filters incoming information for emotional valence and self-relevance, among other functions (see, e.g., Paton, Belova, Morrison, & Salzman, 2006; Rosen, Hitchcock, Sananes, Misrendino, & Davis, 1991). Local microinjections of norepinephrine into the central nucleus of the amygdala potentiate the acoustic startle response, implicating the SNS in startle sensitization (Fendt, Koch, & Schnitzler, 1994). Furthermore, pharmacological blockade of the central nucleus of the amygdala eliminates fear-potentiated startle, but not light-enhanced startle, while preserving the baseline startle reflex (Davis, Falls, Campeau, & Kim, 1993; Walker & Davis, 1997). Consistent with these findings, systemic exposure to anxiolytics blocks startle potentiation to aversive cues in human subjects, but does not decrease overall startle magnitude (Patrick, Berthot, & Moore, 1996). Taken together, these findings suggest that the startle reflex and PPI may be especially useful for assessing fear-conditioning and vulnerability to certain forms of psychopathology that are characterized by excessive or insufficient experience of fear and anxiety.

Links to Psychopathology

Since startle responding is mediated by affective traits and modulated by affective stimuli, both the presence and magnitude of a response may provide insight into affective information processing. Infants as young as 5 months exhibit differential startle in response to acoustic stimuli when paired with positive versus negative visual stimuli (Balaban, 1995). However, such effects are inconsistent in developmental research (e.g. van Brakel, Muris, & Derks, 2006), and may reflect age differences of participants and paradigm heterogeneity between studies (Quevedo, Smith, Donzella, Schunk, & Gunnar, 2010; see below). Nevertheless, increased startle responding in both children and adolescents may mark vulnerability to later anxiety disorders (Grillon, Dierker, & Merikangas, 1998; Merikangas, Avenevoli, Dierker, & Grillon, 1999).

In contrast, reduced startle reflexes characterize child and adolescent samples who are hyporesponsive

to fear- and anxiety-provoking stimuli. For example, diminished acoustic startle is observed among preschoolers who were exposed to cocaine prenatally, which suggests impaired fear conditioning (Mayes, Grillon, Granger, & Schottenfeld, 1998). Similarly, children with disruptive behavior problems exhibit smaller acoustic startle reflexes than typical children when viewing unpleasant stimuli (Goozen, Snoek, Matthys, Rossum, & Engeland, 2004), and juvenile offenders show reduced startle blinks compared to nonoffenders. Even among offenders, conduct problems and psychopathic traits correlate negatively with startle response amplitudes (Syngelaki, Fairchild, Moore, Savage, & van Goozen, 2013).

Aberrant PPI is observed in certain clinical populations, including patients with schizophrenia, Tourette syndrome, and ADHD (e.g. Schulz-Juergensen, Thiemann, Gebhardt, Baumgarten-Walczak, & Eggert, 2014; Swerdlow et al., 2006; see Swerdlow & Neal, 2012). For example, children with ADHD exhibit diminished PPI, which improves following methylphenidate administration (Ashare et al., 2010; Hawk, Yartz, Pelham, & Lock, 2003, but see Schulz-Juergensen et al., 2014).

Developmental Considerations

Preschool-age children exhibit fully mature habituation of sensory-elicited startle, yet prepulse inhibition and facilitation of sensory-elicited startle does not emerge until around 8 years of age, which suggests a developmental lag between processing of a single stimulus and higher-order processing of multiple stimuli in relation to one another (see Ornitz, 1999). Prepulse modulation of startle, by definition, requires presentation of a prepulse stimulus, and differs from attention-modulated startle, which requires participants to actively wait for and attend to target stimuli. Although studies of the effects of attention on startle in pediatric samples are rare, attention may modulate responses more for infants and young children than adults (Ornitz, 1999). In contrast, affective modulation of startle under most conditions may be similar across the life span. For example, McManis et al. (2001) identified startle modulation using emotional images among children, adolescents, and adults. Similarly, Quevedo et al. (2010) reported comparable response patterns of emotion-modulated startle potentiation among 3-, 5-, 7-, 9-year-olds, and adults. However, 3- and 5-year-olds were less likely to respond to stimuli, and produced baseline startle of smaller magnitudes than adults (Quevedo et al., 2010). Additionally, both McManis et al. (2001) and Quevedo et al. (2010) identified significant sex effects, whereby female participants were more reactive to stimuli than male participants, independent of age (see also Kudielka et al., 2004). Furthermore, children between ages 9 and 12 years produce larger auditory-induced startle responses than adults when viewing unpleasant images for very short (60 ms) prepulse-pulse intervals (i.e., duration between onset of an image and an auditory tone), but adults produce larger startle responses for both pleasant and unpleasant images for prepulse-pulse intervals lasting 3500 and 5000 ms (Waters, Lipp, & Spence, 2005). Thus, some aspects of startle, such as attention-modulated responses, exhibit developmental effects that may be mediated by maturation of cortical-subcortical networks (Ornitz, 1999).

Choosing Appropriate Stimulus Conditions

Acoustic-related startle is well suited for laboratory settings given how readily and reliability it is produced. Acoustic startle requires a loud, sudden onset stimulus (typically 100 dB[A] SPL or more), and is evoked best by frequencies within the normal hearing range (Pilz, Schnitzler & Menne, 1987) and sounds that are registered in both ears concurrently (Li & Frost, 1996). In general, increasing the intensity of acoustic stimuli increases the associated magnitude, amplitude, and likelihood of inducing a response, and reduces onset latency (Blumenthal et al., 2005). Vestibular stimulation may also elicit startle responses, which can be modulated when paired with other stimuli, such as auditory tones (Blouin, Siegmund, & Inglis, 2007). Vestibular-evoked startle can be induced by rapid forward accelerations such as those used to test safety of passenger cars (Blouin, Inglis, & Siegmund, 2006). Similarly, tactile stressors, such as airpuffs to the eye and exposure to cold, can induce or moderate startle (Deuter et al., 2012; Hawk & Cook, 1997). Synchronous acoustic, vestibular, and/or tactile stimulation elicits the startle reflex more strongly than temporal summations of a single modality (Yeomans et al., 2002). Compared to other sensory modalities, startle resulting from olfactory and visual stimuli may be difficult to detect reliably in the absence of other sensory stimulation, and thus, are typically paired with other stimulus types to potentiate or diminish startle responses (e.g., Cook et al., 1992; Paschall & Davis, 2002; see Yeomans et al., 2002).

In experiments testing PPI, the lead interval, or the time between presentation of the prepulse and pulse may be varied depending on experimental objectives. Lead intervals of 30–500 ms typically yield PPI, whereas longer lead intervals often potentiate subsequent startle, known as

prepulse facilitation (Ashare et al., 2010). There is no gold standard for optimal prepulse intensity, although acoustic prepulses are typically quantified in terms of intensity above background noise. Importantly, stronger and more salient acoustic prepulses are generally associated with greater PPI (Braff, Geyer, & Swerdlow, 2001).

Since experiments that test the startle reflex typically involve presentation of aversive stimuli, such as distressing images or loud sounds, use of the startle paradigms for research on fear and anxiety may create ethical concerns, especially among certain pediatric populations such as those who suffer from PTSD and other anxiety disorders. Thus, although startle paradigms may be especially useful for studying state and trait anxiety, their utility must be weighed against potential risk to vulnerable participants.

Pupillometry

Since the eyes are an extension of the CNS, assessing certain aspects of ocular function may provide useful information about the physical and psychological integrity of an organism. In fact, ocular response patterns can be used to infer both voluntary and involuntary psychological processes related to attention, inhibitory control, emotional saliency, and social functioning (e.g., Hess & Polt, 1960; Klein & Foerster, 2001; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Wierda, van Rijn, Taatgen, & Martens, 2012).

The pupil, an opening in the center of the iris, allows light to enter the eye. Pupil diameter, which dictates how much light strikes the fovea and retina, is determined by tonic and phasic activity of two types of smooth muscles—radial muscles, which increase pupil size when stimulated, and sphincter muscles, which decrease pupil size when stimulated. Radial muscles are innervated by noradrenergic fibers of the SNS, whereas sphincter muscles are innervated by cholinergic fibers of the PNS. Thus, both sympathetic and parasympathetic efference determine pupil size, and measuring pupil size at rest and in response to changes in internal and external environmental conditions can be used to assess autonomic function. Although pupil size changes reflexively depending on ambient light conditions, pupillary responses are also evoked by mechanisms unrelated to visual perception, which may or may not be recognized consciously (see Laeng et al., 2012). Pupillary responses to psychological manipulations may therefore provide information that cannot be obtained from self-reports.

Pupillometry (PPM) refers to the measurement of pupil diameter, including constriction and dilation. This is accomplished using video recording and eye-tracking technologies. Of note, pupil dilation correlates with activation of noradrenergic fibers originating in the locus coeruleus, which supports use of PPM as an index of SNS function (Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010; Koss, 1986). Pupil dilation is also associated with aspects of emotion and cognition, and therefore varies as a function of emotional saliency (e.g., Hess & Polt, 1960), task difficulty (e.g., Kahneman & Beatty, 1966), and attention deployment (e.g., Wierda et al., 2012). Under some circumstances, pupil dilation may more accurately track temporal aspects of attention effects than imaging methods such as EEG and fMRI (Siegle, Steinhauer, Stenger, Konecky, & Carter, 2003; Wierda et al., 2012).

Links to Psychopathology

Pupillometry has been used among a number of clinical populations. Although it has more limited use in typically developing pediatric samples, the technique has been used extensively among children, adolescents, and adults with ASD. Among children with autism, viewing others' faces is associated with pupillary constriction, in contrast to typical dilatory responses exhibited by mental-age and chronological-age matched controls (Anderson, Colombo, & Shaddy, 2006). In addition, reduced pupil size when viewing neutral faces, virtual faces, and objects differentiates children with autism from mental- and chronological-age matched controls with 72% accuracy, and may therefore serve as a marker for ASD (Martineau et al., 2011). Such findings may result from an imbalance between parasympathetic and sympathetic activity, a finding that has received some support based on neurochemical research in autism (Lam, Aman, & Arnold, 2006), and from studies using cardiac psychophysiology (e.g., Faja et al., 2013; Neuhaus, Bernier, & Beauchaine, 2015; Neuhaus et al., 2014; Patriquin et al., 2013).

Studies of pupil dilation indicate that anxious 9–13-year-olds exhibit prolonged responses to threatening stimuli, and invariant responses to different levels of threat compared to nonanxious controls (Price et al., 2013). In contrast, depressed children and adolescents exhibit reduced pupil dilation to negative words 9–12 s following stimulus presentation compared with controls, an effect that increases with greater symptom severity (Silk et al., 2007). Among adults with major depression, remission following cognitive therapy is associated with either (1) low baseline symptom severity, or (2) high baseline symptom severity, but low sustained pupillary responses to presentation of negative words, suggesting that PPM may be an effective means of predicting treatment response (Siegle, Steinhauer, Friedman, Thompson, & Thase, 2011).

Developmental Considerations

Developmental trajectories in pupillary responding are not well-studied. However, pupillometry and task performance data reveal that 10-year-olds perform similarly to adults on more basic tasks requiring attentional control and working memory, but struggle when performing more difficult cognitive tasks (Karatekin, 2004; Karatekin, Marcus & Couperus, 2007; Karatekin, Marcus, & White, 2007). In contrast, participants in mid- to late-pubescence may be more reactive to emotionally evocative and neutral words compared to pre-/early pubertal participants, as evidenced by greater peak pupil dilation to words, faster reaction times when reporting word valence, and greater recall of emotionally evocative words after task completion (Silk et al., 2009). Importantly, pubertal state—not age—accounts for such differences. Finally, both sympathetic and parasympathetic pupillary responses may diminish with advancing age in adulthood (Pfeifer et al., 1983; Van Gerven, Paas, Van Merriënboer, & Schmidt, 2004).

Choosing Appropriate Stimulus Conditions

As with other psychophysiological measures, both tonic and phasic pupillary responses are often assessed. In event-related designs, PPM may be used to index responses to a wide range of stimuli (most often emotionally salient images), and to evaluate cognitive processes relating to attention, executive load, and working memory. Constriction and dilation velocities are relatively fast, averaging just over 2 mm/sec in healthy samples (Boev et al., 2005). Thus, PPM can provide high temporal resolution if recordings are appropriately deconvolved (e.g., Wierda et al., 2012). However, because psychologically induced pupillary changes are comparatively smaller than light-induced changes, and rarely exceed 0.5 mm (Beatty & Lucero-Wagoner, 2000), it is important to use stimuli of enough saliency to produce detectable changes in pupil diameter, and to control for brightness level across stimulus conditions. As with most psychophysiological measures, PPM diminishes with habituation (Privitera, Renninger, Carney, Klein, & Aguilar, 2010), fatigue (Morad, Lemberg, Yofe, & Dagan, 2000), and age (Van Gerven et al., 2004), so care should also be taken to control for these effects if they are not of experimental interest.

Eye Tracking

Given the importance of social reciprocity in maintaining dyadic relationships (Back et al., 2011), variables such as gaze location and duration have long been of interest to behavioral scientists, including psychopathologists (e.g., Argyle & Dean, 1965). In early eye tracking research, eye movements and gaze location were inferred from either direct observation, or from coded videotapes of participants (e.g. LaFrance & Mayo, 1976). In contrast, contemporary eye-tracking devices record ocular movements with high temporal and spatial resolution. The most common eye-tracking method, video-oculography, involves illuminating the eye with an infrared or near-infrared light beam. A video camera is used to capture reflected images from the cornea and pupil of one or both eyes. The measure is first calibrated to each individual's ocular anatomy, based on the assumption that the reflection from the cornea is the brightest point on the reflected image, and the reflection from the pupil is the second brightest. By contrasting the relative position of these two reflected points, eye-tracking software identifies where an individual is gazing in real-time (Morimoto & Mimica, 2005).

Developed in the later part of the nineteenth century, early eye-tracking devices were quite invasive, requiring direct contact with the cornea of the eye, and motionless participants (Javal, 1878). Eye-tracking techniques became more precise with co-registration of corneal measurement and motion picture technology (see Mackworth & Mackworth, 1958). At present, participants may need to keep their head stationary (using a chin rest or bite board to provide more precise signals), or be able to move freely during recording, depending on the device being used. During free-moving recordings, many devices can be worn as goggles or contact lenses, with the obvious advantage of more naturalistic interaction with the environment.

An alternative to video-oculography, electrooculography, records eye movement and position by measuring the difference in electrical potential between two electrodes affixed to the surface of the skin on either side of the eye (Heide, Koenig, Trillenberg, Kömpf, & Zee, 1999). Notably, this approach is not well suited for evaluating variables such as gaze duration, fixation, or latency during social interactions or lab tasks. Rather, it is more commonly used to measure rapid eye movement (REM) in sleep research and is increasingly a method of interest for human-computer interfaces (e.g., Barea, Boquete, Rodriguez-Ascariz, Ortega, & López, 2010; Lopes, Tabachnik, Muller, Levison, & Bryan, 1983).

Three types of eye movements that occur while we are awake include *fixation* (maintaining gaze on a particular aspect of a visual scene), *saccades* (brief, rapid ocular movements observed while we scan a visual field), and *smooth pursuit* (slow ocular movements associated with tracking a moving stimulus; see Kowler, 2011). Both saccadic and smooth pursuit eye movements are involved in gaze

shifting, which allows large amounts of visual information to reach the fovea, and provides for detailed processing of the visual field (Lisberger, Morris, & Tychsen, 1987; see Henderson, 2003). Although smooth pursuit eye movements are largely voluntary, saccades can be initiated voluntarily (e.g., when targets are purposely attended to) or involuntarily (e.g., when targets suddenly appear and capture attention without conscious processing). Small, abrupt saccades observed during fixation cannot be controlled consciously.

Links to Psychopathology

Eye tracking dysfunction (ETD) is observed in several clinical disorders, including ADHD, conduct disorder, oppositional defiant disorder, Tourette syndrome, reading disorder, ASD, and schizophrenia (for a recent review see Rommelse, Van der Stigchel, & Sergeant, 2008). A voluminous literature links saccadic and smooth pursuit abnormalities in eye tracking to schizophrenia among adults (see Gooding & Basso, 2008; Levy et al., 2010; Mitropoulou et al., 2011). For example, both saccades toward anticipated targets and antisaccades made purposefully away from targets are disrupted in adults with schizophrenia (e.g., Barton, Pandita, Thakkar, Goff, & Manoach, 2008; Crawford, Haeger, Kennard, Reveley, & Henderson, 1995). In their recent meta-analysis, which assessed studies of ETD in schizophrenia conducted since 1993, O'Driscoll and Callahan (2008) determined that differences between patients and controls are most pronounced for global pursuit measures, or the extent to which eye position matches target positions. Specific measures that yield large effect sizes are maintenance gain, defined as the ratio of velocity of eye movement to that of target movement, and leading saccades, a subtype of anticipatory saccades that trace eye movements ahead of the target with small amplitudes (e.g., between 1–4 degrees; see Ross, Olincy, & Radant, 1999).

Importantly, recent research indicates that high error rates in antisaccade performance, an index of one's ability to consciously inhibit actions, can be identified in adolescents with an average age of psychosis onset as young as 13 years (Karatekin, Bingham, & White, 2010). Furthermore, adolescents who carry genetic risk for schizophrenia yet do not express the disorder exhibit increased corrective saccades compared with controls (Schreiber et al., 1997). Such findings suggest considerable promise for premorbid identification of vulnerable individuals, who can then be enrolled in preventive interventions, which may decrease risk for psychosis onset by as much as 65% across three years (McGorry et al., 2002). This is a clear example of the potential value of psychophysiological research in prevention and treatment of an extremely debilitating psychiatric condition (see also Beauchaine, 2009a; Beauchaine & Marsh, 2006; Beauchaine, Neuhaus et al., 2008).

Dysfunctional eye tracking in schizophrenia likely reflects aberrant neural processing of visual information, and compromised ability to anticipate the location of future visual stimuli (Chen, 2011; Levy et al., 2010). The neural substrates for these deficits include the middle temporal area (Chen et al., 2008), an extrastriate region involved in early motion perception, the parietal cortex (Wang, Brown, Dobkins, McDowell, & Clementz, 2010), particularly the ventral intraparietal area (Schlack, Hoffmann, & Bremmer, 2003), and the frontal eye fields (FEFs) of the PFC (McDowell et al., 2002). Both parietal regions and the FEFs are implicated in later-stage processing of motion.

Interestingly, acute nicotine administration improves eye acceleration during smooth pursuit initiation and reduces leading saccadic eye movements during visual tracking in both smoking and nonsmoking patients with schizophrenia, but has no effect on nonsmoking control participants (Avila, Sherr, Hong, Myers, & Thaker, 2003; Sherr et al., 2002). These results may suggest a role for nicotinic acetylcholine receptors in ETD, a conclusion supported by findings indicating that these receptors are hypofunctional in schizophrenia (Leonard et al., 1996). Nicotine may improve eye-tracking deficits via modulation of dopamine (DA) in the brainstem and midbrain. Nicotinic projections originating from the pedunculopontine tegmental nucleus agonize DA neurons in the superior colliculus, a structure implicated in eye movement control (Kobayashi & Isa, 2002). Importantly, effects of nicotine are not specific to eye movements. Nicotine administration improves sustained attention, psychomotor speed, and performance on other cognitive tasks among those with schizophrenia and other forms of pathology, including Alzheimer's disease and ADHD (Rezvani & Levin, 2001).

Eye tracking is also used extensively in research on ASD (e.g., Klin et al., 2002). An assumption of this research is that patterns of gaze shifting and fixation will provide insight into difficulties with social communication and reciprocity experienced by affected individuals. Using eye-tracking technology, Klin et al. (2002) determined that males with autism fixate less on the eye region and more on mouths, bodies, and objects when viewing social scenes compared to males who are not on the autism spectrum. Similarly, individuals with high functioning autism fixate more heavily on the mouth region and less on the eye region than controls when making judgments about facial

emotions (Spezio, Adolphs, Hurley, & Piven, 2007). Such visual fixation differences in autism are not identifiable in early infancy (Key & Stone, 2012; Young, Merin, Rogers, & Ozonoff, 2009) but emerge during the first 12 to 24 months of life (Rogers, 2009). Thus, individuals with ASD may acquire and use socially relevant information differently than typically developing individuals, and these divergent strategies may either help account for or in part cause social difficulties that characterize the spectrum. Consequently, social skills training for autism have begun to integrate eye gaze monitoring using eye-tracking technology (e.g., Lahiri, Bekele, Dohrmann, Warren, & Sarkar, 2013).

Developmental Considerations

Although peak velocity and duration of correct prosaccades is observed among 4–6-year-olds, preadolescents exhibit prolonged reaction times of prosaccades and antisaccades compared with adults (e.g., Klein & Feige, 2005; Munoz, Broughton, Goldring, & Armstrong, 1998; see Karatekin, 2007). Smooth-pursuit gain may develop through adolescence (e.g., Accardo, Pensiero, Da Pozzo, & Perissutti, 1995; Salman, Sharpe, Lillakas, Dennis, & Steinback, 2006; see Karatekin, 2007). Furthermore, implicit learning of a visual sequence matures by around age 8 to 10 years, whereas intentional learning continues to develop through adolescence (Karatekin, Marcus, & White, 2007). Evidence for differential processing of faces using eye tracking across age groups is limited and inconsistent (Marcus, 2005; Schwarzer, Huber & Dümmler, 2005) despite some findings of better facial recognition performance among adults than children (Marcus, 2005).

Choosing Appropriate Stimulus Conditions

In psychiatric research, smooth pursuit eye movements are often studied using a neutral stimulus that moves sigmoidally, although trapezoid and triangular target motion patterns are also used. Target speed (in degrees per s), amplitude, and number of stimulus cycles are sometimes varied depending on the experimental design, although no standardized protocol is used (Smyrnis, 2008). Since certain saccades, such as anticipatory and catch-up saccades, are also inherent to smooth pursuit tasks, both smooth pursuit and saccadic eye movements can be studied in a single paradigm. Antisaccades can also produce involuntary, prosaccades (saccades toward the target stimulus) and thus, both anti- and prosaccades can be used to index inhibitory control over the natural tendency to gaze towards a target (e.g., Klein & Foerster, 2001).

With the advent of mobile, high-precision eye-tracking technologies, much greater experimental flexibility is afforded. Eye movement patterns during passive viewing of faces or during dynamic social interactions, for example, can be quantified and compared within and between participants. Importantly, spontaneous gazing may need to be differentiated from instructed and task-specific behavior. For example, although individuals on the autism spectrum can fixate on the eyes of others in much the same way as controls when they are instructed specifically to do so, they exhibit large fixation differences when viewing faces freely (see above; Senju et al., 2009). Finally, use of mobile eye-tracking technologies is of considerable value in assessing social difficulties among those with autism, and in evaluating populations with eye movement deficits unrelated to social functioning, such as children with reading disorder (e.g., De Luca, Di Pace, Judica, Spinelli, & Zoccolotti, 1999).

Electromyography

Electromyography (EMG) is a technique used to measure electrical activity of muscles, both at rest and while contracting. To record from muscular tissue, electrode needles are inserted into skin directly above the muscles of interest. Electromyography is used in both experimental and clinical settings, primarily for evaluation of neural, muscular, or neuromuscular disorders. The technique is frequently used in nerve conduction studies, which determine the integrity and speed of nerve impulses. Electromyography can also be used to distinguish volitional motor activity, such as psychogenic jerking behavior, from avolitional motor activity, such as tics or myoclonus (involuntary muscle twitching). Electromyographic bursts less than 70 ms may indicate organic motor pathology, whereas prolonged and delayed responses involving coordination of multiple muscle groups suggest that movements are psychogenic (Kirsch & Mink, 2004).

Electromyography is also used to investigate facial mimicry and affective processing, and is particularly sensitive to emotional responding because it detects activity in facial muscles that cannot always be observed outwardly, and that may not be activated during conscious elicitation of facial expression (Tassinary & Cacioppo, 1992). Since unique patterns of facial muscle activity are induced when producing angry, happy, fearful, or sad faces, facial expressivity can be assessed using this technique (Deschamps, Schutte, Kenemans, Matthys, & Schutter, 2012; Ekman, Friesen, & Hagar, 2002). For example, spontaneous but not voluntary facial mimicry is compromised among adolescents and adults on the autism spectrum (McIntosh, Reichmann-Decker, Winkielman, & Wilbarger, 2006).

More recently, facial EMG has been co-registered with fMRI to simultaneously acquire neural and neuromuscular activity associated with particular affective states, enabling more sophisticated experimental designs (Heller, Greischar, Honor, Anderle, & Davidson, 2011).

Salivary Alpha-Amylase

Salivary alpha-amylase (sAA), an enzyme that aids digestion within the oral cavity, is increasingly regarded as a noninvasive marker of SNS responding to acute and chronic stress. This increasing popularity is most likely the result of readily available commercial assay kits and indications from pharmacologic blockade studies that sAA reflects individual differences in adrenergic activation (van Stegeren, Rohleder, Everaerd, & Wolf, 2006). Salivary alpha-amylase is also appealing because it can be assessed using the same salivary collection procedure used in cortisol research (as described elsewhere in this volume), without the equipment and expertise needed to collect impedance cardiographic and or electrodermal measures.

In contrast to free salivary cortisol, which is often used to assess HPA axis function, sAA is a putative index of sympathoadrenal medullar function, and therefore provides information about stress reactivity that cannot be assessed with cortisol alone (Nater & Rohleder, 2009; Nater et al., 2006). For example, following a social stressor, peak sAA and cortisol levels are correlated among control youth, but are uncorrelated among youth with a recent history of physical or sexual abuse or neglect (Gordis, Granger, Susman, & Trickett, 2008). Developmental fractionation of baseline sAA and baseline cortisol is also observed. Compared to young adults (ages 20–31 years) and older adults (ages 59–61), children (ages 6–10) display higher baseline sAA levels, but lower cortisol levels (Strahler, Mueller, Rosenloecher, Kirschbaum, & Rohleder, 2010). Finally, elevations in sAA following psychological stress are typical for adults, but are observed inconsistently among children (e.g., Strahler et al., 2010; Yim, Granger, & Quas, 2010).

Despite this increasing appeal of sAA as an index of sympathetic function, several limitations undermine its usefulness and interpretability. Perhaps most importantly, sAA levels are determined by both SNS and PNS activation, so it suffers from the same interpretability concerns as HR, outlined above. Indeed, sAA is released by the salivary glands, which have prominent PNS innervation (Proctor & Carpenter, 2007). Relatedly, sAA levels are influenced by salivary flow rate, which falls largely under PNS control. This may explain why coactivation of the SNS and PNS yields greater sAA secretion than SNS activation alone (Proctor & Carpenter, 2007). Furthermore, since the time-course of salivary outflow is much longer than the time course of any underlying SNS response, sAA has quite limited temporal resolution—a major limitation compared with impedance cardiographic and electrodermal measures. Finally, methodological issues, such the use of absorbent materials to collect saliva, stimulation of salivary release by chewing, and reliance on enzymatic activity to infer sAA concentration, may erode the validity and reliability of sAA measures (for review, see Bosch, Veerman, de Geus, & Proctor, 2011).

DATA ANALYTIC CONSIDERATIONS

Many data-analytic concerns arise when conducting psychophysiological research. Although some of these are specific to particular methods (e.g., ICG, EMG, etc.), others are more general, and should therefore be familiar to any developmental psychopathologist who uses psychophysiological measures. Several of these issues are presented below. We note, however, that our descriptions are brief. Readers who seek further information are referred to more comprehensive sources (e.g., Bach & Friston, 2012; Gratton, 2007; Jennings & Gianaros, 2007; Kristjansson, Kircher, & Webb, 2007; Strube & Newman, 2007).

Assessing Change in Developmental Versus Psychophysiological Research

Assessing intra-individual change is a fundamental objective of both developmental psychopathology and psychophysiology. As outlined above, developmental psychopathologists seek to characterize ontogenic processes that portend mental illness, which necessarily involves repeated assessments of psychiatric adjustment over time. In fact, longitudinal studies spanning many years and assessment waves are of particular value in mapping pathways of persistence toward and desistance away from psychopathology. In contrast, although psychophysiologists also evaluate change within individuals, they usually do so across much shorter time intervals, often spanning stimulus presentations of a few seconds to a few minutes. For this reason and others, developmentalists and psychophysiologists have arrived at very different approaches to assessing change. Understanding these alternative approaches is essential for developmental psychopathologists who use psychophysiological techniques.

Difference Scores in Developmental Psychology

Avoiding simple difference scores when assessing change is almost canonical in developmental psychology research (see Burt & Obradović, 2013; Rogosa, Brandt, & Zimowski, 1982). This follows from the observation that in some situations, the reliability of a difference score is much lower than the reliability of observed scores from which the difference score is derived (e.g., Lord, 1963). Low reliability creates a number of statistical problems that cannot be reviewed here. From a pragmatic standpoint, however, since low reliability attenuates correlations between measures, difference scores often underestimate associations between behavior change and important external correlates, resulting in Type II errors. This is an obvious problem in developmental psychopathology research, where links between psychiatric adjustment and longitudinal change in vulnerability and risk are primary foci.

Problems with reliability are amplified for certain types of measures (see Beauchaine, 2013). As outlined above, psychopathologists often deal with latent constructs, the causes of which cannot be observed directly (e.g., depression, anxiety, impulsivity), and must therefore be inferred from imperfect manifest indicators, such as observer impressions and teacher reports (Meehl, 1995; Nunnaly & Bernstein, 1994). Rating scales in particular carry halo effects and response biases that induce up to 50% measurement error into observed scores (Hoyt & Kerns, 1999). Moreover, reliabilities of change scores necessarily erode the longer the time interval between assessments given maturation and other developmental processes. Thus, even though difference scores yield an unbiased estimate of change, and may be adequate for use in many longitudinal research contexts (e.g., Rogosa & Willett, 1983), developmentalists favor alternative means of assessing change. These include analysis of residualized change scores, latent difference scores, and latent residual scores, among other approaches (for a review, see Burt & Obradović, 2013). All of these methods are intended to reduce measurement error.

Difference Scores in Psychophysiology

In contrast to a general proscription of difference scores in developmental psychology research, it is difficult to publish a paper in a psychophysiology journal without presenting and analyzing raw change scores (i.e., baseline minus task). Why this difference across literatures, and what are the implications for developmental psychopathology researchers who use psychophysiological measures? In addressing these questions, two important points stand out. First, most psychophysiological indices carry far less error than measures of psychological and psychiatric constructs. Current standards of quantification for most psychophysiological measures (e.g., RSA, PEP) call for 1 kHz resolution, which is far more precise than the resolution of Likert scales.[4] Although precision does not guarantee reliability, more precise measures of a construct yield higher reliabilities than less precise measures, given equivalent validity (for a discussion of the relationship between reliability and validity, see Sechrest, 1984). Second, many psychophysiological studies assess participants' reactions to stimuli in paradigms of very short duration. Thus, intervening maturational effects are of little if any concern. For these reasons, use of change scores in psychophysiological laboratory assessments is fully appropriate under most conditions.

Explicating reasons behind different approaches to assessing change in developmental psychology versus psychophysiology has important implications for research design. Avoiding difference scores and applying latent variable models in psychophysiology research—approaches that follow from the assumption that difference scores are always unreliable—would require recruitment of much larger samples than needed. Nevertheless, those who either (1) conduct research in which psychophysiological reactivity to lab tasks is assessed repeatedly across long time intervals (e.g., annually), or (2) use psychophysiological measures as one among several indicators of outcome, should consider latent variable alternatives (see Burt & Obradović, 2013). Other advantages of latent variable approaches to modeling psychophysiological data are beyond the scope of this chapter (see Bach & Friston, 2012; Lane, Franklin, & Curran, 2013).

Testing Interactions

A primary concern of developmental psychopathologists is to identify subgroups of children who are most likely to develop psychopathology in high risk contexts, so they can be enrolled in targeted prevention and intervention programs. Oftentimes, this involves determining whether psychophysiological responding marks either concurrent

[4]The term *precision* has been used in various ways in the history of psychometric theory and psychological measurement (see, e.g., Mellenbergh, 1996). Here we use the term to distinguish between scales of measurement, as described by Stevens (1946). Using Stevens's classification scheme, Likert scales carry ordinal precision, whereas most psychophysiological signals are processed with ratio precision.

or prospective differences in vulnerability among some children versus others (see, e.g., Beauchaine, Neuhaus et al., 2008; Brenner & Beauchaine, 2011). Making such determinations requires tests of statistical interaction effects (see Beauchaine, Webster-Stratton, & Reid, 2005). A statistical interaction, or moderating effect, occurs whenever the strength of association between two variables changes across levels of a third variable (see, e.g., Aiken & West, 1991). For example, Shannon et al. (2007) reported a positive association between paternal ASPD symptoms and offspring conduct problems for at-risk children and adolescents who scored high on resting RSA, but no such association for those who scored low on resting RSA. Most members of latter group scored high on conduct problems regardless of paternal antisocial behavior (see Figure 22.9). Thus, RSA *moderated* the effect of paternal ASPD on child conduct problems. Consistent with other research reviewed above, this suggests partial protection from psychopathology for children and adolescents who score high on baseline RSA (e.g., Blandon et al., 2008; El-Sheikh, 2005; El-Sheikh et al., 2001; Katz & Gottman, 1995).

As this brief discussion implies, interaction effects address a fundamental question in psychopathology research: Who is more vulnerable to developing mental illness? Like change scores, however, interactions are affected considerably by problems with reliability. In fact, since interaction terms are, by definition, the product of a predictor variable and a hypothesized moderator (paternal ASPD × offspring RSA in the previous example), measurement error inflates *multiplicatively*, with proportionate erosion of reliability. This is more problematic than unreliability of change scores, where error is at worst additive. Furthermore, error continues to be multiplied across each term in higher order interactions (e.g., three-way, four-way). In contrast to the situation with difference scores, however, unreliability of interaction terms has received almost no attention in the developmental psychology or psychophysiology literatures (see Beauchaine, 2009; Whisman & McClelland, 2005).

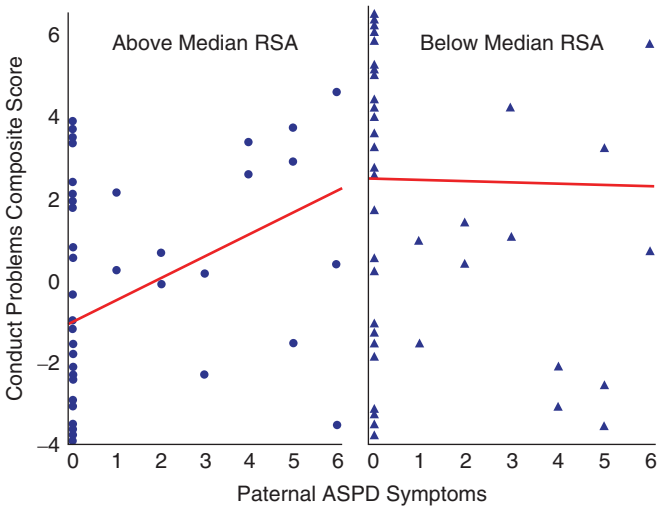


Figure 22.9 Relations between paternal ASPD symptoms and conduct problems for 180 high-risk children and adolescents who scored above and below the sample median on resting RSA. Since the relationship between paternal ASPD and child conduct problems differs as a function of baseline RSA, this represents a statistical interaction, or moderating effect. See footnote 1. *Source:* From Shannon Beauchaine, Brenner, Neuhaus, and Gatzke-Kopp (2007), Familial and temperamental predictors of resilience in children at risk for conduct disorder and depression, *Development and Psychopathology, 19*, 701–727.

As we have noted elsewhere, failure to consider reliability when testing interactions can result in both spurious findings that cannot be replicated (Type I errors), and failure to find important group differences in psychophysiology-psychopathology relations (Type II errors; see Beauchaine, 2009). The latter consequence is particularly unfortunate since the statistical power of interaction effects can (and should) be estimated in the planning stages of a study (see Whisman & McClelland, 2005). At present, many if not most studies in which statistical interaction effects are tested are underpowered because power analyses are conducted on main effects only. Since moderation effects are now routinely hypothesized in developmental psychophysiology research (e.g., El-Sheikh et al., 2009), more attention to reliability is essential.

Problems with Traditional Repeated Measures Analysis

Developmentalists and psychophysiologists alike assess outcomes across multiple time points. In large-scale longitudinal studies, this may involve repeated annual assessments of psychopathology across many years. In psychophysiology research, it is more likely to involve repeated administrations of a stimulus or stimuli within a single testing session. Still other studies involve mixed designs in which patterns of psychophysiological responding during lab tasks are collected across multiple longitudinal assessment points.

Traditionally, both developmentalists and psychophysiologists have analyzed such data using repeated measures analysis of variance (ANOVA). However, problems with repeated measures ANOVA are now well known. Most importantly, repeated measures ANOVA yields many false positives (Type I errors) when certain assumptions are violated and no statistical correction is used. Although such corrections are effective, repeated measures ANOVA

is also underpowered in many situations, which led Vasey and Thayer (1987) to recommend multivariate analysis of variance (MANOVA) as an alternative. At present, although ANOVA and MANOVA are still used, both developmentalists and psychophysiologists have turned increasingly to multilevel modeling (MLM) to analyze much of their data (see, e.g., Hoeksma & Koomen, 1992; Kristjansson et al., 2007).

Multilevel Modeling

Multilevel modeling is a regression-based technique in which separate regression equations are specified at every level of nesting in a data set. Initially, MLM was used in large-scale education research to disentangle variance in achievement scores that was attributable to individual children who were assessed repeatedly across time (Level 1), who were nested within classrooms (Level 2), which were nested within schools (Level 3). Since MLM divides total error variance into smaller components that are specific to each level of nesting, it is often more powerful than repeated measures ANOVA and MANOVA (see Raudenbush & Bryk, 2002; Raudenbush, Bryk, Cheong, Congdon, & Toit, 2011). Furthermore, MLM is not subject to several assumptions of ANOVA.

In most developmental and psychophysiological research, the first level of nesting in any MLM is a repeated measure. In such designs, an individual regression equation is first computed for each participant across the repeated measure at Level 1. The slope of this regression equation represents growth or decline in function. Predictors of growth can then be added to the Level 2 regression equation. For example, Figure 22.10 shows curvilinear growth in the probability of alcohol use across ages 7 to 15 years (Level 1), as predicted by individual differences in cardiac PEP reactivity to monetary incentives in the lab (Level 2) among 206 at-risk children and adolescents (Brenner & Beauchaine, 2011).

A second major advantage of MLM its ability to accommodate time-varying covariates. This enables researchers to determine, among other questions, whether intra-individual responses across levels of analysis (e.g., psychological, physiological) covary over time. For example, in our work addressing expressive and psychophysiological aspects of emotional responding among boys with conduct problems (Marsh et al., 2008), we evaluated time-linked correspondence of sad facial expressions and autonomic reactivity (Level 1) while boys with CD and controls (Level 2) watched an empathy-eliciting film. Although controls exhibited synchrony over time between sad facial expressions and autonomic function, as indexed by skin conductance, cardiac PEP, and RSA reactivity, boys with CD showed no correspondence between facial expressions and autonomic reactivity, even though they exhibited normal levels of facial sadness. This illustrates some of the increased flexibility that MLM affords over more traditional approaches to analyzing repeated measures.

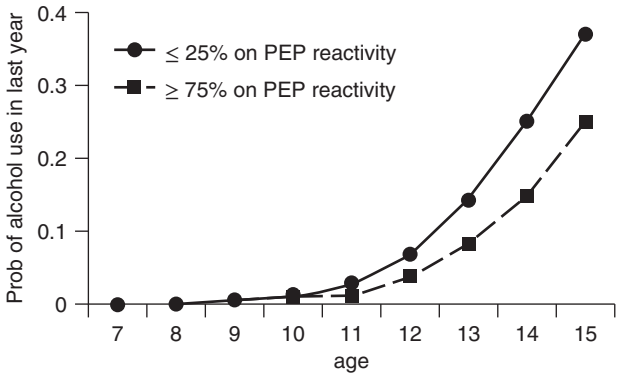


Figure 22.10 Probability of alcohol use in the past year as a function of age for at-risk participants scoring below the 25th percentile and above the 75th percentile on preejection period (PEP) reactivity to incentives ($n = 206$). Greater sympathetic nervous system responding is marked by PEP shortening (i.e., more PEP reactivity). *Source:* From Brenner and Beauchaine (2011), Cardiac pre-ejection period reactivity and psychiatric comorbidity prospectively predict substance use initiation among middle-schoolers: A pilot study, *Psychophysiology, 48*, 1587–1595.

FUTURE DIRECTIONS

In this chapter, we (1) outlined many of the technical intricacies involved in conducting developmentally sensitive psychophysiological research; (2) described the usefulness of psychophysiological methods in elucidating biological vulnerabilities to psychopathology; (3), considered how psychophysiological research can help us understand how such biological vulnerabilities interact with environmental adversity to promote development of psychopathology; (4) explained why psychophysiological biomarkers should be included in intervention research if we wish to identify mechanisms of treatment response and resistance; and (5) summarized certain methodological issues that should be considered when using psychophysiological measures. Along the way, we considered many challenging questions that have always faced developmental psychopathologists. For example, why are individuals differentially susceptible to environmental risk? What etiological mechanisms account for

comorbidities and continuities in psychopathology? Which mechanisms distinguish between those who exhibit developmentally limited forms of psychopathology versus those who traverse life-course persistent patterns? How can basic research better inform prevention and intervention? As we continue to pursue such questions, transdisciplinary and translational research—which developmental psychopathy was central in establishing (see, e.g., Beauchaine & Gatzke-Kopp, 2012; Cicchetti, 2008)—will be necessary as we build truly integrative developmental theories that bridge and combine existing and new methods and findings from behavioral neuroscience, behavioral and molecular genetics, psychophysiology, neuroimaging, and developmental, cognitive, social, and clinical psychology. Such objectives are fully consistent with the RDoC project of NIMH.

Combining psychophysiological and neuroimaging methods enables us to assess neural correlates of autonomic function, and resultant findings can help verify and refine existing theories about autonomic psychophysiology (see, e.g., Chang et al., 2013; Napadow et al., 2006), including psychophysiology-psychopathology relations (e.g., Ahs et al., 2009). For example, the theoretical underpinnings for RSA have been tested, upheld, and refined using multi-method approaches from psychophysiology, neuroimaging, and pharmacology (Thayer, Hansen, Saus-Rose, & Johnsen, 2009; see also Beauchaine & Thayer, in press). The neurovisceral integration perspective describes how top-down, inhibitory influences of the PFC on lower brain structures affect autonomic functioning and modify heart rate through vagal and sympathetic mechanisms (Thayer et al., 2009). More specifically, diminished PFC control over the central nucleus of the amygdala increases HR and reduces RSA through direct and indirect disinhibition of the medullary cardiovascular center (Thayer et al., 2009). By combining HRV with resting state fMRI, Chang et al. (2013) determined that fluctuations in high-frequency HRV are associated with greater functional connectivity from both the dorsal anterior cingulate cortex and amygdala to subcortical regions, including the brainstem, thalamus, and lateral hypothalamus, whereas low-frequency HRV is associated with greater functional connectivity from these two regions to the insula, temporoparietal junction, secondary visual areas, and the right dorsolateral PFC. Such findings elucidate the neural bases of vagally mediated tonic control of the heart. This understanding can be used to refine theoretical models linking tonic RSA to patterns of neural activation and behavioral performance on executive functioning tasks (e.g., Thayer et al., 2009).

Similarly, by combining HRV with measures of cerebral blood flow using PET, Lane et al. (2009) reported that activation of the medial PFC covaries with changes in high frequency HRV among healthy individuals when processing emotionally salient stimuli. Such findings provide novel information regarding relationships between patterns of neural responding and autonomic activity, and enable researchers to draw more precise conclusions about CNS functioning when using psychophysiological techniques in the absence of neuroimaging. For example, our knowledge of the functional nature of the medial PFC can aid in interpreting HRV data acquired during stimulus conditions that evoke affective processing. As stated in the introduction of this chapter, inferring CNS processes in situations where they cannot be observed directly (e.g., in naturalistic settings, among very young children) is a primary objective of psychophysiological research.

Another advantage of combining traditional psychophysiology with modern neuroimaging is the ability to capitalize on both the high temporal resolution afforded by peripheral psychophysiology and the high spatial resolution of MRI and PET, to provide both the when and where of psychological phenomena. For example, in a combined fMRI-EDA study that required participants to perform a difficult motor task, EDA time series recordings were transformed into model waveforms and used to model fMRI BOLD signal activation (MacIntosh, Mraz, McIlroy, & Graham, 2007). The rise-times at the start of each block were similar for the average EDA waveform and hemodynamic model, and both models mapped brain activation in regions implicated in motor activity, including the primary motor cortex, the primary somatosensory cortex, the cingulate gyrus, cerebellum, and putamen. However, the BOLD signal remained relatively constant within and between blocks, whereas peak-to-peak EDA amplitude attenuated within a given block and tended to decrease over successive blocks. This difference enabled an EDA-modeled early versus late block contrast, which revealed differential activation in the thalamus, cingulate gyrus, and insula that was undetectable using the hemodynamic response function, suggesting that this alternative to the hemodynamic response model uniquely captured time-varying effects related to practice and/or changes in attention. Future studies may also capitalize on similar, dual-method approaches to better identify relationships between neural activation and time-sensitive behavioral performance data and better account for individual differences in BOLD signal intensity.

Notably, there are also limitations in combining peripheral psychophysiology with MRI. For example,

impedance cardiography, which is required for evaluating SNS-mediated changes in cardiac function, is exceedingly difficult to perform simultaneously with MRI because the impedance signal is too weak to be detected in such a strong magnetic field. Second, as described throughout this chapter, it is critical that stimulus conditions are appropriately selected for the neurobiological conditions that one wants to assess (e.g., cardiac PEP for monetary incentives; RSA for emotion regulation) to draw valid conclusions about psychophysiological functioning. If a given psychophysiological measure does not index a particular psychological phenomenon under a specific set of stimulus conditions, identifying its neural correlates may be uninformative.

Finally, variables that evaluate interactions between the PNS and SNS often account for far more variance in a given outcome variable than those of single systems (e.g., Beauchaine, Gatzke-Kopp et al., 2013; El-Sheikh et al., 2009). Such variables are constructed by acquiring a measure of parasympathetic functioning, such as RSA, concurrently with that of sympathetic functioning, such as EDA, during or independent of imaging acquisition. As noted previously, however, greater statistical power is required to detect interactions than main effects since error for each main effect is multiplied together. Thus, to understand both the individual contribution of the PNS and SNS and how they interact with one another, future studies should include sample sizes that are sufficiently large to achieve sufficient statistical power.

An emerging area of study is psychophysiology within the context of behavioral and molecular genetics (see Beauchaine, 2015b; Beauchaine & Thayer, in press). Individuals undergo drastic physiological and psychological changes across the life span, following from dynamic transactions between genetic predispositions and environmental risk and protective factors. Psychophysiological measures are well positioned as intermediaries between genes and complex psychological and behavioral phenomena because they often index mutable biological processes. Using a developmental framework, the psychophysiological approach can track changes in ANS functions that are attributable primarily to endogenous factors (e.g., puberty; Silk et al., 2009) versus exogenous factors (e.g., experience of trauma; Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007) and combinations of genetic predispositions and risk/protective factors associated with particular neural correlates and psychosocial outcomes (Bell & Deater-Deckard, 2007). Furthermore, behavioral genetics can improve our understanding of the etiological underpinnings of psychopathology by partialing out heritable factors from nonheritable factors. For example, the high degree of correlation between monozygotic versus dizygotic twins for smooth pursuit eye tracking, a well-characterized endophenotype for schizophrenia, suggests that proficiency in this domain has a strong heritable component (Katsanis, Taylor, Iacono, & Hammer, 2003), although its etiology remains opaque. Similarly, in a study in which fear extinction in PTSD was evaluated, EDA during extinction recall was greater for combat veterans with PTSD compared to both combat veterans without PTSD and their monozygotic twin without combat exposure or PTSD (Milad et al., 2008). This suggests sympathetic hyperresponsivity during extinction recall is engendered by combat trauma itself instead of serving as a genetic vulnerability to PTSD.

Consistent with the new NIMH RDoc initiative (Insel et al., 2010; Sanislow et al., 2010), developmental psychopathology has always incorporated data from genetic, neural, physiological, and behavioral levels of analysis in attempts to provide more comprehensive explanatory models than symptom-based, categorical classification systems afford (e.g., Cicchetti, 2008). One way to achieve this is by engaging in empirical pursuits that identify biomarkers and endophenotyes of maladaptive *traits* that span conventional diagnostic categories (e.g., impulsivity; emotion dysregulation; Beauchaine, 2009a; Beauchaine & Gatzke-Kopp, 2012). Such efforts can improve our understanding of the etiological mechanisms of psychopathology, including why and how seemingly different collections of symptoms stem from common etiologies (multifinality). By improving our understanding of etiology and how psychopathology develops and is maintained, we are better positioned to target mental illness directly for a given individual, and thus refine the ways we implement prevention and treatment strategies.

CONCLUSIONS

Peripheral psychophysiology has a long history of use in psychopathology research, and continues to be used by developmental psychopathologists as they construct truly ontogenic, transactional models of mental illness that span levels of analysis from genes, to intervening biological systems, to family contexts, to broader social systems. Although modern neuroimaging techniques such as EEG and fMRI, as described elsewhere in this volume, are now used routinely with child and adolescent samples, peripheral psychophysiological methods are still valuable tools for developmental psychopathologists who

seek to understand how individual attributes interact with contextual risk factors to promote psychopathology among vulnerable individuals. When used in well designed experiments with appropriate stimulus conditions, proper consideration of maturational and developmental processes, and carefully planned data analysis, peripheral psychophysiology is an important component of a broader network of methods spanning molecular genetics, neuroimaging, behavioral genetics, behavior observation, dyadic interaction analysis, and sociometrics. All of these approaches—and others—will be needed as we build a more comprehensive understanding of developing psychopathology in the twenty-first century.

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CHAPTER 23

Neurodevelopmental Theories of Schizophrenia: Twenty-First Century Perspectives

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INTRODUCTION

Schizophrenia is a severe mental illness afflicting about 1 percent of the population (Cannon, 1996; McGrath, Saha, Chant, & Welham, 2008; van Os & Kapur, 2009). Its characteristic symptoms include hallucinations, delusions, disorganized speech and thought, grossly disorganized behavior or catatonia, and abnormalities in emotional expression and motivation along with chronicity and poor functioning (APA, 2013; Tandon et al., 2013). Throughout most of the twentieth century, our understanding of the origins and developmental course of this disorder was substantially influenced by Emil Kraepelin, who proposed that schizophrenia is a neurodegenerative brain disorder similar in natural history to Alzheimer's disease, but with onset in early adult life (Kraepelin, 1918). More recently however, there has been a major shift toward a neurodevelopmental model of schizophrenia, which posits that the neural underpinnings of the disorder arise during early central nervous system development that are subsequently exacerbated during cerebral maturation in adolescence and early adulthood (Figure 23.1; Cannon, 1997, 2008; Lewis & Levitt, 2002; Rapoport, Addington, Frangou, & Psych, 2005; Weinberger, 1987).

Several lines of evidence support the early neurodevelopmental viewpoint. Numerous prospective studies have revealed associations between obstetric events, particularly those involving fetal hypoxia and infection, and elevated risk for schizophrenia, thus implicating early adverse events as contributing to the development of the disorder (Brown, 2011; Cannon, Rosso, Bearden, Sanchez, & Hadley, 1999). Recent advances in genomics have also shed light on the involvement of rare genetic mutations (copy number variants) as well as additive effects of common genetic variants in the etiology of schizophrenia (Malhotra & Sebat, 2012; Owen, Williams, & O'Donovan, 2009).

[1]Color versions of Figures 23.1–23.3 are available at http://onlinelibrary.wiley.com/book/10.1002/9781119125556

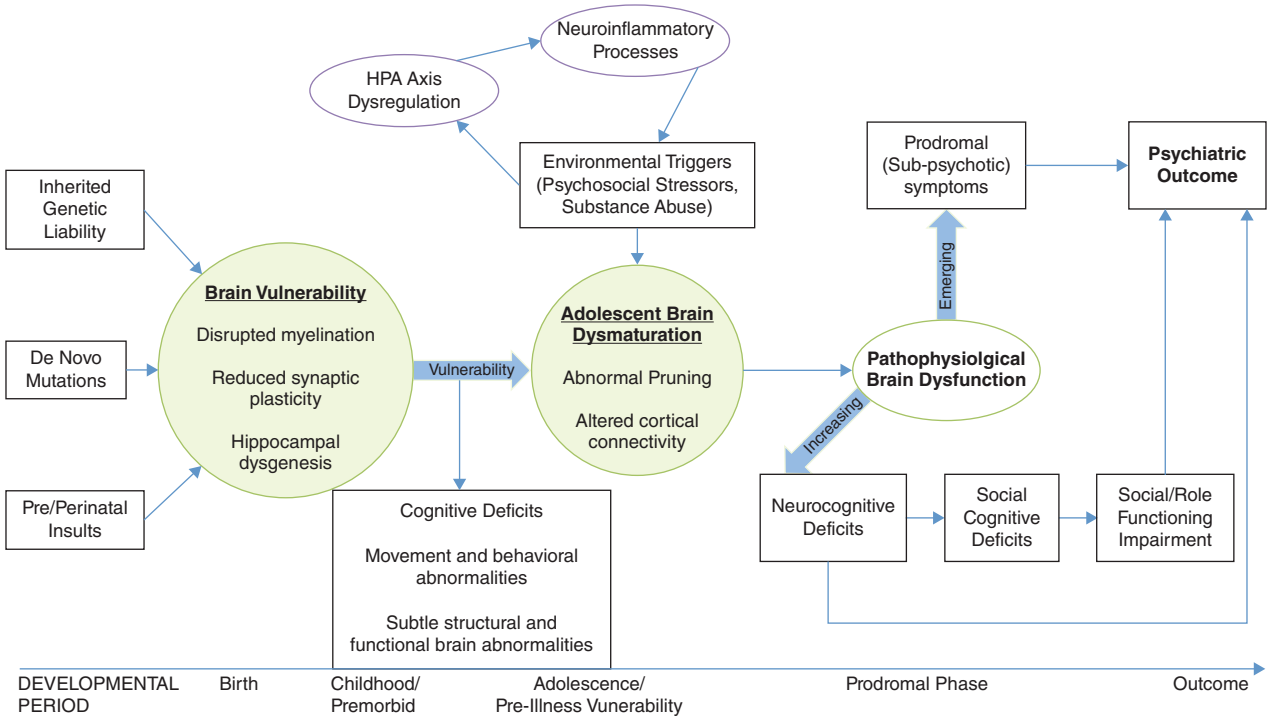


Figure 23.1 Early and late neurodevelopmental abnormalities in schizophrenia. Conceptual model of the hypothesized relationship of vulnerability-related and progressive neuroanatomic abnormalities to the development of neurocognitive and functional impairment in the early phases of psychosis. See footnote 1.

Furthermore, the presence of subtle deficits in cognition and behavior during childhood among individuals who ultimately develop schizophrenia as adults suggests that brain compromise is present long before acute illness onset (Agnew-Blais & Seidman, 2012; Bearden et al., 2000; Cannon, Rosso, et al., 2000; Reichenberg et al., 2010; Rosso, Bearden, et al., 2000; Seidman et al., 2013).

Despite these indications that multiple liability markers for schizophrenia emerge during early brain development, formal diagnostic symptoms and signs of the disorder do not typically manifest until the late adolescent period. Indeed, there is a remarkable consistency in age-at-onset distributions for schizophrenia in diverse cultures around the world, implicating the late adolescent/early adult period as the peak period of risk for onset (Gogtay, Vyas, Testa, Wood, & Pantelis, 2011; Jablensky et al., 1992; Paus, Keshavan, & Giedd, 2008). Adolescence represents a period of active brain development, during which increases in neuronal efficiency are accompanied by a reduction (i.e., pruning) of excess synapses and by myelination of axonal connections in regions critical for higher order cognition, particularly the prefrontal cortex (Huttenlocher, 1979; Petanjek et al., 2011), and these processes during adolescent brain development may play a role in the pathogenesis of schizophrenia (Feinberg, 1990; Hoffman & McGlashan, 1997; P. D. McGorry, 2011). Interestingly, some structural magnetic resonance imaging (MRI) studies have observed progressive gray matter reductions in first-episode patients with schizophrenia (Andreasen et al., 2011; Asami, Bouix, Whitford, & Shenton, 2012; Witthaus, Kaufmann, Bohner, & Özgürdal, 2009) and in individuals at clinical high risk, particularly in those who subsequently convert to psychosis (Brent, Thermenos, Keshavan, & Seidman, 2013; Sun et al., 2009; Witthaus et al., 2009). The sources of this progression require further investigation, but it may reflect a disruption of mechanisms underlying synaptic pruning. Such processes may be overly aggressive in individuals predisposed to developing schizophrenia (e.g., due to a disease-related defect in synaptic plasticity mechanisms), or may be normal but interact with previously existing brain vulnerability in winnowing neuronal connectivity to below some hypothetically critical threshold. Ascertaining individuals who are initially showing symptoms consistent with a high risk for imminent onset of psychosis (i.e., prodromal patients) and following them over time is necessary to characterize the course of neurobiological change among those who develop full-blown psychosis and to elucidate predictors of this outcome (Cannon et al., 2003).

This chapter reviews and evaluates evidence bearing on the relative contributions of early (i.e., genetic and pre/perinatal) and late (i.e., adolescent) neurodevelopmental influences to the etiology and pathogenesis of schizophrenia. We first describe briefly the various neural disturbances that have been detected in schizophrenia, followed by a review of the research supporting both early developmental vulnerability factors and later developmental influences on frank illness onset. These studies provide a useful framework for hypothesis generation concerning the timing of onset and course of brain abnormalities in schizophrenia. Certain brain abnormalities in schizophrenia appear to be reflective of an inherited vulnerability state and are thus likely to emerge prior to illness onset and be fairly stable after their initial appearance, while other abnormalities are unique to (or more severe in) individuals who manifest the illness phenotype and may thus first appear or significantly progress and worsen as one moves beyond an inherited vulnerability state to a fully symptomatic state. We then investigate potential causal mechanisms that may influence the timing of frank illness onset, including neurobiological effects of stress as well as genetic and hormonal influences on synaptic pruning. The principal conclusions that can be reached from this review are that: 1) the case for involvement of early neurodevelopmental influences in the etiology and pathogenesis of schizophrenia is consistent and compelling, including evidence from human epidemiological studies, prospective studies of birth cohorts and samples at risk, post-mortem neuropathology studies, experimental studies using animal models and molecular and behavioral genetics studies; and 2) the case for involvement of later neurodevelopmental processes, as elucidated by neurobiological studies of the prodromal phase and early-onset psychosis, suggests that such processes appear likely to influence the onset and timing of diagnostic symptoms and signs. These processes may include stressful events, potentially inducing a cascade of neuroinflammatory processes leading to accelerated synaptic pruning and consequent gray matter loss. We conclude this chapter with an updated version of the neurodevelopmental hypothesis of schizophrenia, specifying a number of ways particular sets of early and late influences might interact in determining the timing of onset and course of the disorder, and finally with a set of key future directions for the field.

BRAIN ABNORMALITIES IN SCHIZOPHRENIA

The use of noninvasive neuroimaging technologies has facilitated significant progress in the characterization of brain abnormalities in schizophrenia. Disturbances in prefrontal and temporo-limbic systems and their inter-connections appear particularly prominent in the disorder (Cohen & Servan-Schreiber, 1992; Grace, Moore, & O'Donnell, 1998; Gray, Feldon, Rawlins, & Hemsley, 1991). At the structural-anatomical level, patients with schizophrenia show a variety of volumetric changes throughout the brain, including reduced cortical, hippocampal, and thalamic volumes and increased sulcal and ventricular volumes; recent meta-analyses indicate that there is a relatively greater degree of reduction in frontal and temporal cortical volumes compared with posterior cortical volumes (Bora et al., 2011; Olabi et al., 2011; Shepherd, Laurens, Matheson, Carr, & Green, 2012; Vita, De Peri, Deste, & Sacchetti, 2012).

Post-mortem evidence of decreased prefrontal cortical thickness without a reduction in the number of cell bodies (Selemon, Rajkowska, & Goldman-Rakic, 1995, 1998) suggests that a reduction of interneuronal neuropil underlies these *in vivo* MRI findings of cortical gray matter reduction in schizophrenia (Selemon & Goldman-Rakic, 1999), a prediction that has been confirmed by observations of reduced dendritic spine density on prefrontal cortical pyramidal neurons (Broadbelt, Byne, & Jones, 2002; Glantz & Lewis, 2000; Harrison & Weinberger, 2004). This pattern implies a disruption in cellular plasticity mechanisms rather than neuronal degeneration *per se*. This interpretation is also supported by the lack of gliosis, or scarring associated with degeneration of cortical neurons, in the brains of patients with schizophrenia which would be expected to result from an active neurodegenerative process (Bogerts et al., 1993; Roberts & Harrison, 2000). These post-mortem findings were more recently replicated in a study that also found reduced dendritic spines on pyramidal cells involved in corticocortical connectivity after controlling for effects of age and postmortem interval, with the greatest reduction in temporal and frontal association cortex (Garey, 2010). These authors reiterated that this appears to be due to reduced neuropil, given that the number and position of neurons remain unaffected. By examining the glial subtypes independently, the authors also found an increase of microglia in the frontal and temporal cortices. The increase is postulated to result from perinatal damage and persist into adulthood as a method of neuroprotection, again suggesting a neurodevelopmental process. Additionally, this interpretation is supported by findings of cellular positioning abnormalities consistent with disturbances of neuronal migration during gestation (Akbarian et al., 1993; Arnold, Hyman, Van Hoesen, & Damasio, 1991; Falkai, Schneider-Axmann, & Honer, 2000; Jakob &

Beckmann, 1986; Ross, Margolis, Reading, Pletnikov, & Coyle, 2006). In particular, individuals with schizophrenia have demonstrated dysfunction of neocortical networks, which may be attributable to improper cell migration and corresponding faulty arrangement of inhibitory neurons (Sultan, Brown, & Shi, 2013). While these latter findings clearly imply that risk factors for schizophrenia are operative *in utero*, the role of cellular positioning abnormalities in the pathophysiology of schizophrenia and their relationship to the gross morphological findings such as gray matter reduction is not yet known.

Further support for involvement of a developmental rather than degenerative process is provided by research addressing the well-documented role of GABA and glutamate in schizophrenia (Coyle, 2006; Marsman, Heuvel, et al., 2013). Typical cortical development involves the formation and organization of layers of both excitatory (glutaminergic) neurons and inhibitory (GABAergic) interneurons that in turn have long- and short-distance projections thoughout the brain. Early disruption to these complicated processes and cellular signals (e.g., via glutamatergic and GABAergic cell migration) is postulated to result in abnormal development of the specific connections neccesary for proper functional networks, leading to disorders such as schizophrenia (Sultan et al., 2013). In particular, both glutamatergic and GABAergic neurons synapse onto the spines of pyramidal cells, potentially explaining the reduced dendritic spine density and gray matter volume highlighted previously (Garey, 2010), the compromised neurotransmission/cortical connectivity of these cells (Lewis, 2000), and reported deficits in glutamate and GABA receptors (Anticevic et al., 2013; Krystal & Moghaddam, 2010). These developmental aberrations are further reflected in work demonstrating that patients with schizophrenia evidence faster rates of glutamate reduction with age compared with healthy controls (Marsman, Mandl, et al., 2013).

The consequences of these structural and cellular abnormalities in schizophrenia appear to manifest as a wide variety of clinical signs, cognitive impairments and alterations in brain function. For example, Gur et al. (1998) found associations between structural brain changes and clinical presentation during the first two years of illness such that reductions in frontal and temporal lobe volume were associated with less improvement in negative symptoms and hallucinations in first episode adult patients, even when controlling for medication dose and compliance. This pattern of findings has been similarly reported by Sporn and colleagues (2003), Ho et al. (2003), and DeLisi, Sakuma, Ge, and Kushner (1998), among others. However, somewhat counter-intuitively Gur et al. also reported greater *improvement* with regard to delusions, and Sporn et al. found greater clinical improvement associated with a higher rate of gray matter reduction. The investigators proposed that this inverse relation may be reflective of a process by which diseased tissue is removed through compensatory pruning (Gur et al., 1998; Sporn et al., 2003). In other words, it may be that the brain's normative process of synaptic elimination results in the removal of deviant neural connections, thus leading to clinical improvement.

Cognitive performance and functional neuroimaging research have also identified behavioral and brain activation abnormalities corresponding to these structural alterations. Patients with schizophrenia have been found to show performance deficits on nearly all measures of neurocognitive functioning (Kahn & Keefe, 2013). Against this background of generalized deficit, working memory, attention, abstraction, episodic learning and memory, and language functions appear to be particularly severely affected (Cannon, Huttunen, et al., 2000; Reichenberg & Harvey, 2007; Saykin, Shtasel, Gur, & Kester, 1994). These findings have been corroborated by evidence of abnormal physiologic activity (i.e., altered blood flow) in prefrontal and temporal lobe regions in patients with schizophrenia during performance of tests assessing these same domains of functioning (Callicott et al., 1998; Ragland et al., 2012; Ranganath, Minzenberg, & Ragland, 2008; Wolf et al., 2007; Yurgelun-Todd et al., 1996). Dorsolateral prefrontal cortex (DLPFC) function in particular may be compromised early in the developmental course of psychosis (Weinberger et al., 2001; Molina et al., 2005); these abnormalities may be due to relatively localized neuropil reduction in this brain region (Selemon, Mrzljak, Kleinman, Herman, & Goldman-Rakic, 2003).

Abnormalities in neural connectivity between brain regions are also proposed to play a fundamental role in schizophrenia (Friston & Frith, 1995; Karlsgodt et al., 2008). Functional connectivity, defined as the statistical association between spatially distributed neurophysiological time series (Friston, 2004), is one method that allows for evaluation of integrated networks of activation across multiple brain regions. Patients with schizophrenia show decreased cortical network efficiency across the whole brain as measured by various functional connectivity network metrics (e.g., small-worldness, which represents the degree to which topographically separate regions are linked through relatively few connections) (Alexander-Bloch, Lambiotte, Roberts, & Giedd, 2012; Bullmore & Sporns, 2009; Lynall et al., 2010).

Patients with schizophrenia demonstrate patterns of both over- and under-connectivity during task performance (Haut et al., in press; Quidé, Morris, Shepherd, Rowland, & Green, 2013; Wolf et al., 2009) and within intrinsic networks active during rest (Alonso-Solís et al., 2012; Camchong, MacDonald, Bell, Mueller, & Lim, 2011; Zhou et al., 2007). In particular, there appears to be reduced functional integration in cortical connectivity with frontal regions, including frontotemporal (Lawrie et al., 2002), frontoparietal (J. J. Kim et al., 2003), frontostriatal (Koch et al., 2008), and frontothalamic circuits (Anticevic et al., 2013), as well as local prefrontal cortical circuits (Cole, Anticevic, Repovs, & Barch, 2011). On the other hand, patients with schizophrenia show increases in thalamic connectivity with sensory motor regions (Anticevic et al., 2013) and within regions of the default mode network, which is more active during rest (Whitfield-Gabrieli et al., 2009). These altered connectivity patterns appear to have functional implications, as disrupted functional connectivity has been associated with clinical symptom severity and cognitive performance (Cole et al., 2011; Garrity et al., 2007; Rotarska-Jagiela et al., 2010). Disrupted connectivity has also been associated with overall and negative symptom severity in recent onset, antipsychotic naïve schizophrenia patients (Lui et al., 2009), indicating that these abnormalities are not due to effects of treatment chronicity or long-term effects of illness. Furthermore, diffusion tensor imaging (DTI), which allows for the measurement of the integrity of white matter tracts, suggests structural correlates to these findings of disrupted functional connectivity in schizophrenia. These structural connectivity abnormalities appear particularly prominent in tracts connecting the frontal lobe with the thalamus, cingulate gyrus, hippocampus, temporal and occipital lobe (Ellison-Wright & Bullmore, 2009).

THE CASE FOR INVOLVEMENT OF GENETIC AND EARLY NEURODEVELOPMENTAL PROCESSES IN SCHIZOPHRENIA

The Genetic Architecture of Schizophrenia

Given the substantial body of evidence indicating very high heritability of schizophrenia (~80–85%) (Cardno et al., 1999; McGuffin, Farmer, & Gottesman, 1984), it should be possible to identify specific genes that underlie these disturbances. Nevertheless, until recently, genetic findings in schizophrenia were notoriously inconsistent and difficult to replicate. With the advent of ever-larger genome-wide association studies (GWAS) and increasingly sophisticated technology for the detection of small copy number variants (CNVs), the field of schizophrenia genetics has been rapidly advancing on two fronts, leading to substantial progress in our understanding of the genetic architecture of this complex disorder. In particular, recent studies support the notion that the high heritability of schizophrenia reflects a combination of relatively common alleles of small effect, and some rare alleles with relatively large effects (Owen et al., 2009).

Common Sequence Variation

Genetic variation can involve differences in DNA sequence, as well as changes in chromosome structure (Thapar & Cooper, 2013). Single nucleotide polymorphisms (SNPs) are common DNA sequence variations of individual nucleotides that are frequently observed in the population (>1%). SNP variation is typically investigated through genetic association studies. These studies originally investigated allelic variation within single candidate genes, but the advent of high-throughput genotyping methods has enabled interrogation of the entire human genome with increasing numbers of genetic markers (Mulle, 2012). The first genome-wide association studies (GWAS) of schizophrenia (in samples of up to 7,000 individuals) did not reveal any risk loci reaching genome-wide significance, suggesting that there are no common risk alleles of large or moderate effects size (O'Donovan et al., 2008; Sullivan et al., 2008). Researchers from the International Schizophrenia Consortium then tested an alternate hypothesis: specifically, that schizophrenia is due to an aggregation of multiple risk alleles at thousands of loci (i.e., a polygenic inheritance model) (Purcell et al., 2009), as originally postulated by Gottesman and Shields (1967). This study revealed that, indeed, common polygenic variation may accounts for as much as one-third of the total variation in schizophrenia risk; and further, that this liability is substantially shared with bipolar disorder, but is largely *not* shared with several nonpsychiatric diseases. This kind of highly polygenic model suggests that genetically influenced variation in brain development and function may create a diathesis for severe mental illness. Recently, a large, multi-stage GWAS involving over 13,000 schizophrenia cases and 18,000 controls identified 22 genetic loci that reach the threshold for genome-wide significance, one of which was also significantly associated with bipolar disorder (Ripke et al., 2013). Several of the significant SNPs were in genes involved in calcium signaling, implicating disruption of neuronal calcium signaling in the pathophysiology of schizophrenia. Calcium channels

have fundamental importance in synaptic plasticity and in learning and memory functions (Woodside, Borroni, Hammonds, & Teyler, 2004).

Structural Variation

In the past decade, copy number variation (CNV) has been established as a major source of human genetic variation (Iafrate et al., 2004). These submicroscopic variations (<500 kb in size) arise by *de novo* mutation in the individual or in recent ancestry (Malhotra & Sebat, 2012) and appear to play a key role in multiple complex neuropsychiatric diseases, particularly autism and schizophrenia, as well as other disorders of neurodevelopmental origin such as epilepsy and intellectual disability (Gill, 2012; Mulle, 2012; Owen, 2012). Certain CNVs have now been shown to be incontrovertibly associated with schizophrenia, and provided some of the first evidence for a role of rare chromosomal rearrangements in disease pathogenesis (Tam, Redon, Carter, & Grant, 2009). In particular, 25 to 30% of adults with 22q11.2 Deletion Syndrome (Velocardiofacial/DiGeorge Syndrome; 22q11DS) develop schizophrenia, making 22q11DS one of the greatest known risk factors for schizophrenia identified to date (Murphy, Jones, & Owen, 1999; Schreiner, Lazaro, Jalbrzikowski, & Bearden, 2013) and the only known recurrent CNV responsible for introducting new cases of schizophrenia into the population (Karayiorgou, Simon, & Gogos, 2010). This disorder also involves cardiac and craniofacial anomalies, marked deficits in visuospatial cognition, and elevated rates of other psychiatric disorders in childhood including autism spectrum disorders, anxiety disorder, and attention deficit disorder (Schneider et al., 2014). However, psychosis appears to be the most specific association with this mutation. In most diagnosed cases, the syndrome results from a 3 megabase (Mb) *de novo* deletion. This particular region of the genome is thought to be highly susceptible to chromosomal rearrangement due to the groups of low copy repeat sequences flanking the deletion breakpoints, which may cause misalignment due to high sequence homology (Shaffer & Lupski, 2000).

The greatly increased risk for psychosis in this syndrome suggests that a gene or genes within the 22q11.2 locus may contribute to schizophrenia susceptibility in the broader population. Support for this notion is provided by genetic linkage and association studies implicating genes within the 22q11 region in schizophrenia (i.e., proline dehydrogenase (*PRODH*), catechol-*O*-methyltransferase (*COMT*), *ZDHHC8*, G-protein-coupled receptor kinase (*GRK3*), *GNB1L*, and the micro-RNA processing gene *DGCR8* (Mukai et al., 2004; Paterlini et al., 2005; Williams et al., 2007), as well as suggestive findings in GWA studies for genes within this locus (Purcell et al., 2009), and the finding that mice heterozygously deleted for some of the genes in this region have sensorimotor gating and memory impairments similar to those observed in schizophrenia (Karayiorgou et al., 2010). As such, individuals with this syndrome may have genetically determined differences in brain anatomy that predispose to schizophrenia (Van Amelsvoort et al., 2004), although currently the mechanism for the development of schizophrenia in individuals with this syndrome is not known.

Recent large-scale association studies have additionally revealed three novel schizophrenia-associated recurrent CNV loci at chromosomes 1q21.1, 15q13.3, and 15q11.2 (Tam et al., 2009). Although these rearrangements were extremely rare events, occurring in just 0.1% to 0.55% of schizophrenia cases, estimated odds ratios for association of schizophrenia with these regions were high (~2.7 – 18) (Stefansson et al., 2008; J. L. Stone et al., 2008). Several highly plausible schizophrenia candidate genes are located within these regions. In particular, the 15q11.2 CNV partially overlaps with the Prader-Willi Syndrome locus and contains the cytoplasmic FMR1 interacting protein 1 isoform (*CYFIP1*) gene, which plays a role in synaptic plasticity and brain development. Also of interest, the *CHRNA7* (alpha7 nicotinic receptor) gene is a schizophrenia candidate gene that is targeted by neuregulin1-erbB signaling to axons for surface expression in sensory neurons (Hancock, Canetta, Role, & Talmage, 2008).

While CNVs thus appear to play an important role in schizophrenia risk, aside from 22q11DS the specific CNV regions that have been implicated are often extremely rare, sometimes even unique, events. Nevertheless, there appears to be some convergence of the biological pathways affected by these structural rearrangements. Notably, one common characteristic is the involvement of proteins related to synaptic development and functions (Walsh et al., 2008; Xu et al., 2008). These biological functions have also been implicated by GWAS findings, as discussed above. Thus, convergent evidence from studies of both common and rare genetic variation suggests that genes involved with neurodevelopmental processes including cell migration and proliferation, axonal outgrowth, myelination, and synaptogenesis are implicated in schizophrenia.

Liability-Related Versus Disease-Specific Brain Abnormalities

Given the strong genetic contributions to schizophrenia and the well-documented neuroanatomic abnormalities

associated with the illness, liability to disease may be reflected at the level of neural abnormalities in clinically unaffected relatives. As such, a question of major importance is whether some of the brain abnormalities associated with schizophrenia are shared by the nonpsychotic first-degree relatives of these patients. Such a pattern would be expected to occur given the complexity of the inheritance of the disorder, in which multiple genes of small effect and a nontrivial environmental component appear to aggregate to increase risk for phenotypic expression (Purcell et al., 2009). That is, many first-degree relatives of schizophrenia patients would be expected to carry a subset of the vulnerability genes in a predisposing configuration but remain clinically unaffected. Understanding the effects on these nonaffected relatives and other individuals with genetic high risk (GHR) is an important way to differentiate genetically and familial-based vulnerability or predisposing factors from individual environmental causes, disease process specific effects or associated but noncausal features.

Neurocognitive Findings in Genetic High-Risk Cohorts

Many studies have demonstrated that unaffected biological relatives of patients with schizophrenia display qualitatively similar, but quantitatively milder, neuropsychological impairments when compared with normal controls, even after accounting for substance abuse and other psychiatric diagnoses (Cannon, Huttunen, et al., 2000; Park, Holzman, & Goldman-Rakic, 1995). Healthy relatives of patients with schizophrenia exhibit patterns of deficits similar to patients on verbal memory performance (Toulopoulou, Rabe-Hesketh, King, Murray, & Morris, 2003) as well as frontal lobe functions (Staal, Hijman, Hulshoff Pol, & Kahn, 2000) including spatial working memory (Glahn et al., 2003), attention (Michie et al., 2000), and language (Cannon & Marco, 1994; Snitz, MacDonald, & Carter, 2006). A recent meta-analysis found global cognitive function (as assessed by measures of IQ) to be the most strongly affected in individuals at GHR, with additional moderate effects in more specific domains such as declarative memory, working memory and attention (Agnew-Blais & Seidman, 2012). Additionally, Faraone, Seidman, Kremen, Toomey, Pepple, and Tsuang (2000) found that relatives from multiplex families (as defined by two or more first degree relatives with schizophrenia) had significantly lower scores on measures of estimated intelligence and verbal and visual recall than relatives from simplex families (one relative). These shared cognitive impairments account for a significant portion of overall genetic risk for psychosis (Toulopoulou et al., 2010). Such findings support the view that cognitive deficits are reflective of a diathesis for schizophrenia and may serve as an indicator of genetic vulnerability to the disorder, rather than resulting from the disease process or pharmacological intervention.

Genetically Mediated Structural Neuroanatomic Anomalies

Findings of neuroanatomic abnormalities among unaffected relatives of patients with schizophrenia may also be reflective of underlying genetic influences. Evidence from structural MRI studies of healthy relatives of patients with schizophrenia has revealed global volumetric deficits (Cannon et al., 1998) and ventricular enlargement (Reveley, Reveley, Clifford, & Murray, 1982), as well as more specific structural anomalies. Reduced gray matter volume has also been found among unaffected relatives outside the period of risk for developing psychosis (Seidman et al., 1997; Seidman et al., 1999; Suddath, Christison, Torrey, Casanova, & Weinberger, 1990), indicating that these volumetric reductions may be a stable vulnerability factor. Recent comprehensive reviews of the literature indicate that individuals at GHR show consistent gray matter deficits within temporal lobe regions (particularly the hippocampus) and that reduced prefrontal cortical volume or thickness was the most consistent finding across studies, implicating reduced hippocampal and PFC volume as potential risk factors for schizophrenia (Thermenos et al., 2013).

Neurophysiologic Alterations and Functional Dysconnectivity in Genetic High-Risk Cohorts

Functional neuroimaging techniques have also been used in those at genetic risk for schizophrenia to identify neural systems that might be especially vulnerable to the genetic factors that influence psychosis risk. Early research found that children of mothers with schizophrenia show decreased dorsolateral prefrontal and inferior parietal lobe activity during working memory tasks, similar but attenuated compared with the degree of hypoactivation found in patients with schizophrenia (Keshavan et al., 2002). Siblings of individuals with schizophrenia also show altered patterns of neural activity in prefrontal and parietal regions (Brahmbhatt, Haut, Csernansky, & Barch, 2006). Reduced activity in medial prefrontal, thalamic and cerebellar regions was found during an executive functioning task involving verbal initiation in those at genetic risk of schizophrenia (Whalley, 2004), suggesting that GHR individuals are less able than healthy controls to appropriately recruit these regions with increasing task demands. Furthermore, using a technique known as

cerebral perfusion, which involves quantifying the flow of radioactively tagged blood to brain regions, Blackwood et al. (1999) found reduced perfusion during verbal memory in inferior prefrontal regions and the anterior cingulate, as well as increased perfusion in subcortical regions. These results highlight metabolic dysfunction in those regions even among those identified as GHR, though to a lesser extent than clinically affected individuals.

On the other hand, studies demonstrating reduced frontal activation in patients with schizophrenia as well as GHR were often confounded by lower levels of performance compared with controls. Indeed, when controlling for performance accuracy GHR individuals show *hyperactivation* in DLPFC and ventrolateral prefrontal cortex (VLPFC) during working memory tasks (Callicott et al., 2003; Seidman et al., 2006), as well as increased anterior cingulate and thalamic activity (Thermenos et al., 2004). Furthermore, symptomatic adult GHR subjects show hyperactivation in the spatial working memory network (Choi et al., 2012), as do adolescent offspring of schizophrenia patients (Diwadkar et al., 2012). These patterns of hyperactivation are intermediate to those typically observed in patients with schizophrenia and do not appear to be specific to working memory related functions, as nonpsychotic siblings also demonstrate increased right middle frontal and precentral gyrus activity during facial emotional processing (Li et al., 2012). Right PFC hyperactivity in GHR individuals has also been shown during performance on a language task (Li et al., 2007) and during declarative memory encoding (Bonner-Jackson, Csernansky, & Barch, 2007; Whyte et al., 2006). It is speculated that these observed patterns of hyperactivity are indicative of cortical inefficiency (Callicott et al., 2000; Schlösser et al., 2008) or a compensatory response (Tan et al., 2006), similar to that found in patients with recent-onset schizophrenia.

Genetic liability for psychosis is also associated with reduced neural activity in subcortical regions such as the hippocampus, which is critically involved in learning and memory, and the striatum (Callicott et al., 2003; Thermenos et al., 2004), which plays an important role in response to reward (Delgado, 2007) and motivation (Shohamy, 2011). GHR individuals demonstrate a failure to activate the striatum during inhibition of saccades (Raemaekers, Ramsey, Vink, van den Heuvel, & Kahn, 2006), similar to what has previously been reported in patients with schizophrenia, as well as reduced amygdala activation to negative mood induction (Habel et al., 2004). Collectively, these findings suggest that structural and functional neural abnormalities—particularly in prefrontal and medial temporal brain regions critical for working and declarative memory processes and emotional processing—may reflect a genetic diathesis to schizophrenia.

Additionally, studies of cortical networks at rest have shown atypical functional connectivity in individuals predisposed to the development of psychosis that are similar to patterns identified in patients with schizophrenia but represent more circumscribed dysfunction. In particular, while patients with schizophrenia showed widespread dysregulation of functional connectivity between the striatum and other cortical regions, unaffected relatives demonstrated reduced connectivity between the dorsal striatum and dorsal, medial, and lateral prefrontal cortex and hyperconnectivity between the ventral striatum and orbitofrontal and insular regions (Fornito et al., 2013), which the authors speculate may be reflective of the roles those networks play in cognition and salience, respectively. Furthermore, while patients with schizophrenia demonstrated unique alterations in cerebellar and frontotemporal networks (which were not observed in their clinically unaffected relatives), relatives did share decreased network connectivity in frontooccipital and frontal/thalamic/basal ganglia networks and increased connectivity in sensorimotor networks (Khadka et al., 2013). Alterations in functional connectivity shared between schizophrenia patients and relatives are present both at rest and across different task conditions, supporting the notion that these are stable alterations reflecting genetic liability (Repovs & Barch, 2012). In addition, altered thalamo-cortical connectivity was found to be stronger in GHR individuals showing subthreshold psychotic symptoms than those who were asymptomatic (Dauvermann et al., 2013). These findings are notable given that the thalamus is a central relay station in the brain thought to integrate cortical and subcortical functions (Haber & Mcfarland, 2001), which computational modeling suggests may be critically involved in the development of acute psychotic symptoms (Lisman, Pi, Zhang, & Otmakhova, 2010).

Overall, these functional neuroimaging findings suggest that individuals at genetic risk for psychosis show abnormalities in brain activity that may reflect inherited neural vulnerability factors rather than disease-specific effects. Across studies, and similar to patients with established psychosis, GHR individuals show inefficient prefrontal and reduced subcortical activity (MacDonald, Thermenos, Barch, & Seidman, 2009), as well as disrupted cortical connectivity betweeen frontal, striatal and thalamic regions. Although patients with established illness generally show more extensive neural abnormalities relative to GHR

subjects, the shared abnormalities must be prospectively investigated over time to determine their predictive value for emergence of psychotic illness.

Twin Studies

Neurocognitive and neuroimaging studies of twins discordant for schizophrenia allow for further clarification of genetic and nongenetic contributions to the brain abnormalities associated with the illness. Because healthy monozygotic (MZ) and dizygotic (DZ) cotwins of patients with schizophrenia differ by a ratio of 2:1 with regard to genetic liability for the disease, it becomes possible to test whether the degree of cognitive or neuroanatomical deficit increases with genetic proximity to a proband. Further, because discordant MZ cotwins are 100% genetically identical, any abnormalities that are unique to or more severe in the affected compared with unaffected cotwins are likely to be nongenetic in origin. A study of an epidemiologically ascertained sample of Finnish twins revealed that impaired performance on tests of spatial working memory and structural abnormalities in prefrontal brain regions varied in a dose-dependent fashion with degree of genetic loading for schizophrenia. Specifically, MZ unaffected cotwins were significantly more impaired than DZ unaffected cotwins, who in turn were significantly impaired compared with control subjects (Glahn et al., 2003). Decreased white matter volume has also been found in twin pairs discordant for schizophrenia (Hulshoff Pol et al., 2004), indicating that these abnormalities are likely reflective of genetic vulnerability factors. Subcortical structures including the hippocampus (van Erp et al., 2004) and thalamus (Ettinger et al., 2007) also show intermediate genetic effects such that unaffected cotwins show reduced volumes relative to controls but to a lesser extent than probands. Unaffected twins also demonstrate abnormalities in functional activation intermediate to probands, suggesting that cortical activation inefficiency may also be a partially heritable component of the disorder (Karlsgodt et al., 2007).

In contrast, deficits in long-term memory and anatomical changes in the hippocampus and adjacent temporal cortex were specifically more pronounced in patients with schizophrenia compared with their own healthy MZ cotwins (Cannon, Huttunen, et al., 2000). Furthermore, while verbal memory was impaired in both patients and cotwins, greater behavioral impairment and unique reductions in hippocampal volume in probands suggests structural compromise due to nongenetic factors (van Erp et al., 2008). Similarly, a study of monozygotic twin pairs discordant for schizophrenia found relatively reduced gray matter volume in the affected twin in brain regions including the insula, superior/medial frontal gyrus, cingulate, superior temporal gyrus and paracentral lobule (Borgwardt et al., 2010). Taken together, these studies generally indicate more widespread or pronounced gray matter decreases in the affected cotwins (Hulshoff Pol et al., 2004), suggesting that nongenetic, disease-related factors are likely to be more involved in these abnormalities.

The Role of Prenatal and Perinatal Complications in the Development of Schizophrenia

In addition to genetically influenced neurodevelopmental factors, early environmental factors are also proposed to play a role in the etiology of schizophrenia. Environmental exposures, including infections, nutritional deficits, and neurotoxins, are known causes of neuropsychiatric disorders, and are potent disruptors of brain development which have also been shown to contribute to increased risk for schizophrenia later in life (Brown, 2011). Prenatal and perinatal complications, particularly those associated with fetal hypoxia, appear to be particularly robustly associated with increased risk for schizophrenia. Fetal hypoxia appears as a risk factor in a larger proportion of the cases (30–40%) than all forms of pregnancy complications (including viral exposure) and signs of fetal maldevelopment (Cannon, 1997; Fatemi & Folsom, 2009).

Complications associated with fetal hypoxia are also of interest because fetal oxygen deprivation represents a plausible mechanism for explaining much of the structural pathology of the brain detected in neuroimaging studies of adult patients with schizophrenia. For example, in a Finnish birth cohort, a history of fetal hypoxia was associated with significant reductions in gray matter density in both prefrontal and temporal lobe regions among patients with schizophrenia and their healthy siblings, but not in controls at low genetic risk for the disorder, and more so in the patients than in their siblings (Cannon, van Erp, & Glahn, 2002). This pattern appears to be consistent with a genotype-environment interaction, in which hypoxia-related obstetric complications represent random environmental events, which may add to or multiply the risk for phenotypic expression of schizophrenia when they occur in a genetically vulnerable individual. Schmidt-Kastner and colleagues (2006) suggest that susceptibility genes for schizophrenia were more likely to be expressed in the cerebrovasculature or regulated by hypoxia than randomly selected genes, and rates of interaction between some of these hypoxia-related genes and obstetric complications were found to be increased in patients with schizophrenia (Nicodemus et al., 2008).

The hippocampus in particular is acutely vulnerable to hypoxic-ischemic damage (Gonzalez-Rodriguez, Xiong, Li, & Zhou, 2014; Zola & Squire, 2001). Among monozygotic twins discordant for schizophrenia, relatively small hippocampi in the ill twin were significantly related to labor and delivery complications and to prolonged labor, both risk factors associated with fetal oxygen deprivation (McNeil, Cantor-Graae, & Weinberger, 2000). We have previously found that schizophrenia probands who experienced fetal hypoxia have smaller hippocampal volumes than those who did not, a difference not noted among unaffected siblings and healthy comparison subjects (van Erp et al., 2002). Moreover, hippocampal volume differences occurred in a stepwise fashion with increasing genetic load for schizophrenia, suggesting that, in patients with schizophrenia spectrum disorders, hippocampal volume is influenced in part by schizophrenia susceptibility genes, as well as an interaction of these genes with fetal hypoxia.

At the cellular level, the neural sequelae of hypoxia vary in severity from alterations in neurite outgrowth to neuronal cell death (Nyakas, Buwalda, & Luiten, 1996). In the former case, immature neurons may survive the hypoxic insult but still have a compromised elaboration of synaptic interconnections (Nyakas et al., 1996). Evidence from animal studies indicates that sublethal hypoxia results in global dysynchrony in brain maturation programs due to profound loss of coordinated regulation of neuronal gene transcription (Curristin et al., 2002). Specifically, in a mouse model chronic sublethal hypoxia resulted in up-regulation of genes subserving presynaptic function, and suppression of genes involved with synaptic maturation, postsynaptic function, and neural transmission. Genes involved in myelination, glial maturation and cytoskeletal organization were also affected, leading to retardation of synapse formation and reduction of cytoskeletal systems needed to form neuritic processes and synaptic structures. In addition, fetal hypoxia leads to up-regulation of stress and hypoxia response pathways, which may further slow neuronal maturation. Intriguing findings come from a rat model of schizophrenia, in which direct lesions of the hippocampus early in life were found to produce deficits in prepulse inhibition, enhanced sensitivity to stress, and differential response to amphetamine, all of which do not become apparent until the postpubertal period (Lipska & Weinberger, 2002). Further, these investigators found that even transient inactivation of the ventral hippocampus during a critical period of development may be sufficient to disrupt normal maturation of the prefrontal cortex and trigger behavioral changes comparable to those observed in animals with permanent excitotoxic hippocampal lesions (Lipska & Weinberger, 2002). Supportive data in humans comes from the Philadelphia Collaborative Perinatal Project (Cannon, Yolken, Buka, & Torrey, 2008), which found a differential response to fetal hypoxia, involving differential reduction of the neurotrophic factor BDNF in cord blood, in cases versus controls.

Evidence for Cognitive, Motor, and Behavioral Impairment in Infancy and Childhood

Central to the neurodevelopmental hypothesis of schizophrenia (Fatemi & Folsom, 2009; D. A. Lewis & Levitt, 2002; Weinberger, 1987) is the identification of developmental anomalies preceding overt clinical symptoms of schizophrenia. Retrospective studies, as well as high-risk studies of the offspring of parents with schizophrenia, have consistently demonstrated the existence of cognitive impairment and behavioral and neurobiologic abnormalities long before the onset of schizophrenia. Such studies offer substantial evidence that such early events may be less quiescent and more functionally apparent than was previously believed. Although the majority of patients with schizophrenia show no signs of outright psychotic symptomatology until adolescence or early adulthood, there is substantial evidence that the pathologic processes that predispose to the disorder are evident earlier in life in more subtle forms.

In the domain of cognitive development, a meta-analysis of the high-risk literature (Aylward, Walker, & Bettes, 1984) revealed that preschizophrenic children showed deficits on standard IQ tests compared with matched groups of peers or siblings who did not develop psychiatric illness, and these deficits were shown to predict an early onset, poor prognosis form of the illness. Early receptive (Cannon, Jones, & Murray, 2002) and expressive (Bearden et al., 2000) language abnormalities are also a robust finding among retrospective studies of individuals with schizophrenia. Similarly, first-generation longitudinal high-risk studies initiated in the early 1960s and 1970s, some of which have followed children of parents with schizophrenia from birth onwards, have consistently found these high-risk children to perform more poorly on neuropsychological measures, across a variety of cognitive domains, relative to children of parents with no psychiatric history (Keshavan, Diwadkar, Montrose, Rajarethinam, & Sweeney, 2005) particularly measures requiring integrated information-processing (e.g., Niendam et al., 2003). These impairments appear early in development, prior to overt behavioral signs of illness (e.g., Cornblatt,

Lenzenweger, Dworkin, & Erlenmeyer-Kimling, 1992; Erlenmeyer-Kimling & Cornblatt, 1987) and have high specificity and moderate sensitivity for predicting serious behavioral disturbances, including social impairment and behavioral problems, emerging in high-risk subjects during midadolescence (Cornblatt & Erlenmeyer-Kimling, 1985).

Neurologic and motor abnormalities have also been identified in children vulnerable to schizophrenia (Marcus, Auerbach, Wilkinson, & Burack, 1981; Mednick & Schulsinger, 1964), the severity of which is associated with adult psychiatric status (Fish, 1987). Longitudinal follow-up of infants studied as part of the Jerusalem Infant Development Study revealed that the neurobehavioral deficits displayed in infancy by offspring of schizophrenic parents persisted over time, and the children who had developed schizophrenia spectrum diagnoses by adolescence demonstrated poor neurobehavioral functioning across the developmental periods studied (Hans et al., 1999). A study of home movies obtained from families in which one child later developed schizophrenia indicated that preschizophrenic children had significantly more neuromotor abnormalities and less developed motor skills than both their healthy siblings and individuals who later developed affective disorder (Walker, Savoie, & Davis, 1994). These findings have been confirmed in general-population studies, which find that delayed gross motor milestones are predictive of psychosis outcome (Crow, Done, & Sacker, 1995; Isohanni et al., 2001; Jones, Rodgers, Murray, & Marmot, 1994). Moreover, in young adolescent Danish children who were videotaped while eating lunch at school, those who subsequently developed schizophrenia (particularly boys) evidenced differences on measures of sociability and general neuromotor functioning relative to children who developed other psychiatric disorders, or no disorder (Schiffman et al., 2004). Delayed motor development during infancy and impaired motor coordination during childhood consistently discriminate between individuals at high and low genetic risk for schizophrenia, suggesting that early motor deviance may be a marker of genetic liability (Egan et al., 2001). Consistent with this interpretation, in the Philadelphia cohort of the National Collaborative Perinatal Project (NCPP), we found that deviance on motor coordination measures at age 7 was associated with both adult schizophrenia and unaffected sibling status, suggesting that a co-familial (and perhaps genetic) factor underlies motor coordination deficits in schizophrenia (Rosso, Bearden, et al., 2000). In addition, adolescents with schizotypal personality disorder have been reported to have elevated rates of involuntary movements relative to non-ill comparison subjects and adolescents with other personality disorders, further supporting the notion that certain motor abnormalities may reflect a genetic vulnerability to schizophrenia (Koning et al., 2011; Walker, Diforio, & Baum, 1999).

Second-generation high-risk studies such as the Edinburgh High Risk study have focused on prospective ascertainment of premorbid risk indicators, and on following genetically at-risk individuals through the critical adolescent period, to disentangle genetic liability factors from those associated with disease onset (Johnstone, Russell, Harrison, & Lawrie, 2003). This study has been highly informative regarding clinical and neuroimaging markers, which are identifiable years before actual illness onset in genetically at-risk individuals. In particular, high-risk adolescents and young adults in this cohort exhibited significantly lower IQ at baseline relative to controls (Byrne, Hodges, Grant, Owens, & Johnstone, 1999), and those who experienced an increase in psychotic symptoms exhibited an apparent decline in IQ and memory over two-year followup (Cosway et al., 2000), suggesting that onset of psychosis may coincide with a decline in cognitive function. Additionally, neuroimaging studies in this cohort suggest that the progression from genetic vulnerability to overt psychosis may be preceded by structural and functional changes in the temporal lobe (Lawrie, McIntosh, Hall, Owens, & Johnstone, 2008).

While these studies have been instrumental in revealing a relationship between genetic liability to schizophrenia and early forms of impairment, such findings may not be generalizable given that only 5 to 10 percent of patients with schizophrenia have a parent with schizophrenia. Further, because offspring in most high-risk samples have not passed through the period of elevated risk for onset of schizophrenia, and those that have include only a small number of participants who ultimately develop psychotic disorder, there is limited data on the degree to which early deficits predict adult schizophrenia in such samples. Thus, population-based cohorts are necessary to determine which precursors, or combination thereof, represent true risk factors for schizophrenia. Three such studies, conducted in England (Jones et al., 1994), Sweden (David, Malmberg, Brandt, Allebeck, & Lewis, 1997), and the United States (Cannon, Bearden, et al., 2000), have showed a linear trend of increased risk for schizophrenia across decreasing levels of cognitive performance. Moreover, at age 7, children who would later go on to develop schizophrenia demonstrated lower academic achievement, verbal ability and attention/working memory relative to children who did not develop a psychotic illness (Seidman et al., 2013).

The bulk of the evidence suggests that, against a background of longstanding cognitive deficit compared with the general population, additional decline may occur prior to illness onset (Woodberry, Giuliano, & Seidman, 2008). For example, a study of Israeli military draftees found that draftees who eventually developed schizophrenia showed a measurable decline in cognitive performance that began about 2 years prior to illness onset, concomitant with impaired social functioning that became progressively worse during the course of late adolescence (Davidson et al., 1999). Using a prospective population cohort design, Reichenberg et al. (2010) demonstrated patterns of cognitive impairment indicative of both longstanding cognitive deficits and increasing cognitive lag in children who would go on to develop schizophrenia. Specifically, children who would later develop schizophrenia demonstrated early, stable deficits in verbal and visual knowledge, reasoning, and conceptualization whereas they demonstrated increasing deficits (developmental lag) on attention and visuo-spatial problem solving abilites, with greater cognitive impairment in the subset who also had known familial risk.

There is also evidence of early behavioral problems displayed by individuals who ultimately develop schizophrenia, albeit with considerable variation. Retrospective and prospective population-based cohort studies have consistently documented the existence of abnormalities in premorbid social development in preschizophrenic individuals, ranging from solitary play preference at age 4 to social anxiety, withdrawal, and acting-out behavior in adolescence (Jones et al., 1994). Studies of childhood films have additionally revealed affective abnormalities in preschizophrenic children, with increases in negative facial expression as early as age 1 (Walker, Grimes, Davis, & Smith, 1993), suggesting that vulnerability to schizophrenia may be associated more generally with difficult infant temperament (Walker, Lewine, & Neumann, 1996). In a prospective longitudinal study of a Philadelphia birth cohort, social maladjustment at age 7 was a significant predictor of adult schizophrenia (Bearden et al., 2000). Moreover, rates of deviant behaviors (e.g., echolalia, meaningless laughter, and stereotyped behaviors) at age 4 and 7 were significantly elevated in both preschizophrenic children and their unaffected siblings, suggesting that such problems may indicate genotypic susceptibility to the disorder, or shared early environmental influences.

Both high-risk (Keshavan et al., 2005) and population-based studies (Cannon et al., 1999) have found that the presence of multiple premorbid indicators, across domains of functioning, are associated with an elevated risk for schizophrenia, over and above single risk factors. Similarly, the Dunedin New Zealand Health and Development Study observed that persistent, multidimensional impairment in early childhood was predictive of psychotic symptoms in childhood and adulthood (Cannon et al., 2002). Whereas emotional problems and interpersonal difficulties were present in children who later developed psychotic, mood, or anxiety disorders, significant impairments in neuromotor, receptive language, and cognitive development were unique to children later diagnosed with schizophreniform disorder. This study also provides some of the first evidence of continuity of psychotic symptoms over the life span: self-reported delusional beliefs and hallucinatory experiences at age 11 predicted a 16-fold increase in risk for schizophreniform disorder (but not mood disorder) at age 26 (Poulton et al., 2000). Such investigations are critical for the delineation of compelling risk factors that may increase positive predictive value in the identification of young people at risk for schizophrenia.

Not surprisingly, emerging evidence suggests that functional impairment during adolescence may have more predictive value in the identification of young people at high risk for schizophrenia than that attained in studies of childhood functioning (Davidson et al., 1999; Keshavan et al., 2005). Because of this, epidemiologic studies of schizophrenia risk have begun to move forward in the illness, progressing from stages that clearly precede clinical signs of the disorder to those more proximal to the onset of psychosis.

THE CASE FOR INVOLVEMENT OF LATER NEURODEVELOPMENTAL PROCESSES IN SCHIZOPHRENIA

By definition, a substantial decline in role functioning and a severe disruption in integrated cognitive and emotional processing occurs around the time of onset of schizophrenia during late adolescence and early adulthood. In view of this pattern, it is tempting to postulate that there are brain changes in addition to those instantiated through early neurodevelopmental influences that occur proximally to the onset of psychosis, thus acting as triggers for this functional decline and psychotic symptom expression (Figure 23.1). As noted previously, the most well established disease-related deficits in schizophrenia involve frontal and temporal lobe structures, abnormalities of which have been linked to the occurrence of hypoxia-associated birth complications among individuals with schizophrenia. Nevertheless, as we shall see, additional progressive deficits in these brain structures appear

to characterize the period proximal to illness onset. While there is debate regarding the interpretation of longitudinal MRI studies, as the reported rates of annualized gray matter decline seem unsustainably high (Weinberger & McClure, 2002), emerging evidence suggests that rates of decline in gray matter may level off with age, distinct from the course of atrophy typically associated with neurodegenerative disorders (Mathalon, Rapoport, Davis, & Krystal, 2003). The question then becomes, if these disease–related deficits are present to some degree from early in life, what mechanisms cause them to further deteriorate in adolescence/early adulthood, and are these mechanisms primary or secondary to the emergence of psychosis?

Clinical High-Risk Studies and Early Detection

With the shift in focus from an early neurodevelopmental model of schizophrenia to increasing interest in more proximal developmental risk factors, a new research strategy has emerged and gathered considerable support. Building on traditional high-risk approaches, the so-called clinical high-risk (CHR) paradigm (Yung & McGorry, 1996; Yung et al., 1998) goes beyond indicators of genetic vulnerability to focus on clinical features that are believed to reflect heightened vulnerability for imminent onset of psychosis. A central goal in CHR research is to prospectively follow a well-characterized group of putatively prodromal individuals through the period of conversion to gain a deeper understanding of the progression of clinical, biological, and neurocognitive changes that characterize the onset of overt illness. Such studies may enhance our understanding of the pathophysiology of psychotic illness, and allow for the discrimination of the schizophrenia prodrome from that of other conditions (e.g., affective psychosis), thus informing early treatment strategies. Finally, results of CHR research may aid in identifying late risk factors for the transition into psychosis, as well as protective factors or interventions that may alleviate, delay, or possibly prevent the onset of psychotic illness (Cannon et al., 2003; Yung et al., 2003).

Developmentally, the prodrome or CHR state can be viewed as the transition between the premorbid and psychotic stages of illness (Cornblatt, Lencz, & Obuchowski, 2002; Yung & McGorry, 1996). Retrospective studies indicate that the first indication of deterioration occurs within 3 to 5 years of onset and consists of a constellation of gradually developing, low-grade psychiatric symptoms and signs, including reduced concentration (attention), decreased drive and motivation (anergia), depressed mood, sleep disturbance, anxiety, social withdrawal, suspiciousness, deterioration in role functioning, and irritability. These symptoms are followed by gradual emergence of transient psychotic symptoms, including hallucinations, delusions, or disorganized speech. Full-blown schizophrenia is considered to have evolved when CHR behavioral features have been present continuously for at least six months, and psychotic symptoms have persisted continuously for at least 1 month (APA, 1994).

Over the past decade, investigators have identified three putative prodromal syndromes that map onto the developmental sequence described above. Criteria for these syndromes currently focus on three groups of individuals: 1) those who are experiencing attenuated positive psychotic symptoms that have emerged or worsened in the past year, 2) those who describe brief and intermittent periods of frank psychotic symptoms with recent onset, and 3) those with familial risk for a psychotic disorder, and who have experienced a significant decline in functioning in the past year. Operational definitions for these syndromes differ slightly across research programs, but are largely comparable.

Early studies using these criteria found that 22 to 54% of treatment-seeking individuals ascertained in a putatively prodromal state will convert to full-blown psychotic disorder within two years (McGlashan, Miller, & Woods, 2001; P. D. McGorry, Yung, & Phillips, 2003; Yung & McGorry, 1996). However, larger and more recent studies have typically found lower rates of conversion to overt psychosis among those initially ascertained in a CHR state, ranging from 20 to 35% over a 2-year period (Cannon, Cornblatt, & McGorry, 2007). Additionally, while some recent work suggests a decelerating rate of conversion over longer follow-up periods (Cannon, 2008), a much wider range of rates of conversion (9–76%) has been reported across several studies when the follow-up period has been expanded to a 9-year period (review: Cannon, Cadenhead, et al., 2008). The reasons for this are not entirely clear, but some investigators have speculated that it may be due to various assessment measures capturing different stages of developing illness compared with others, as well as to possible effects of early intervention following CHR identification. Regardless, rates of psychosis in these samples far surpass those in the population in general. Thus, these studies continue to offer the unique opportunity to identify behavioral and neurobiological markers most predictive of schizophrenia outcome, and, by extension, to develop interventions that may be implemented prior to onset of the full-blown disorder. At the same time, given that the majority of these at-risk individuals will not develop psychosis, it is critical to improve our predictive criteria so that preventive treatments can be offered to those who need them most.

Results thus far have identified several baseline clinical variables that appear to be predictive of conversion to psychosis, over and above prodromal criteria alone. Specifically, findings from the Melbourne Prodromal Study (Yung et al., 2003) suggest that poor functioning, prolonged duration of untreated prodromal symptoms (>900 days), high overall level of psychopathology, subthreshold psychotic symptoms, depression severity, as well as clinically significant avolition and anxiety were all predictive of conversion to psychosis in their prodromal sample. Strikingly, 87% of those participants who had four or more of these risk factors converted to psychosis within 6 months after study entry. In a multisite study in the United States, Cannon et al. (2008) found that five baseline features contributed uniquely to prediction of psychosis: genetic risk for schizophrenia with recent functional decline, more severe unusual thought content and suspicion/paranoia, greater social impairment, and a history of substance abuse. Prediction algorithms, which combined two or three of these variables, greatly increased in positive predictive power (i.e., 68–80%) relative to prodromal criteria alone, suggesting that prospective ascertainment of individuals at risk for psychosis is indeed possible. The use of more sensitive and specific prediction algorithms is critical for minimizing exposure of false-positive cases to potential stigma or adverse events; moving toward individualized prediction algorithms is an ultimate goal of this area of research, which has clear public health benefits.

Along these lines, investigators have also explored neuropsychological changes associated with conversion to psychosis. Seidman et al. (2010) compared typically developing individuals to GHR and CHR cohorts. Results revealed significant differences in general neuropsychological functioning among the CHR group compared with healthy controls, with greater degree of baseline impairment in those who subsequently converted. In particular, verbal learning, processing speed, and verbal memory were most impaired in CHR youth, with the latter most sensitively predicting rapid transition to psychosis. Other studies investigating neurocognitive predictors of overt psychosis have similarly found impairments in the above areas and in measures of attention among the CHR group (Keefe et al., 2006; Lin et al., 2011; Niendam et al., 2006), and have demonstrated that verbal episodic memory performance of those who subsequently convert more closely resembles the performance of schizophrenic patients relative to those who do not, suggesting it may be useful as a predictive factor (Eastvold, Heaton, & Cadenhead, 2007). Another recent study found that a combination of neurocognitive factors (e.g., executive functioning, theory of mind, and visual and working memory) provided the best predictive model of psychosis conversion (Kim et al., 2011).

Associated Neuroanatomical Changes in CHR Patients

Longitudinal prospective studies during the early stages of illness can deepen our understanding of late processes underlying onset of schizophrenia, as these patients have had minimal exposure to potential confounding factors, such as pharmacological agents and chronicity (Bagary et al., 2003) and structural brain changes associated with schizophrenia appear to be at their peak intensity during the initial stage of illness (Gur et al., 1998; Kasai et al., 2003). Pantelis and colleagues (Pantelis, Velakoulis, et al., 2003) reported baseline differences in regional grey-matter volume between CHR participants who subsequently developed a psychotic illness versus those who did not. Specifically, those who developed psychosis had less gray matter *at baseline* in the right medial temporal, lateral temporal, and inferior frontal cortex, and in the cingulate cortex bilaterally. Longitudinal follow-up indicated that CHR individuals who developed psychosis showed additional gray matter reduction in the left parahippocampal, fusiform, orbitofrontal and cerebellar cortices, and the cingulate gyri, whereas longitudinal changes were restricted to the cerebellum in those who did not become psychotic. Additional research in CHR samples has also revealed reduced hippocampal and amygdala-hippocampal complex volumes, smaller thalami, and several morphological abnormalities, including cingulate and paracingulate folding patterns (review: Pantelis et al., 2005). More recently, a pattern of progressive brain tissue loss has been reported in CHR samples that appears more pronounced in individuals who subsequently convert to psychosis. Longitudinal anatomical MRI studies have shown greater cortical gray matter volume loss or contraction in CHR patients who convert, especially in prefrontal and temporal lobe regions, compared with individuals who do not convert to psychosis during the follow-up period (Sun et al., 2009; Takahashi et al., 2009). This pattern of results mimics that found in first-episode schizophrenia and appears to be an exaggeration of the pattern of prefrontal contraction seen during cortical maturation, suggesting that late developmental deviations may play a role in the onset of psychosis (Sun et al., 2008), see Figure 23.2.

However, this body of work has not fully addressed potential confounds including duration of prodromal symptoms and effects of antipsychotic medication, which are often prescribed to patients who develop psychosis before post-conversion imaging scans take place. Therefore,

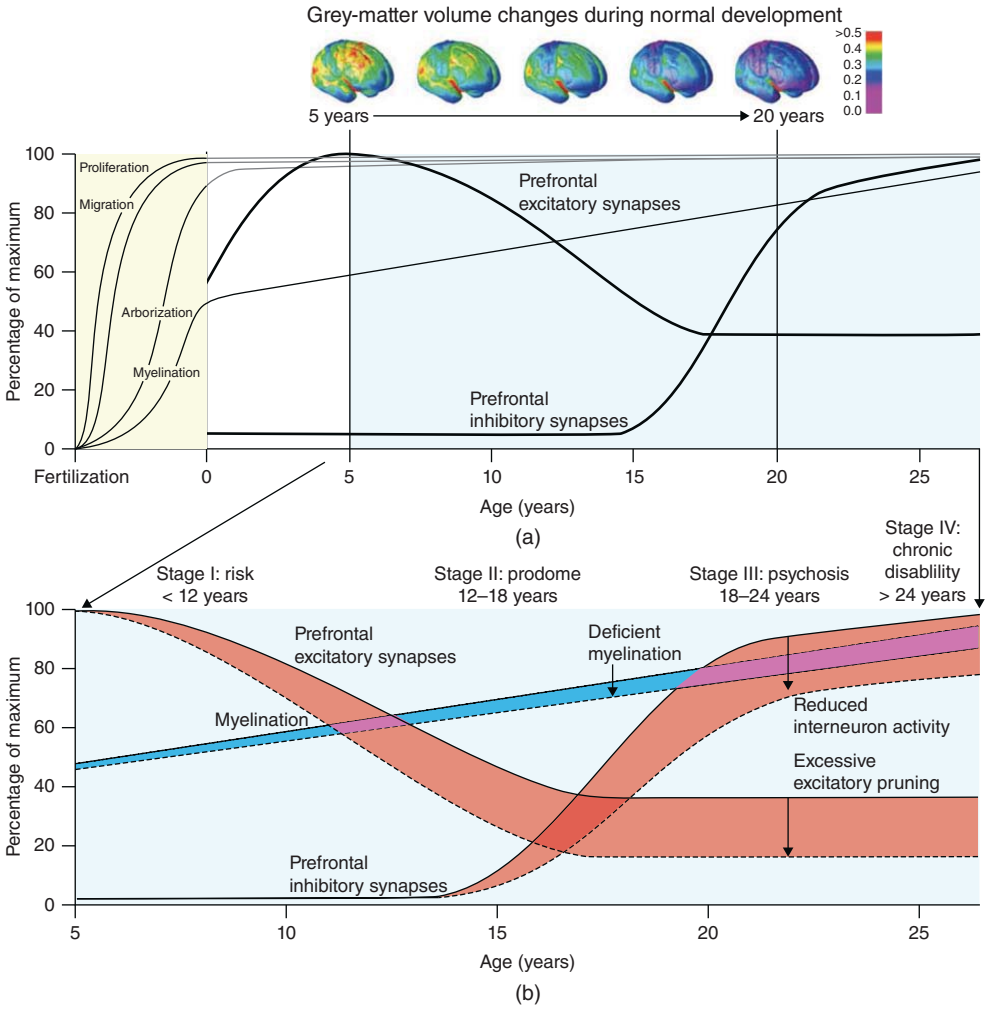


Figure 23.2 Neurodevelopmental model of schizophrenia. (a) Normal cortical development involves proliferation, migration, arborization (circuit formation) and myelination, with the first two processes occurring mostly during prenatal life and the latter two continuing up to about age 20. The combined effects of synaptic pruning and myelin deposition are theorized to account for the progressive gray matter loss observed in in vivo longitudinal neuroimaging studies. Underlying the overall reduction, local changes are far more complex. Data from human and nonhuman primate brain indicate increases in inhibitory, with concomitant decreases in excitatory synaptic strength occurring differentially in prefrontal cortical regions throughout adolescence and early adulthood, during the period of prodromal symptom development and emergence of psychosis. (b) The trajectory in children developing schizophrenia could include reduced elaboration of inhibitory pathways and excessive pruning of excitatory pathways leading to altered excitatory–inhibitory balance in the prefrontal cortex. Reduced myelination would alter connectivity. Although some data support each of these possible neurodevelopmental mechanisms for schizophrenia, none has been proven to cause the syndrome. Detection of prodromal neurodevelopmental changes could permit early intervention with potential prevention or preemption of psychosis. See footnote 1. *Source:* Figure reprinted with permission from Insel 2010.

a recent multisite longitudinal study examined rates of gray matter reductions in prefrontal, temporal, and parahippocampal regions among medicated and unmedicated converters, nonconverters, and healthy control participants (Cannon et al., 2015). Results replicated previous findings of steeper rates of gray matter loss in frontal regions, concomitant with third ventricle enlargement, among converters compared with nonconverters and healthy controls. Further, this study demonstrated identical gray matter changes in unmedicated converters, suggesting that such structural changes are not related to exposure to antipsychotic medications. The duration of the prodrome also appeared to play a role, as shorter periods of prodromal symptoms among converters (regardless of medication exposure) were marked by steeper reductions in prefrontal cortical thickness and greater ventricle expansion

compared with converters with longer prodromal symptom duration, nonconverters and healthy controls.

Diffusion tensor imaging studies probing white matter organization have also identified disrupted patterns of development in CHR patients. For example, Karlsgodt et al. (2009) found reduced FA in working memory-related tracts (e.g., superior longitudinal fasciculus) that predicted declines in social and role functioning, as well as a failure of CHR patients to demonstrate age-appropriate FA increases in several white matter tracts. As white matter volume typically increases in adolescence due to increasing myelination, especially within the frontal lobes and hippocampus (Paus, Collins, Evans, Leonard, & Pike, 2001), evidence for a disrupted developmental trajectory during this period further supports the role of later neurodevelopmental processes in the onset of psychosis.

Functional Brain Abnormalities in CHR Patients

Functional neuroimaging techniques (including fMRI, MRS, and PET) have been used to investigate the neurophysiologic correlates of the reported neurocognitive deficits (Brewer et al., 2006; Niendam et al., 2006) that precede the onset of psychosis. There is now an emerging literature indicating that neurocognitive abnormalities in CHR subjects are often qualitatively similar to those found in individuals who have developed schizophrenia, with functional activation patterns intermediate between schizophrenia patients and controls (Broome et al., 2009; Fusar-Poli et al., 2007). Exploration of the functional abnormalities that precede the development of overt psychotic symptom onset can help to identify early pathophysiological changes that may be potential targets for early treatment to prevent or ameliorate psychosis onset.

Abnormal prefrontal activation during cognitive tasks has been found in the CHR phases of psychosis (Fusar-Poli et al., 2007) and a recent meta-analysis found evidence for consistent reductions in neural activation across tasks utilizing multiple modalities in the medial frontal gyrus, superior frontal gyrus and anterior cingulate and in the left inferior frontal gyrus (Fusar-Poli, 2012). Prefrontal dysfunction during working memory and episodic memory tasks has been found in CHR individuals (Allen et al., 2011; Broome et al., 2010; Broome et al., 2009) and is related to striatal dopamine functioning (Fusar-Poli, Howes, et al., 2011). These deficits mirror reductions in DLPFC activity found in individuals with first-episode or untreated schizophrenia during working memory (Mendrek et al., 2004), executive functioning tasks utilizing context processing (Barch et al., 2001; MacDonald et al., 2005) and planning (Rasser et al., 2005) and that have been shown to be associated with patient symptoms (MacDonald et al., 2005; Snitz et al., 2005).

While DLPFC hypoactivation is one of the most consistent functional abnormalities identified in CHR patients, a number of other cortical regions have been implicated in psychosis risk showing hyperactivation. Studies of working memory performance have found increased activity in other prefrontal cortical regions such as VLPFC as well as other medial and inferior prefrontal regions in CHR samples (Fusar-Poli, Broome, Woolley, et al., 2011; Pauly et al., 2010). CHR individuals also show increased activation across frontal and temporal regions implicated in language processing that are associated with symptoms and functioning (Sabb et al., 2010) and increased inferior frontal gyrus activation during verbal fluency is associated with elevated striatal dopamine function (Fusar-Poli, Howes, et al., 2011). Increased prefrontal cortical activation during a verbal fluency task was also found in high-risk subjects who subsequently converted in contrast to subjects who did not go on to develop psychosis (Allen et al., 2012). During a theory of mind task, CHR subjects show more activation than both controls and established schizophrenia patients in the inferior frontal gyrus and multiple regions surrounding the temporal-parietal junction (Brüne et al., 2011). Increased inferior frontal gyrus activation has also been shown in at-risk individuals when inhibiting self-perspective taking (van der Meer, Groenewold, Pijnenborg, & Aleman, 2013). As discussed earlier, the evidence for increased prefrontal activation relative to controls has been hypothesized to reflect cortical inefficiency (Callicott et al., 2000; Schlösser et al., 2008) or a compensatory response (Tan et al., 2006). Individuals with recent-onset schizophrenia also demonstrate increased VLPFC activity in conjunction with reduced DLPFC activity during working memory maintenance and manipulation (Tan, Choo, Fones, & Chee, 2005), and a recent meta-analysis (Smieskova, Fusar-Poli, Allen, & Bendfeldt, 2010) noted evidence for decreased prefrontal activation and potentially compensatory increased activation in connected brain areas, similar to a pattern found in a meta-analysis of fMRI studies of schizophrenia patients (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009).

Increasing severity of prefrontal cortical functional abnormalities are also found as disease chronicity increases. For example, Morey et al. (2005) found a decreasing pattern of activation in frontal regions of the brain in the anterior cingulate, middle frontal gyrus, and inferior frontal gyrus during a visual oddball task between controls, CHR individuals, individuals with early schizophrenia and those with chronic schizophrenia. Studies such as these suggest

that prefrontal function is impaired prior to the onset of a full psychosis episode and may represent a vulnerability marker or an early sign of disease development. Furthermore, normalization of prefrontal activation is related to improvement in severity of positive symptoms in CHR individuals (Fusar-Poli, Broome, Matthiasson, et al., 2011). These differences in functional activation may be related to the patterns of gray matter loss previously described (Fusar-Poli, Broome, Woolley, et al., 2011) but functional alterations in the inferior frontal gyrus and insula have been shown to remain following correction for group differences in gray matter volume (Smieskova et al., 2011).

Studies of psychosis risk samples also frequently implicate medial temporal lobe regions such as the hippocampus and parahippocampal cortex. In addition to structural abnormalities in high-risk individuals in these regions (Pantelis, Velakoulis, et al., 2003), parahippocampal dysfunction was found during verbal memory performance in CHR patients (Allen et al., 2011) and a spatial working memory task produced reduced activation in right middle temporal gyrus (Fusar-Poli et al., 2010). In addition to prefrontal and temporal lobe activation abnormalities, fMRI has implicated many other cortical regions in the development of psychosis. CHR samples have also been shown to demonstrate altered cortical functioning in parietal, occipital, and basal ganglia regions (Broome et al., 2010; Sabb et al., 2010) and decreased insula activity during negative mood induction (Pauly et al., 2010). Furthermore, CHR individuals who transition to psychosis also show reduced middle frontal gyrus (Marjoram et al., 2006) and reduced posterior cingulate gyrus activation (Brüne et al., 2011) at baseline during theory of mind tasks, as well as a failure to increase lingual gyrus activation with increasing task difficulty (Whalley et al., 2006) relative to those who do not transition to psychosis.

Functional Connectivity Abnormalities in CHR Patients

Additionally, there is increasing evidence that alterations in the networks underlying the integration of multiple brain areas may be associated with the development of psychosis (Andreasen, Paradiso, & O'Leary, 1998; Frith, 2005; Honey et al., 2005). Resting state fMRI, which probes the functional connectivity networks inherent in the brain during wakeful rest, has shown that CHR subjects show increased connectivity within the default mode network (DMN) as well as decreased anti-correlation between default regions and task-positive networks (Shim, Oh, Jung, Jang, & Choi, 2010), indicating less differentiation between these networks. Activation within the DMN (Raichle et al., 2001) may represent self-referential (Gusnard, Akbudak, Shulman, & Raichle, 2001) or spontaneous thought, and is also implicated in social cognition (Buckner, Andrews-Hanna, & Schacter, 2008). These results are similar to those found in established psychosis (Whitfield-Gabrieli et al., 2009; Zhou et al., 2008), and are associated with symptom severity (Shim et al., 2010; Sorg et al., 2013). Furthermore, CHR individuals demonstrate a pattern of thalamic overconnecitivty with sensory-motor regions and underconnectivity with prefrontal regions that is more pronounced in individuals who subsequently convert to psychosis (Anticevic et al., in submission) and is similar to thalamic dysconnecitivity found in patients with schizophrenia (Anticevic et al., 2013).

In addition to abnormal functional networks at rest, analyses of functional connectivity during task performance have identified a number of atypical patterns in individuals at risk for developing psychosis. Complementing the evidence for altered regional activation in prefrontal and temporal lobe regions, disruptions of frontal and temporal task-related networks have been implicated in psychosis vulnerability (Fusar-Poli et al., 2007). Altered activation in the superior temporal gyrus as well as disrupted frontotemporal connectivity was also shown during a working memory task, such that CHR individuals show superior temporal gyrus activation and functional coupling to middle frontal gyrus intermediate to the deactivation and negative coupling of controls and the activation and positive coupling of recent-onset psychosis (Crossley et al., 2009). Interactions between frontal and parietal brain regions show progressively less working memory modulation between control, CHR, and first-episode psychosis, suggesting alterations in functional integration preceding psychosis onset that may also be modulated by antipsychotic treatment (Schmidt et al., 2013). Functional connectivity during an episodic memory task is also reduced between medial temporal lobe regions and stimulus processing regions in both CHR and first-episode patients (Haut et al., in press). Taken together, these functional activation and connectivity studies suggest that individuals exhibiting clinical signs of psychosis risk also demonstrate functional abnormalities in prefrontal, temporal, and subcortical regions that are attenuated but qualitatively similar to those found in patients with schizophrenia. Many of these abnormalities are also more pronounced in CHR who develop a psychotic disorder prior to the onset of frank psychotic symptoms and thus may be reflective of both clinical state and risk for subsequent conversion to psychosis.

Effects of Early Intervention

Targeted early intervention for CHR youth shows some promising results. A recent review of randomized clinical trials to date revealed lower rates of conversion to psychosis among those receiving specialized treatment (11%) compared with treatment as usual or control (no treatment) groups (31.6%) after one year of intervention (Preti & Cella, 2010). For example, family-focused psychoeducation for CHR youth has demonstrated improvements in positive symptoms and social/role functioning (O'Brien et al., 2007), leading to the development and current implementation of a more extensive randomized-controlled trial for family-focused therapy (Schlosser et al., 2012). Similarly, several lines of research have demonstrated the benefits of cognitive behavioral therapy (CBT) for delaying or preventing psychosis onset (review: Okuzawa et al., 2014), including a meta-analysis that suggested intensive CBT leads to at least a 50 percent reduction in the rate of conversion to psychosis (Hutton & Taylor, 2014).

Early-Onset Schizophrenia

Another burgeoning research strategy has focused on early-onset schizophrenia (EOS), a potentially more neurodevelopmentally severe form of illness, which may therefore be uniquely informative regarding mechanisms underlying late developmental processes. EOS is sometimes further subcategorized into adolescent-onset (AOS) and childhood-onset schizophrenia (COS), both of which are particularly virulent and chronic forms of schizophrenia. AOS is typically defined as emergence prior to age 18, in contrast with childhood-onset (COS) for which the disorder is present before the age of 12 (Kumperscak, 2011). Unlike the transitory CHR stage, EOS is characterized by fully psychotic levels of symptomatology, with diagnostic criteria that are identical to that of the adult-onset disorder (Kumperscak, 2011; Thomsen, 1996). Both of these disorders are relatively rare: only 0.1 to 1 percent of all schizophrenic disorders occur before the age of 10, 4 percent before the age of 15, and 10 percent between the ages of 16–20 (Kumperscak, 2011). EOS is associated with poor prognosis across symptomatology and functioning domains (Vyas & Gogtay, 2012), and characterized by more severe cognitive deficits, particularly in the areas of working memory and attention, as well as greater genetic loading relative to the adult-onset form of illness (Frangou, 2010; Rajji, Ismail, & Mulsant, 2009; Zabala et al., 2010). This model may therefore provide greater insight into the abnormalities associated with the disorder, while simultaneously allowing for investigations of the effects of adolescent development on symptom emergence.

Neuropsychological Changes in EOS

Age of onset is a source of heterogeneity in neurocognitive functioning; earlier onset typically yields more significant impairment across multiple domains (Basso, Nasrallah, Olson, & Bornstein, 1997; Collinson et al., 2003). For example, Basso et al. (1997) compared adolescent-onset and adult-onset patients with chronic schizophrenia, and showed that patients with adolescent-onset performed significantly less well than did patients with adult-onset schizophrenia, particularly on memory and executive function tasks. Pantelis and colleagues (2003) hypothesized that brain functions that typically develop during the peak period of risk will be most impaired among patients with schizophrenia. Supporting this point, they found that working memory, a skill that develops throughout adolescence and peaks at age 20 was more compromised among adolescents and young adults with schizophrenia than was set-shifting, a cognitive function that purportedly emerges earlier in development. Finally, a recent meta-analysis of the relationship between cognition and age at onset concluded that individuals with EOS had significantly larger deficits than those with adult first-episode schizophrenia in the areas of arithmetic, executive function, processing speed, verbal memory, and global IQ (Rajji et al., 2009).

Associated Neuroanatomical Changes in EOS

Several lines of evidence suggest that developmental anomalies associated with schizophrenia may vary depending on the developmental stage of the individual at illness onset (Brewer et al., 2003; Mathalon et al., 2003; Mehler & Warnke, 2002); thus, longitudinal studies of EOS may be particularly informative in this regard. The NIMH study of childhood-onset schizophrenia has been instrumental in shedding light on the ways age of onset may interact with normative developmental processes during early disease progression. Thompson et al. (2001) analyzed repeated high-resolution MRI brain scans of adolescent patients with early-onset schizophrenia, discovering a dynamic pattern of gray matter loss that began in the parietal region and progressed forward to the temporal and frontal cortices. The final pattern of loss was consistent with cross-sectional studies of adults with schizophrenia showing a relatively greater degree of reduction in frontal and temporal cortical volumes. Up to 5 percent annual loss was noted in bilateral parietal, temporal, and motor regions and rates of loss were faster for younger patients, demonstrating a nonlinear effect (Thompson et al., 2001).

Further reports from the NIMH study have revealed deviant patterns of development in the corpus callosum and the cerebellum among patients with COS (Keller, Castellanos, et al., 2003; Keller, Jeffries, et al., 2003), sugggesting developmental disruptions to interhemispheric communication and cognitive function superimposed over typical brain development. Notably, there appears to be diagnostic specificity to this pattern of progressive gray matter loss: for children and adolescents with transient psychotic symptoms that did not meet criteria for schizophrenia, gray matter reduction over time did not differ from that observed in healthy comparison subjects (Gogtay et al., 2003). These patients provide a valuable comparison group to the child-onset schizophrenia patients because they had a similar level of cognitive functioning and had received a similar course of treatment with antipsychotic medication, indicating that these brain changes are intrinsic to the illness and do not result from medication exposure. In addition, the unaffected siblings of these childhood-onset schizophrenia patients were found to have smaller total brain volume and reduced total, frontal, and parietal gray matter volume compared with healthy controls (Gogtay et al., 2003), suggesting a genetically influenced pattern of neuroanatomic abnormalities. However, observed gray matter abnormalities in siblings may be an age-dependent endophenotype, as longitudinal follow-up indicated that these deficits normalized by the typical age of onset of schizophrenia. These deficit reductions correlated with overall functioning at the final scan, suggesting a relationship between degree of neural plasticity and outcome for siblings that did not develop the illness (Gogtay et al., 2007).

Other longitudinal studies of EOS patients have highlighted decreased gray matter volume loss in the prefrontal cortex only, as well as smaller thalamic and increased CSF volumes, though sample size was limited (Arango et al., 2008; Moreno et al., 2005). Another small longitudinal study failed to find progressive reduction in gray matter volume (James, Javaloyes, James, & Smith, 2002), except in the posterior inferior vermis among male participants (James, James, Smith, & Javaloyes, 2004). Here, the authors speculated that their negative findings may have reflected a leveling off of gray matter loss in late adolescence, as was found in the NIMH study (Sporn et al., 2003). Thus, replication remains critical in this population to determine if the degree of progressive gray matter loss found in the NIMH study is specific to COS, or if similar patterns will be seen among adolescent-onset patients as they go through the same period of development.

Further research is also necessary to better understanding age-related differences in brain development in early psychosis. While some longitudinal prospective studies of adult first-episode patients have revealed broad changes in whole brain volume with no detectable progression in specific regions (e.g., temporal or frontal lobe structures) (Cahn et al., 2002; DeLisi et al., 1997; Pantelis, Yucel, et al., 2003), other studies of adults have revealed similar patterns of change to those seen in patients with COS, but of a much smaller magnitude (Gur et al., 1998). One study of adolescents and adults with recent-onset schizophrenia showed progressive decreases in gray matter volume in the left superior temporal gyrus during the first 1.5 years following initial hospitalization, followed by a leveling off of cortical loss (Kasai et al., 2003). These results were not observed in a control group of individuals with first-episode affective psychosis (e.g., mania), suggesting that the observed grey matter deficits may result from an early, schizophrenia-specific progressive process in the temporal region. Notably, gray matter loss specific to superior temporal regions was also associated with increasing psychotic symptom severity over time in 22q11DS patients, suggesting some convergent abnormalities associated with symptom emergence (Jalbrzikowski & Bearden, 2011).

Diffusion tensor imaging studies have revealed reduced white matter integrity (i.e., decreased FA values) in the pyramidal and corticopontine tracts, superior thalamic and optic radiations, corpus callosum, and arcuate fasciculus (Douaud et al., 2007), and in parietal and cerebellar regions in patients with AOS (Kyriakopoulos, Vyas, Barker, Chitnis, & Frangou, 2008). Furthermore, Douaud et al. found that the observed FA reductions were correlated with gray matter deficits in superior temporal, inferior parietal, and motor regions. Reduced FA in AOS patients was also observed in the left superior and inferior longitudinal fasciculi (Clark et al., 2012; Douaud et al., 2007), tracts implicated in working memory. These findings suggest that abnormal patterns of myelination or axonal organization may underlie cognitive deficits associated with schizophrenia.

Adolescent-onset schizophrenia has also been associated with several morphological abnormalities, such as enlarged cavum septi pellucidi (deviated membrane separating left and right lateral ventricles) and reduced gyral folding in the left anterior cingulate cortex, which are in accordance with chronic (adult) schizophrenia literature (Pantelis et al., 2005). Decreased overall cortical thickness and abnormal gyral and sulcal curvature indices have also been reported among AOS individuals compared with controls, even after covarying for age and gender (Janssen

et al., 2009; White, Andreasen, Nopoulos, & Magnotta, 2003). In related analyses, patients evidenced smaller sulcal width in the frontal, parietal, and temporal lobes, and reduced gyral thickness in the temporal lobe (White et al., 2003). Given that sulcal and gyral patterning is essentially fixed early in life, these kinds of anomalies may be markers of subtle neurodevelopmental disturbance (Pantelis et al., 2005). Additionally, regional cortical thinning has been identified in several areas including the bilateral precuneus, left insula, and right operculum (Voets et al., 2008), brain structures that are critically involved in memory, visuospatial processing, emotion, and global cognitive functioning. Of note, however, several of these structural anomalies have also been observed in other disorders such as autism, therefore perhaps representing a more nonspecific neurodevelopmental vulnerability (Pantelis et al., 2005). Further, the structural anomalies reported in AOS do not entirely converge with those from studies of adult-onset patients; this may be due to true structural neuroanatomic differences as a function of age at onset, but the relatively small sample sizes and heterogeneous methodologies of these cross sectional AOS studies precludes any firm conclusions. Prospective studies involving direct comparison of early and later-onset cohorts are needed to better understand the way age at onset impacts the developmental trajectory of the illness.

Associated Functional Changes and Deficits in EOS

Related anomalies in EOS samples compared with age-matched controls have also been revealed via functional neuroimaging, notably in the domains of emotion processing and working memory. For example, EOS patients show greater difficulty discriminating sad, angry, and fearful faces, with related aberrations in neural activity in regions such as the fusiform and occipital gyri and cuneus, regions important for emotion processing and regulation and visual processing (Seiferth et al., 2008). EOS patients have also demonstrated increased activation in orbitofrontal and medial frontal regions, key areas involved in emotion processing, during a negative valence induction and verbal working memory task, indicating impaired emotion-cognition interactions (Pauly et al., 2008).

Additional studies utilizing visuospatial and verbal working memory tasks have revealed both abnormal patterns of neural activity in several regions (e.g., ventrolateral prefrontal cortex, anterior cingulate cortex) and disrupted functional connectivity within working memory networks in EOS patients relative to healthy controls (Thormodsen et al., 2011; White, Hongwanishkul, & Schmidt, 2011; White, Schmidt, Kim, & Calhoun, 2011). Taken together, results suggest that EOS patients evidence abnormal functioning in attentional control and working memory circuitry, and perhaps develop atypical cognitive compensatory responses to increasing task-based performance demands. Event-related potential designs have further suggested that EOS individuals have deficits in early visual processing that may contribute to such working memory impairments, particularly in information encoding (Haenschel et al., 2007).

Synthesis: Neuroimaging Evidence for Involvement of Later Neurodevelopmental Processes

Overall, these results suggest that individuals at risk for developing psychosis show abnormalities in cognition, neuroanatomy and functional activity prior to the onset of primary psychotic symptoms, which appear to be attenuated but similar to those found in early psychosis. In addition, those CHR individuals who go on to convert to psychosis show more pronounced baseline deficits.

A cautionary note is warranted, however, as many of the functional imaging studies done to-date are cross-sectional comparing some combination of high-risk, first-episode and control individuals. Even those with clinical follow-up rarely report on neural activation changes within individuals before and after conversion to psychosis. This highlights the need for more longitudinal studies to follow the dynamic changes in functional activity and connectivity that precede transition to psychosis. Further study is additionally warranted to determine if the degree of progressive gray matter reduction and other morphological abnormalities found among adolescent patients with childhood-onset schizophrenia is specific to this severe variant of the disorder, or if a similar pattern can be detected among adolescent-onset patients as they go through the same period of development.

Magnetic Resonance Spectroscopy Studies

Despite the evidence suggesting the importance of adolescent neural maturational processes in the onset of schizophrenia, direct measures of abnormal neuronal growth and degeneration processes are difficult to quantify in vivo. Nuclear magnetic resonance spectroscopy (MRS) offers a method of assessing brain phospholipid and energy metabolism that corresponds to developmental neuronal changes. This methodology allows a noninvasive investigation of human brain development and is well suited to identifying abnormalities in synaptic pruning that may occur in adolescence (Pettegrew, Klunk, Panchalingam,

McClure, & Stanley, 2000). Two MRS techniques that are currently utilized in schizophrenia research are phosphorus magnetic resonance spectroscopy (^{31}P-MRS) and proton magnetic resonance spectroscopy (^{1}H-MRS). In vivo ^{31}P-magnetic resonance spectroscopy examines indirect indicators of cell membrane synthesis and degradation in addition to measures of energy metabolism (Ross & Michaelis, 1994). ^{31}P-MRS studies have identified alterations of membrane phospholipid metabolites in the frontal cortex of first-episode, neuroleptic naïve schizophrenia subjects, compared with matched controls (Keshavan, Pettegrew, Panchalingam, & Kaplan, 1991; Pettegrew, Keshavan, Panchalingam, & Strychor, 1991; Williamson, Pelz, Merskey, & Morrison, 1991), suggesting decreased synthesis and increased breakdown of membrane phospholipids in recent-onset schizophrenia patients. This pattern resembles an exaggerated form of the changes observed in normal aging (Pettegrew & Minshew, 1992). Such findings may reflect an increase in membrane phospholipid turnover, perhaps because of an accelerated synaptic pruning process during late childhood and early adolescence (Keshavan, Stanley, Montrose, Minshew, & Pettegrew, 2003).

To further address this neurodevelopmental perspective, Stanley et al. (1995) used ^{31}P-MRS to examine phospholipid synthesis in the DLPFC in 11 drug-naïve, 8 newly diagnosed and medicated, and 10 medicated and chronic patients with schizophrenia. Decreased phospholipid synthesis was observed in all three groups, which implies lower levels of cell membrane synthesis at all stages of the disorder. Additionally, there was an increased level of phospholipid breakdown in the drug-naïve group, suggesting that earlier stages of schizophrenia may be characterized by increased breakdown of cell membranes. At the level of structural neuroanatomy, these metabolic changes may correspond to increased gray matter volume loss in the early stages of illness. Abnormalities in phospholipid metabolism have also been observed in the DLPFC of high-risk adolescents (Keshavan et al., 2003; Rzanny et al., 2003), suggesting a pattern of increased membrane turnover at illness onset with a continued pattern of membrane abnormalities throughout the course of the disorder (Berger et al., 2002).

^{1}H-magnetic resonance spectroscopy also provides indirect measures of metabolites related to neuronal and glial energy metabolism as well as phopholipid metabolism (Ross & Michaelis, 1994). Of the metabolites examined in ^{1}H-MRS, *N*-acetylaspartate (NAA) is primarily seen as an index of neuronal integrity (Keshavan, Stanley, & Pettegrew, 2000) that can be used to identify neurons and their dendritic and axonal extensions and is mostly concentrated in pyramidal neurons. NAA increases during the course of normal development until the adolescent period, when there is a decrease associated with pruning of superfluous neuronal connections; however, this decrease is less drastic than the sharp decrease in NAA that is seen in neurodegenerative diseases (Moore, Slovis, & Chugani, 1998). Choline includes metabolites that are involved in the synthesis of myelin and cell membrane metabolism (Ross & Michaelis, 1994) and creatine (Cr) is defined as a general marker of energy metabolism (Passe, Charles, Rajagopalan, & Krishnan, 1995). The observation of decreased levels of NAA or a decreased NAA/Cr ratio is believed to indicate some form of neuronal loss, such as synaptic pruning or neuronal dysfunction, while increased levels of choline or an increased choline/Cr ratio signals deafferentiation (Ross & Michaelis, 1994). Glutamine is primarily found within glial cells; decreased levels of this metabolite are thought to represent neuronal loss, dysfunction, or deafferentiation (Ross & Michaelis, 1994).

Studies of ^{1}H-MRS in schizophrenia have consistently reported reduced NAA levels in the hippocampus, mesial temporal lobe and the frontal lobe, including the DLPFC, in both adult (Bertolino & Weinberger, 1999; Steel et al., 2001) and child-onset schizophrenic patients (Bertolino et al., 1998). Significant reductions in NAA/Cr ratios have been found in these regions in both chronic schizophrenia patients (Bertolino et al., 1996; Yamasue et al., 2002; Yurgelun-Todd et al., 1996) and neuroleptic-naïve first episode patients (Cecil et al., 1998) and in children with schizophrenia spectrum disorders (Brooks et al., 1998). Supporting the idea that NAA/Cr ratio may mark genetic vulnerability to schizophrenia, Callicott et al. (1998) showed a decreased NAA/Cr ratio in the hippocampi of both schizophrenic patients and their unaffected siblings when compared with healthy controls. Moreover, Keshavan and colleagues (1997) found that offspring of parents with schizophrenia showed a reduced NAA/choline ratio in the anterior cingulate region when compared with healthy controls. Studies of neuroleptic-naive patients with schizophrenia (Bartha et al., 1997; Theberge et al., 2002), as well as nonill offspring of parents with schizophrenia (Tibbo, Hanstock, Valiakalayil, & Allen, 2004) have also revealed increased glutamate/glutamine levels in the medial frontal cortex, anterior cingulate and thalamus, signaling possible dysfunction of glutamate in the pathogenesis of schizophrenia.

Similar to adults with schizophrenia, temporal gray matter deficits in high-risk, medication-naïve patients were found to be dose-dependently correlated with abnormal

glutamate function in corresponding regions (Stone et al., 2009). Similar glutamatergic deficits have been observed in the thalamus, and appear to be associated with altered neural activity during verbal cognitive demands (Fusar-Poli, Stone, Broome, & al, 2011). However, increases in glutamate in the dorsal caudate (de la Fuente-Sandoval et al., 2011), anterior cingulate and medial frontal cortex (Fusar-Poli, McGuire, & Borgwardt, 2012) have also been noted, suggesting nonuniform dysfunction. Nevertheless, these findings suggest the possibility for early psychopharmacological intervention targeting the glutamate system.

Thus, while these studies demonstrate that altered NAA levels in frontal and temporal regions are associated with risk for schizophrenia, it is not yet clear how anomalies in brain metabolites highlighted by MRS techniques correspond to brain volumetric changes and abnormalities of cellular migration in schizophrenia. Some researchers have also suggested that findings of decreased frontal NAA ratios may be related to effects of long-term antipsychotic treatment (Bustillo et al., 2001; Bustillo et al., 2002). Future refinements in MRS methodology offer the promise of more detailed exploration of neurogenesis and the processes of myelination, synaptic pruning, and gliosis in living human subjects.

POTENTIAL CAUSAL MECHANISMS

The Role of Stressful Life Events and Their Neurobiological Effects

We have described the role of prenatal stress as an early occurring factor previously in this chapter, and now turn our attention to the potential moderating role of psychosocial stress as a late factor in adolescence and adulthood (Figure 23.1). Diathesis-stress models of schizophrenia suggest that environmental stress may interact with genetic vulnerability in triggering the onset of psychotic symptoms and exacerbating symptoms during the course of the disorder. A 1985 review of the behavioral literature regarding the role of psychosocial stress in schizophrenia concluded that evidence for a causal role was weak, while some findings pointed to a potential role of stress in activating symptoms in previously diagnosed psychotic patients (Tennant, 1985). Additional research since that time has continued to support these conclusions, with the addition of a more complex understanding of the neurobiological effects of stress on the central nervous system.

Several studies have examined the temporal relationship between stressful life events and symptom severity, pointing to a role for environmental stressors in psychotic symptom exacerbation and relapse. In a landmark study, retrospective assessments indicated that independent life events (those life events judged *not* to be due to the mental illness) were more likely to occur in the three weeks prior to onset of a psychotic episode in schizophrenia patients than in a similar period of time for nonpsychiatric control participants (Brown & Birley, 1968). This sample included first-episode and more chronic patients, all of whom had a rapid increase in symptoms prior to episode onset. The authors calculated that onset was brought forward by 10 weeks, on average, for these patients, thus providing the first evidence for the triggering hypothesis (Birley & Brown, 1970; Brown & Birley, 1968). This theory proposes that an underlying biological vulnerability causes psychosis, while environmental stress, may trigger the precise timing of onset.

In a review of the behavioral literature on stress and schizophrenia, Norman and Malla (1993) examined 23 studies that retrospectively assessed life events prior to psychotic onset or relapse (only three assessed first-episode patients) and reported that seventy-seven percent of the studies showed significant evidence that higher stress levels were associated with more severe symptoms within schizophrenic samples. However, none of the studies that compared schizophrenia patients to control subjects with other psychiatric disorders showed higher rates of life events for the schizophrenia patients compared with patients with other psychiatric disorders, suggesting that schizophrenia patients may be more vulnerable to the effects of stress, but do not necessarily experience more stressful events (Norman & Malla, 1993). More recent work found that recent-onset patients with schizophrenia assessed longitudinally endorse lower rates of negative and positive life events than healthy adults. Of note, of the events they did report, patients with schizophrenia rated events as less controllable and endorsed having fewer or less effective coping strategies, suggesting lower self-efficacy (Horan et al., 2005). This underreporting of life events may be due to the withdrawal of recent-onset schizophrenia patients from social activities or interactions, particularly if they believe themselves to be less capable of coping with stress or change. Regardless, the observed higher reactivity to events compared with healthy controls has been replicated and is proposed to be a driving predictor of increases in psychotic symptoms (Docherty, St-Hilaire, Aakre, & Seghers, 2009).

Although the measurement of independent events attempts to control for the effect of illness in creating life stress, the direction of causality is not yet clear: life events

could exacerbate symptoms, and increased symptoms could increase the level of stressful events in a patient's life. Additionally, psychosocial stress may not have a unique effect on psychotic symptoms, as life events have also been linked to an increase in mood symptoms in patients with schizophrenia (Ventura, Nuechterlein, Subotnik, Hardesty, & Mintz, 2000) and patients with purely affective disorders (Brown & Harris, 1978). Life stress is thought to exacerbate psychiatric symptoms across a variety of mental disorders, and may also exacerbate immune system functioning and the symptoms of physical illness in diseases such as diabetes, cardiovascular disease, and cancers (Cohen & Herbert, 1996; Spiegel & Kato, 1996; Strike & Steptoe, 2004).

High-risk paradigms examining the link between stress and symptoms may shed some additional light on this matter. Cullen et al. (2014) examined the effects of stress on children at high risk for developing schizophrenia. These children either had a family history of the disorder or showed several prodromal features (e.g., subclinical psychotic symptoms, poor functioning, speech/motor abnormalities). Results indicated that both groups reported more frequent exposure to negative life events and daily stressors, as well as greater corresponding stress, compared with typically developing children. *Post hoc* analyses further revealed correlations between daily stressors and current psychopathology. These results were replicated in another high-risk cohort of adolescents with schizotypal personality disorder (Tessner, Mittal, & Walker, 2011); the authors found greater rates of undesirable life events and greater associated distress compared with those with no personality disorders. Reported negative life events also correlated with current prodromal symptoms and predicted future increases in positive prodromal symptoms over one year. Therefore, results from both studies suggest that the experience of and reactions to environmental stressors are associated with vulnerability to psychosis.

A hypothetical neurochemical mechanism linking the stress system to symptoms of schizophrenia is altered activity of the hypothalamic-pituitary-adrenal (HPA) axis. The cascade of hormones in response to stress proceeds through the HPA pathway as cells in the periventricular nucleus of the hypothalamus secrete corticotropin-releasing hormone, which increases adrenocorticotropic hormone secretion by the pituitary gland, which stimulates the adrenal gland to release glucocorticoids, which then feedback via glucocorticoid receptors in the hippocampus to dampen the system once the stressor has passed (see Figure 23.3).

Elevated levels of cortisol may exacerbate symptoms through a neurotoxic effect on the hippocampus (McEwen & Seeman, 1999), and by ultimately increasing dopaminergic activity in the prefrontal cortex (Walker & Diforio, 1997). In animal models, prolonged stress has been shown to result in a dysregulated negative feedback circuit, whereby damaged hippocampi fail to correctly modulate HPA axis activity (Sapolsky, Uno, Rebert, & Finch, 1990). On the basis of animal models, some have argued that stress also increases glutamate in both the prefrontal cortex (PFC) and the hippocampus, which can also result in altered dopamine levels (Moghaddam, 2002). The increase in PFC glutamate, as opposed to the hippocampus, does not appear to be dependent on glucocorticoids, and therefore, may represent a second pathway that is activated as part of the brain's fast response to stress, which occurs prior to and during the stress response via the HPA

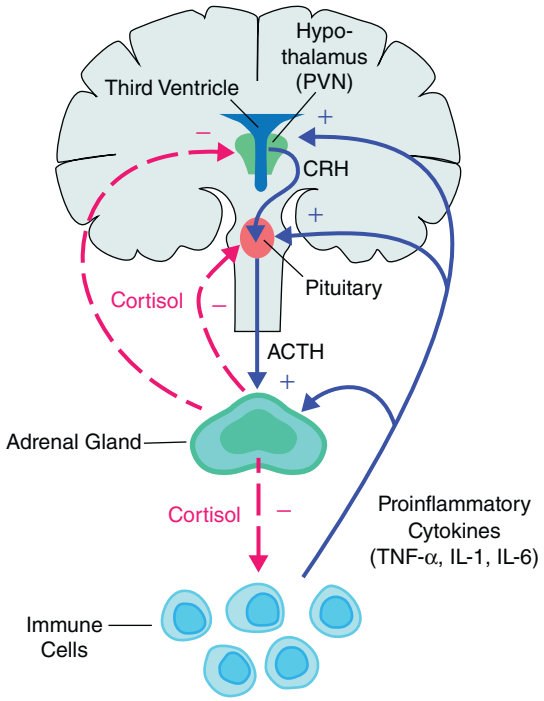


Figure 23.3 Bidirectional communication between the immune system and HPA axis. Pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, stimulate glucocorticoid release by acting at all three levels of the HPA axis (solid blue lines). In turn, glucocorticoids negatively feedback on the immune system to suppress the further synthesis and release of proinflammatory cytokines (dashed red line). In addition, glucocorticoids regulate their own production through negative feedback on the upper levels of the HPA axis, including corticotropin-releasing hormone (CRH) in the paraventricular nucleus (PVN) of the hypothalamus and adrenocorticotropin (ACTH) in the anterior pituitary (dashed red lines). See footnote 1. *Source:* Reprinted with modifications from M. N. Silverman, B. D. Pearce, & A. H. Miller, Cytokines and HPA axis regulation, in *Cytokines and Mental Health*, ed. Z. Kronfol, pp. 85–122, Norwell, MA: Kluwer, 2003.

axis (Lowy, Gault, & Yamamoto, 1993; Moghaddam, Bolinao, Stein-Behrens, & Sapolsky, 1994). Although a review of basic research on stress in animal models as related to schizophrenia is outside the scope of this chapter (see Corcoran et al., 2003, for a review), this type of research has vastly increased our understanding of the body's complex stress response and its effects on the mind and brain.

Studies of patients with schizophrenia have primarily utilized cortisol assays to assess HPA axis integrity. A recent comprehensive review of this literature (Walker, Mittal, & Tessner, 2008) reached several important conclusions: (1) HPA activity indices are elevated in a substantial proportion of patients with psychotic illness, including medication naïve and first-episode patients; (2) antipsychotic agents tend to reduce cortisol, with more pronounced reductions in those who respond to treatment, whereas agents that increase dopamine levels or exacerbate psychotic symptoms increase cortisol levels; (3) glucocorticoid receptors appear to be downregulated in individuals with schizophrenia, suggesting there may be reduced negative feedback on the HPA axis; and (4) reduced hippocampal volume, which is related to hypercortisolemia, is a consistently reported neuroanatomic abnormality in schizophrenia. Moreover, cortisol levels and hippocampal/amygdala volumes have also been independently shown to be predicted by a combination of stress-system genetic profiles (e.g., HPA axis-related genes) and early stressful life events among children with depression, highlighting the developmental link between neuroanatomical changes and stress-related genes and environmental factors (Pagliaccio et al., 2014).

In a prodromal sample, individuals at clinical high risk of developing psychosis demonstrated higher levels of cortisol than healthy controls. In addition, higher levels of cortisol within this cohort were associated with greater symptom severity and subsequent conversion to a psychotic disorder (Walker et al., 2013). Adolescents with schizotypal personality disorder have also been shown to have higher levels of salivary cortisol than adolescents with other personality disorders and normal controls, especially at the first sample of the day (Weinstein, Diforio, Schiffman, Walker, & Bonsall, 1999). At present, the direction of causality regarding elevated cortisol and HPA axis dysregulation is unclear. That is, heightened cortisol may be the consequence of developing subthreshold psychotic-like symptoms, or it may play a role in triggering or exacerbating symptoms. Alternatively, biological stress systems could trigger the expression of symptoms in vulnerable individuals. Longitudinal studies involving densely spaced assessments proximal to the time of illness onset are critical to help disentangle these multiple possibilities.

Genetic and Hormonal Regulation of Synaptic Pruning

In addition to the role of hormones in mediating stress response, hormones are likely to play a key role in adolescent brain maturation (Walker & Bollini, 2002). Gonadal and adrenal hormones have been shown to affect structural development, as well as immediate functional properties, of the brain. While some of the behavioral influences exerted by these hormones are short-term nongenomic effects, mediated by receptors on the surface of neurons, steroid hormones also affect later gene expression via intracellular hormonal receptors in neurons (McEwen, 1994; Watson & Gametchu, 1999). Animal research has demonstrated that hormones can trigger gene expression relevant to postpubertal neuromaturational processes (Ojeda & Ma, 1999). For example, estrogen-induced cyclic synaptogenesis has been observed in the adult rat hippocampus (McEwen, 1994). These genomic effects of hormones involve changes in the expression of messenger RNA that codes for specific proteins that, in turn, play a role in receptor density, reuptake, and neurotransmitter synthesis. These proteins can also trigger the expression of genes that impact neuronal survival (govern maturational processes such as proliferation and elimination of neurons). Thus, structural plasticity is an important aspect of steroid hormone action in the developing nervous system (McEwen, 1994). There is now extensive evidence from animal models indicating that steroid hormones affect brain organization during adolescence (Vigil et al., 2011), and recent studies show similar effects in humans (Peper, Hulshoff Pol, Crone, & van Honk, 2011). While the role of genomic hormonal effects in triggering onset of schizophrenia is purely speculative, some investigators have hypothesized that hormonal changes during adolescence, especially of the reproductive steroids, may trigger the expression of faulty genes, possibly affecting synaptic pruning or myelination (Amateau & McCarthy, 2002). This is supported by observations that age-related gray matter volume reductions during adolescence in healthy males might be steeper than those of healthy females (De Bellis et al., 2001). One mechanism by which rising hormone levels in adolescence may trigger expression of a latent genetic predisposition to schizophrenia is through dysregulation of the HPA axis. It is also possible that early hippocampal insult (i.e., due to prenatal complications) may increase the likelihood that a latent genetic predisposition to schizophrenia will be expressed in adolescence (Walker & Bollini, 2002). Thus,

early environmental insult may alter gonadal hormone expression; alternatively, effects of hormones may alter the nature of the early insult (Andersen, 2003).

Inflammation and Immune Factors

Inflammation and the activation of immune cells in the brain (e.g., microglia) has also been suggested to play a role in the development and symptomatology of schizophrenia (Monji, Kato, & Kanba, 2009; Watanabe, Someya, & Nawa, 2010). Increased levels of proinflammatory cytokines have been consistently found in patients with established illness (Potvin et al., 2008), and are associated with positive symptoms and overall symptom severity (Dimitrov et al., 2013). Meta-analysis suggests that some cytokines appear to show transient, state-related increases in conjunction with symptom exacerbation, whereas others show more consistent alterations (Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011). Antipsychotics are also known to produce anti-inflammatory effects (Tourjman et al., 2013). Another marker of inflammation, S100B, has been found to be elevated in unmedicated patients with schizophrenia and decreases with antipsychotic treatment (Zhang et al., 2010).

In addition to the evidence for increased inflammation subsequent to illness onset, recent studies suggest a potential role in disease pathophysiology. Patients with schizophrenia and their relatives have increased incidence of autoimmune disorders (Benros, Mortensen, & Eaton, 2012) and genome-wide studies have shown an association between schizophrenia and genes associated with regulating immune function and inflammation (Jia, Wang, Meltzer, & Zhao, 2010; Stefansson et al., 2009). Furthermore, abnormal expression of immune-related genes has been found in post-mortem studies of schizophrenia patients (Saetre et al., 2007), particularly in the prefrontal cortex (Arion, Unger, Lewis, Levitt, & Mirnics, 2007). Inflammatory cytokines may also play a role in the relationship between maternal viral infections and increased subsequent schizophrenia risk, as many viral infections do not cross the placenta (Ashdown et al., 2005; Deverman & Patterson, 2009). The effects of these prenatal infections may lead to immune cells in the brain that are more responsive to subsequent infection even into adulthood (Bland et al., 2010) and may have wide-ranging effects on cognition and brain morphology (Miller, Culpepper, Rapaport, & Buckley, 2013).

The relationship between schizophrenia and immune/neuroinflammation needs further clarification. For example, it remains uncertain whether inflammatory increases are the primary cause of the associated symptom increases or co-occur in response to other pathological processes. As such, the CNS immune response may prove either neuroprotective or detrimental. However, initial indications that pro-inflammatory cytokines may inhibit neurogenesis in the hippocampus (Liu et al., 2006) and disrupt synaptogenesis (Stellwagen & Malenka, 2006) suggest that these processes may exacerbate cognitive deficits or prolong acute psychotic episodes. Targeting these inflammatory cytokines or microglial activation has been suggested as a possible novel therapeutic target for treatment development (Mansur et al., 2012; Monji et al., 2013). In addition, recent multi-site longitudinal work has investigated blood-based biological correlates of a psychosis high-risk state (Perkins et al., 2015). An extensive algorithm selected 15 plasma analytes of inflammation, oxidative stress, metabolism, and hormonal status that significantly differentiated clinical high-risk individuals who later developed psychosis from clinical high-risk individuals who did not develop psychosis, as well as from unaffected control participants. The majority of the identified analytes were immunomodulatory (i.e., cytokines and proteins involved in inflammation modulation, particularly within the HPA), suggesting a potential blood biomarker of psychosis based on indicators of oxidative stress, immune system dysfunction, altered HPA function, and their interactions. Higher levels of these proinflammatory analytes at baseline evaluation have also been shown to strongly predict increased rates of gray matter loss in the prefrontal cortex among CHR converters (Cannon et al., 2015), highlighting the link between inflammation and neuroanatomic changes associated with psychosis onset and emphasizing the need for more research into the developmental order of these effects.

Interactions Between Early and Late Risk Factors

Theories regarding the development of psychotic symptomatology in the adolescent period must also account for findings of early childhood abnormalities in patients with schizophrenia (Walker & Bollini, 2002). Keshavan and colleagues (Keshavan, 1999; Keshavan & Hogarty, 1999) proposed that schizophrenia arises from both an early brain abnormality and late maturational processes of brain development interacting with adverse biochemical and psychosocial factors during adolescence and early adulthood. That is, prenatal or early postnatal factors (genetic or environmental) produce anomalous neural connectivity, resulting in premorbid impairment. Subsequently, during adolescence, the onset of prodromal or

fully psychotic symptoms may result from excessive elimination of synapses and secondarily, phasic dopaminergic overactivity (see Figure 23.2). Because normal ingrowth of dopamine fibers occurs during the late adolescent period (Benes, 1997), other investigators have hypothesized that developmental changes in dopamine levels may drive the onset of positive symptoms of schizophrenia during the adolescent period, thereby moderating the expression of congenital neuropathology in vulnerable individuals (Walker et al., 2008; Weinberger, 1995).

Such a progressive developmental pathophysiology of the illness during adolescence may result from several factors working singly, or in combination. First, genetic factors may predispose to excess synaptic elimination, increased neuronal apoptosis (i.e., programmed cell death), decreased cell somal size, or a combination of these processes during adolescence. Such changes might result from altered expression of genes that are critical for neurodevelopmental processes (Nawa, Takahashi, & Patterson, 2000; Olney & Farber, 1995), or altered dynamics of dopaminergic and GABAergic neurotransmitter systems (Costa et al., 2001). Second, hormonal changes, especially of the reproductive steroids, could modulate brain maturational processes such as synaptic pruning or myelination (Amateau & McCarthy, 2002). Third, psychosocial environmental factors might play a significant role as well. It is well established that environmental enrichment leads to increased spine density and dendritic arborization (Globus, Rosenzweig, Bennett, & Diamond, 1973; Lewis, 2004). Likewise, environmental deprivation or stress can lead to the opposite, i.e., an increased fall-out of synapses or neurons, and decreased neuronal viability. Synaptic plasticity mechanisms (e.g., long-term potentiation (LTP) and long-term depression (LTD)) are critical for sculpting the nervous system (Whitt, Petrus, & Lee, 2014). LTP and LTD can be elicited by activating N-methyl-d-aspartate-type glutamate receptors (NMDARs) (Lüscher & Malenka, 2012), and evidence from both animal models and human studies implicates NMDAR dysfunction in both symptoms of schizophrenia and disease progression (Gao & Snyder, 2013). Thus, one appealing hypothesis regarding schizophrenia pathogenesis is that genetically mediated hypofunction of NMDA receptors, and consequent weakening of these NMDA-dependent mechanisms of synaptic plasticity lead to an overabundance of weak synapses during adolescence that thus become targets for over-pruning.

Additionally, findings linking gray matter reductions and other gross morphological changes in schizophrenia to fetal hypoxia (Cannon, van Erp, Rosso, et al., 2002) suggest another possible mechanism by which such early influences interact with later maturational changes in influencing the timing of onset of schizophrenia. Importantly, fetal hypoxia has been associated with earlier onset forms of the disorder (Cannon, Rosso, et al., 2000; Rosso, Cannon, et al., 2000; Verdoux et al., 1997), suggesting that the presence of this risk factor may in some manner predispose to an earlier age at onset. The neural sequelae of hypoxia vary in severity from alterations in neurite outgrowth to neuronal cell death (Nyakas et al., 1996). In the former case, immature neurons may survive the hypoxic insult but still have a compromised elaboration of synaptic interconnections (Nyakas et al., 1996). Studies in fetal sheep have shown that hypoxia secondary to chronic placental insufficiency is associated with reduced cortical thickness and increased cortical neuronal density, without any observable neuronal loss (Rees et al., 1998). The pattern of morphologic changes associated with hypoxia in studies of schizophrenia is thus compatible with an animal model of chronic fetal hypoxia and with the observed cellular pathology in schizophrenic patients. In this context, processes associated with cortical synaptic pruning during late adolescence and early adulthood (Feinberg, 1982; Keshavan, Anderson, & Pettegrew, 1994) might interact with the earlier hypoxia-related effects in lowering interneuronal connectivity to below a threshold critical for integrated cognitive activity, leading to further behavioral deterioration at that time.

Thus, current models offer promising hypotheses regarding mechanisms by which processes associated with postpubertal brain development might interact with earlier compromises of the brain in predisposing to schizophrenia. Nevertheless, theories as to why adolescence represents a time of increased risk for schizophrenia onset remain speculative. It may be that heterogeneity in the course and outcome of schizophrenia is a function of the interaction of early brain pathology with normal or abnormal developmental factors occurring throughout life, up until the time when the illness commences (Pantelis, Yucel, et al., 2003). Findings of accelerated gray matter loss proximal to the time of illness onset may reflect aberrant maturational processes during adolescence, or may reflect an interaction of early neurodevelopmental anomalies with adolescent maturational processes. Whatever the cause, recent studies that follow patients longitudinally through the prodromal phase into the first episode of illness do provide evidence for progressive structural changes during this time period. The role of later environmental stressors, and how they may impact upon an already vulnerable individual, warrants further investigation in both naturalistic human studies and via experimental animal models.

SUMMARY AND CONCLUSIONS

According to the original neurodevelopmental hypothesis of schizophrenia, the disorder results from a set of basic biological errors that occur early in life and lead to a combination of structural, functional, or biochemical anomalies in the developing brain. This model of schizophrenia has been highly influential, and has moved the field substantially forward by focusing attention on early developmental deviation in individuals who develop the illness in adulthood. Specifically, in the area of epidemiology, this model has led to the investigation of early signs of functional compromise in individuals destined to develop schizophrenia in adulthood, and the interaction of specific obstetric complications with genetic factors in the etiology of psychotic illness. Convergent evidence from neuropathological investigations indicates patterns of neuronal displacement consistent with a neurodevelopmental origin.

However, a major limitation of this model is that it does not account for the delay in onset of the disorder. Why is it that the full-blown diagnosis of schizophrenia so typically manifests during the late adolescent/early adult period? Taken together with recent evidence of neuroanatomic change during the early phase of illness, it seems likely that additional factors active during this time period play a role in the disease process.

Recent advances in our understanding of processes that occur proximal to onset call for an update to the neurodevelopmental model. It is important to keep in mind that progressive anatomic changes do not preclude the existence of a neurodevelopmental insult in schizophrenia, as an inherited neurodevelopmental abnormality may also have progressive features (Mathalon et al., 2003). Here we have outlined a model in which some neurocognitive and neuroanatomical abnormalities reflect genetic trait markers, others are environmentally mediated, and the development of frank psychosis may involve a third, partially overlapping series of structural and functional changes. Theorists have focused on two sources of influences that might account for neuronal disruption proximal to the time of onset of illness, one of which is pruning-related plasticity processes that occur as a normative aspect of brain development during adolescence, and the other of which is stress-related and other hormonal changes that may have neurotoxic effects in pathways implicated in the pathophysiology of schizophrenia. In regard to the former, certain schizophrenia-related factors (e.g., genes that predipose to disrupted synaptic plasticity or neuroinflammatory processes) may disrupt the regulation of regressive brain maturational events at this time. However, it is also possible that there is nothing intrinsically wrong with these later maturational brain processes in individuals predisposed to schizophrenia, but these processes nevertheless participate in determining the timing of onset of functional deterioration and psychotic symptom formation by reducing the reserve of interneuronal connectivity to below some hypothetically critical threshold (Hoffman & McGlashan, 1997).

Brain maturational processes during adolescence are thought to underlie the development of a number of cognitive abilities, including working memory, reasoning, planning, and problem solving, that are critical for adaptive life functioning during adulthood. The specific mechanisms underlying the development of these functions are not well understood, but are likely to involve a complex interplay of genetic and nongenetic factors regulating the brain maturational processes active at that time, including synaptic pruning and myelination. Identifying the determinants and developmental course of these processes and their relationships to the phenotypic expression of adaptive cognitive functions is a critical step in the development of strategies to enhance these abilities in the population and to prevent their disability in complex neuropsychiatric diseases such as schizophrenia. The question of whether brain abnormalities in schizophrenia are static versus dynamic has been a critical issue for the field to resolve; and indeed, over the past decade some consensus has emerged that progressive neural changes do occur around the time of disease onset (Pantelis et al., 2005).

Nevertheless, it has yet to be resolved whether this process results from a failure of normal development due to a fixed early insult, a failure in an ongoing maturational process such as synaptic pruning, a degenerative process from a stage achieved through normal development, or some combination of these factors (Cannon et al., 2003). A deeper understanding of normal neurodevelopmental events is clearly critical for elucidating the potentially abnormal pathophysiological processes at work in schizophrenia.

Increasingly sophisticated in vivo neuroimaging methodologies currently offer researchers the possibility of investigating these neurobiological processes as they unfold. However, it is not yet known whether such alterations are causally relevant to onset, or merely epiphenomena of other neurodevelopmental processes at work. In this regard, the functional significance of volumetric reduction noted in longitudinal MRI studies is a paramount question. As such changes do not appear to be accompanied by neurodegenerative processes at the cellular level, it is possible they may reflect short-term

physiological variability or plasticity that does not signify ongoing deterioration.

A second, related issue is the differentiation of risk factors that are causal, and could thus represent potentially important therapeutic targets, compared with markers of vulnerability that may identify those at greatest risk, but are merely epiphenomena that do not necessarily impact the later course of illness. The identification of causal risk factors, such as particular neurocognitive deficits or brain abnormalities, has obvious implications both for research and for the development of new treatments that may improve the quality of life for individuals suffering from the disorder, and is thus a primary goal of current clinical high-risk research.

From a developmental perspective, the unfolding of the clinical disorder is a long-term process, involving multiple developmental phases, different types of risk factors, and the understanding that psychosis is in no way an inevitable outcome (Cornblatt et al., 2002). A better understanding of the developmental trajectory of neurobiological processes in schizophrenia will inform early intervention strategies as to the most vulnerable brain functions or structures, as well as the stages of the illness most amenable to treatment (Pantelis, Yucel, et al., 2003). Such intervention strategies offer promise that the functional deterioration related to onset of the clinical disorder may be delayed, attenuated, or ultimately prevented altogether.

FUTURE DIRECTIONS

Moving Forward: Mechanistic Studies in Earlier Phases of Illness

It is clear from literature summarized above that the first few years of psychosis represent a critical period in that many patients show substantial cognitive and social deterioration which has extremely detrimental effects upon long-term success in functioning independently. Nevertheless, because current mental health care practices are largely reactive rather than proactive in nature, and because the public is poorly educated about the nature and early signs of mental illness, there is often a substantial delay before young people with onset of psychotic symptoms are evaluated and treated psychiatrically (Cannon et al., 2003; Yung et al., 2003). Consistent findings indicating poorer treatment response and functional impairment given longer duration of untreated psychosis (Norman & Malla, 1993) argue for a new approach attempting to ascertain at-risk individuals before the onset of schizophrenia and to provide interventions designed to stave off illness progression and to improve functioning and long-term outcome. Indeed, over the past 20 years there has been a paradigm shift, which has enabled identification of the earliest clinical signs of psychosis, thus allowing for the possibility of preemptive interventions (McGorry, 2013). Neurobiological biomarkers may enhance our ability to predict risk at an individual level, a key step toward personalized medicine in the mental health arena.

A better understanding of the neurodevelopmental trajectory in high-risk individuals who develop schizophrenia, compared with those who do not, will allow researchers to elucidate the temporal and spatial pattern of neural and behavioral changes associated with the emergence of prodromal and psychotic symptoms. Recent longitudinal studies investigating these processes have begun to provide important evidence validating the early prodromal phases as critical periods for testing the effectiveness of primary preventive intervention programs, and may suggest strategies for the development of novel preventive treatments that can correct or compensate for the specific neurodevelopmental and psychological changes associated with the formation of psychotic symptoms during late adolescence and early adulthood. In addition, improved understanding of the neurodevelopmental trajectory preceding onset of psychosis may help to identify biomarkers present earlier in development, leading to an improved mechanistic understanding of the disease pathophysiology. Youth experiencing prodromal symptoms are likely already impacted by the disrupted neurodevelopmental processes, but earlier detection may prevent further functional deterioration, as well as amelioration of already present symptoms.

Of particular importance is determining the relative timing and contribution of the various genetic, early developmental and later developmental factors described in this chapter. For example, there is a recent expansion of research focused on understanding the pathophysiology of schizophrenia as altered connectivity within the brain. Early implications are that some but not all of the deficits precede psychosis onset, but current research is very limited. As such, it is currently unknown how the anatomical changes and connectivity alterations found in those who develop psychosis relate to particular genetic variations or environmental influences. Additional functional and structural connectivity studies are needed to clarify what alterations are present early in development, which develop more proximal to the onset of symptoms, and which appear concurrently with onset or as part of further deterioration in the active disease state. In addition, longitudinal studies of high-risk individuals are needed to determine if the progressive anatomical changes highlighted earlier are also

reflective of altered structural and functional connectivity patterns, and if these appear sequentially or concurrently. Finally, as noted above, further research is needed to differentiate which neurological differences are causal risk factors versus those that are more likely epiphenomena that are markers of the disorder but do not represent direct causal pathways.

On the other hand, it may also prove beneficial to expand outcomes research beyond psychosis incidence to functional disability and other outcomes in high-risk individuals overall (Cannon, 2008). While one important goal of research in the early phases of illness is understanding the neurodevelopmental processes underlying conversion to psychosis and developing interventions to reduce the incidence of psychosis, many individuals with clinical risk who do not develop frank psychosis remain symptomatic and functionally impaired (Addington et al., 2011). This suggests that the neurodevelopmental phenomenon addressed by high-risk studies expands beyond that of risk of psychosis onset to risk of long-term social and occupational impairments. A better understanding of the factors that predispose an individual showing risk symptoms to recover versus maintain a symptomatic state is needed.

Understanding Epigenetic, Epistasis, and Gene Environment Contributions

As described in this chapter, the understanding of genetic contributions to the development of schizophrenia through DNA structural and sequence variation has advanced considerably in recent years. These findings implicate a number of neurodevelopmental processes including cell migration and proliferation, axonal outgrowth, myelination and synaptogenesis, as well as neuronal cellular functioning mechanisms (e.g., calcium channels). Importantly, a recent large scale GWAS (~37,000 cases and 113,000 controls) identified 108 genome-wide significance risk loci for schizophrenia including genes involved in glutamatergic neurotransmission and immune function (Schizophrenia Working Group of the Psychiatric Genomics, 2014). At the same time, effect sizes for these risk variants are quite small, and current genetic models explain only part of the known heritability, suggesting the need for continued genetic exploration utilizing sophisticated statistical techniques in conjunction with GWAS for gene discovery (Lee et al., 2012). In addition, epigenetic variation, epistasis, and gene-environment interactions are important avenues for future research.

Epigenetic influences, changes in gene activity that are not caused directly by the DNA sequence but that produce long-term alterations in the transcription of genes, have been suggested to play an important role in the expressions of genes contributing to the pathophysiology and developmental of psychosis (Dempster, Viana, Pidsley, & Mill, 2012; Labrie, Pai, & Petronis, 2012). Epigenetic processes including methylation (Dempster et al., 2011; Mill et al., 2008) and histone modification (Tang, Dean, & Thomas, 2011) show altered profiles in individuals with psychosis (Halene, Peter, & Akbarian, 2014). Epigenetic alterations are often associated with prenatal (Maćkowiak, Bator, Latusz, Mordalska, & Wędzony, 2014) and postnatal (Zhang et al., 2010) environmental factors, suggesting an explanatory role in the neurodevelopmental processes underlying schizophrenia. However, examination of these effects is complicated by the potential for differential expression in different tissue types and confounds of using postmortem samples from the brain. During the process of cellular differentiation in fetal development, cells shift from pluripotent stem cells to specific tissue types and expression/epigenetic alterations may differ between tissues. Further research is necessary to determine the relationship of more accessible peripheral tissues (e.g., blood) to neuronal expression (Heijmans & Mill, 2012).

In addition to the differential effects of different levels of individual gene expression, the interaction of genes with each other is an important avenue for future study into neurodevelopmental influences on psychosis. Epistasis, when the action of one or more genes depends on the action of other modifier genes, can produce complex interactions between different combinations of genes. These interactions between genes may lead to nonadditive effects (both suppressive and enhancing), which can therefore complicate more traditional methods of gene discovery. For example, genetic variation in AKT1 was found to increase risk for schizophrenia when combined with risk alleles for COMT and BDNF but not alone (Tan et al., 2012). Similarly, multiple interactions have been found between genes associated with neurodevelopmental processes and schizophrenia risk that predict structural brain changes (Andreasen et al., 2011). As with epigenetic influences discussed above, epistatic effects likely account for some of the missing heritability and so continued research into the interactions between different gene actions will allow for clarification of the underlying pathophysiological processes.

In addition to genetic expression patterns and gene-gene interactions, the interaction between genetic factors and environmental risk factors is also an important avenue for future research. As discussed previously, understanding of the impact of environmental factors such as prenatal

hypoxia, stress, and inflammation on gene expression is in its infancy. For example, many candidate genes for schizophrenia susceptibility have been shown to be regulated by hypoxia (Schmidt-Kastner et al., 2006) and obstetric complications show greater behavioral impacts in individuals with genetic susceptibility (Forsyth et al., 2013). There are many additional environmental factors that increase the incidence of schizophrenia (Brown, 2011; van Os, Kenis, & Rutten, 2010); however, their mechanisms of action and interaction with particular genes are not known. These epigenetic, epistasis and gene-environment interactions likely work in concert to produce the pathophysiological processes that influence the development of schizophrenia and more research is needed to understand their complex relationships.

Improving Treatment and Interventions for Schizophrenia

Despite major advances in neuroscience, drug discovery and pharmacogenomics, the treatments currently available for schizophrenia have only limited effectiveness. In addition, current medications have significant side effects and do not appear to impact the neurodevelopmental alterations in individuals prior to psychosis onset, suggesting limited prophylactic utility (Amminger & McGorry, 2012; McGorry et al., 2002). Taken together, this suggests that the currently available pharmaceutical treatments do not fully address the causal mechanisms of psychosis and are likely most effective at treating some of the associated affects of the underlying pathophysiology. Currently, the antipsychotic medications primarily used to treat psychosis rely on modulation of dopamine receptors, particularly the dopamine D2 receptor (Kapur & Mamo, 2003). However, improved understanding of the neurodevelopmental mechanisms underlying schizophrenia may provide additional targets for treatment and prevention. For example, the role of glutamate and GABA (Agnew-Blais & Seidman, 2012; Coyle, 2006; Krystal & Moghaddam, 2010) discussed previously suggest that future pharmacotherapy may prove more effective by targeting these symptoms. Similarly, the white matter alterations noted in schizophrenia and high-risk patients have suggested a potential role for myelination disruption in the onset of psychosis. Levels of nervonic acid, a component of the myelin sheath, at baseline predict rate of conversion and supplementation with omega-3 fatty acids has been found to reduce rates of conversion in preliminary studies (Amminger & McGorry, 2012). Future studies based on a mechanistic understanding of schizophrenia pathophysiology are essential for identifying novel targets for intervention.

Existing diagnoses rely on symptoms so far removed from drug targets that discovery of new treatments is almost always serendipitous. Development of rational pharmacotherapies for schizophrenia may be aided by more discrete definitions of pathological phenotypes to replace currently defined syndromal targets. Conventional diagnostic phenotypes are marked by such heterogeneity and overlap that genomic analyses using current syndrome definitions are questionable. Defining new phenotypes of the disorder at a neural-systems level, with links to drug mechanisms-of-action and patterns of gene expression, could yield dramatic advances in neuropsychiatric therapeutics, like those that resulted from the identification of neuropathological and neurochemical targets in Parkinson's disease (Fiandaca & Bankiewicz, 2010). A focus on endophenotypes expressed across multiple syndromes and species, examined using a multidisciplinary approach that capitalizes upon convergent technologies from molecular to behavioral, will likely accelerate the discovery of new treatments.

In particular, cognitive abnormalities, known to be a core feature of schizophrenia, offer quantitative phenotypes for genomic studies and clinical trials, and provide strong bridging relations to informative neural systems models. Measurement of cognitive constructs is highly scalable, enabling phenotype assessments to be conducted with the high throughput necessary for adequately powered genomic association studies and multi-center clinical trials. For example, a recent study of cognitive remediation in schizophrenia found improvement in reality monitoring with cognitive training, which correlated with increased medial prefrontal cortical activity (Subramaniam et al., 2012)

Notably, technological advances are making it increasingly feasible to screen populations on a large scale to identify at-risk individuals at an early age. At the same time, these advances (such as web- or smart-phone based applications) can greatly improve access to cognitive training programs or other therapies that can be administered remotely. Combining such methods with in vitro models of disease may open revolutionary prospects for both pathophysiological modeling and avenues for new interventions.

Translational Implications

Human-Induced Pluripotent Stem Cells

The recent discovery that fibroblasts (skin cells) can be reprogrammed into a pluripotent state and subsequently differentiated into neural progenitor cells and neurons has

great potential to lead to the discovery of molecular and cellular defects that may be critical to disease pathogenesis (Brennand & Gage, 2011; Dolmetsch & Geschwind, 2011). Recent studies of major mutational models of autism such as Timothy syndrome have led to some remarkable new findings of cellular phenotypes that can be rescued with pharmacologic agents that specifically target the observed cellular defects (Paşca et al., 2011).

The human-induced pluripotent stem cell (hiPSC) approach appears very well suited to the study of neurodevelopmental disorders, but there are still many questions and limitations to this approach (Rapoport, Giedd, & Gogtay, 2012). Heterogeneity within and across populations and lack of standardization of protocols are major challenges in the field. Nevertheless, investigation of neuronal developmental phenotypes in hiPSC-derived neurons from patients with schizophrenia may be highly informative. Recently, Brennand et al. (2011) reprogrammed fibroblasts from four patients with schizophrenia into hiPSCs and subsequently differentiated them into neurons. The hiPSC-derived neurons from schizophrenia patients showed diminished neuronal connectivity as well as decreased neurite number, PSD95-protein levels and glutamate receptor expression. These findings are consistent with post-mortem data and animal models indicating reduced dendritic arborization in schizophrenia (Selemon & Goldman-Rakic, 1999). Intriguingly, reduced neuronal connectivity in the hiPSC was rescued by treatment of the cells with an antipsychotic.

Conducting these cellular assays on a larger scale and linking them to variability in phenotypic expression, as well as validating them against *in vivo* neuroimaging data from the same patients, are key next steps. Additionally, investigating hiPSC models in the context of homogeneous genetic subtypes of psychosis such as individuals with 22q11.2 deletions will likely increase the robustness of the cellular phenotypes detected and reduce heterogeneity.

Cross-Disorder Neural Endophenotypes

The investigation of biologically based endophenotypes—quantitative traits or markers proposed to represent more direct expressions of underlying genes—may yield far more informative results than studies of aggregate psychiatric phenotypes (Gottesman & Gould, 2003). As such, an endophenotype-based approach is likely to aid in unraveling the complexity of transmission of complex mental disorders like schizophrenia. Combining information across multiple levels of phenotypic expression, with modeling of the neural systems that support these functions, can advance definitions of phenotypes that will be useful in developing more effective treatments.

With revisions to our current diagnostic classification system (DSM-V; APA, 2013) underway, it is critical that scientific evidence be better utilized in its development. Several investigators in the field have highlighted the need to increasingly strive for classification that more closely represents expression of underlying biologic systems (Merikangas & Risch, 2003). This principle is embodied in the National Institute of Mental Health's new Research Domain Criteria (RDoC) initiative, the goal of which is to develop a research classification system for mental disorders based upon fundamental biobehavioral dimensions that may cut across current heterogeneous categories of psychiatric disorder (Casey et al., 2013). For example, while schizophrenia and bipolar disorder have traditionally been viewed as distinct disorders, recent work from the Psychiatric Genomics Consortium (Lee et al., 2013) has revealed a high degree of genetic correlation between schizophrenia and bipolar disorder, consistent with prior findings from linkage and association studies indicating substantial familial co-aggregation and overlap in the genomic regions associated with these two disorders. Elucidating the specific genetic and neural mechanisms influencing susceptibility to and expression of these illnesses, and explaining the nature of the overlap between them, is critical to understanding the necessary and sufficient conditions for overt psychosis and to the development of more effective treatment and prevention strategies.

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CHAPTER 24

Neuropsychological and Structural Neuroimaging Endophenotypes in Schizophrenia

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INTRODUCTION

The concept of an endophenotype was adapted from insect genetics (John & Lewis, 1966) and introduced to psychiatric genetics in the early 1970s by Gottesman and Shields (Gottesman & Shields, 1972; Gottesman & Shields, 1973; Gottesman & Shields, 1982). At that time, the molecular genetics of psychiatric disorder was barely even a fantasy, and the considerable intellectual debate over the ethics of studying genetics of mental illness and cognition (i.e., intelligence in particular) dominated the discussion (Gould, 1981, 1996). Nevertheless, after a long dormant period, and changes in the zeitgeist, interest in a genetic approach grew remarkably strong, with a dramatic acceleration of endophenotype studies in the last decade or two (Braff et al., 2008) (see Figure 24.1).

The interest in and conceptualization of endophenotypes extends beyond schizophrenia, to bipolar disorder (Hasler et al., 2006), attention-deficit/hyperactivity disorder (ADHD) (Doyle et al., 2005a; Doyle et al., 2005b) and other psychiatric disorders (Gottesman & Gould, 2003; Gottesman & Hanson, 2005). In fact, the approach is applicable to any disorder, whether psychiatric or other medical (such as diabetes, heart disease, etc.); however, in this chapter, we will largely limit the focus to schizophrenia, which has developed a voluminous literature on endophenotypes in the past two decades (Braff & Freedman, 2002; Braff et al., 2007; Gottesman & Gould, 2003; Tsuang, et al., 1993).

What then, is an endophenotype? Most researchers agree on a number of core principles. Most essential is that endophenotypes are measures that are quantitative and often laboratory based, and may not be observed directly within a standard clinical framework (in which symptoms predominate, at least in psychiatry). Thus, measures like eye-tracking, working memory measures of cognition, prefrontal function measures using functional magnetic resonance imaging (fMRI), or gamma oscillation measures of event related potentials (ERPs) are just a few examples of potential endophenotypes that may show certain characteristics but currently do not play specific roles in the current diagnostic criteria for disorders. Further, endophenotypes are conceptualized as important heritable links between genetic variation and the disorder itself. In theory, endophenotypes can occur based purely on genetic factors, or can emerge as a result of interactions with non-genetic factors (e.g., perinatal complications, stress etc.).

Gottesman and colleagues proposed that endophenotypes would have genetic etiologies that were simpler

[1]Color versions of Figures 24.2, 24.3 and 24.4 are available at http://onlinelibrary.wiley.com/book/10.1002/9781119125556

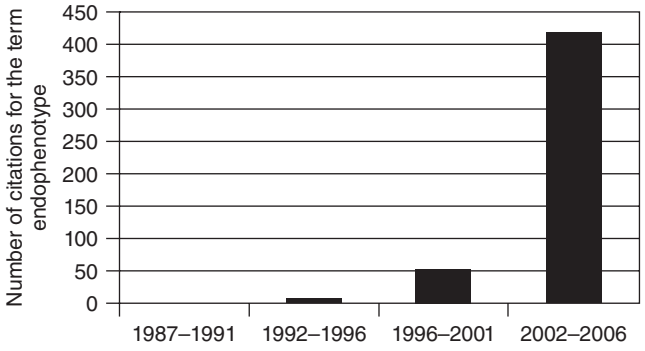


Figure 24.1 Endophenotype publications between 1987 and 2006. *Source:* Used with permission from Braff et al., 2008.

TABLE 24.1 Proposed criteria for endophenotypes

Endophenotypes are related to the illness
Endophenotypes are heritable
Endophenotypes are present in all phases of the illness, though their expression may vary by developmental phase, age, gender, phase of illness, treatment or other environmental or co-morbid conditions
Endophenotypes are present at higher rates in the ill relatives of ill patients, compared with healthy relatives of ill patients
Endophenotypes occur in unaffected biological relatives at higher rates than they do in the general population
Endophenotypes are quantitative traits that can be measured reliably and are associated more with the particular illness than they are with other disorders

Source: Adapted from Gottesman and Gould, 2003, and Lenzenweger, 2013.

than those of the clinical illness. Though this has not been borne out clearly yet (Flint & Munafo, 2007), proof of this hypothesis may reflect the need to identify endophenotypes that are closer to their underlying genetic etiologies than those thus far identified (Glahn et al., 2014). This view is consistent with the likelihood that clinical diagnostic symptoms in psychiatry are relatively distal effects arising from pleiotropic genes with small effect sizes (Meyer-Lindenberg & Wienberger, 2006). This, in turn, reflects the likelihood that observable effects, though heritable, represent cumulative effects of multiple genes, with their attendant complex genetic architectures (Almasy, 2003; Glahn et al., 2014; Munafo & Flint, 2011). The more directly endophenotypes reflect the genes that produced them, however, the simpler the underlying genetic architecture may be. It also follows from this view that these more proximal expressions of genetic effects would be less amenable to direct observation than more complex distal clinical symptoms (Gottesman & Gould, 2003).

Gottesman and colleagues (Gottesman & Gould, 2003; Gould & Gottesman, 2006; Hasler et al., 2006; Lenzenweger, 2013) proposed several criteria for the identification of endophenotypes in schizophrenia. The criteria listed below were adapted from these sources (Gottesman & Gould, 2003; Lenzenweger, 2013) and listed in Table 24.1. In short, the criteria require that the deficits: 1) occur in association with the illness; 2) are trait-like and largely stable and largely independent of the influences of clinical state; 3) show heritability; 4) co-segregate with the illness; 5) occur at a higher frequency (and usually lesser severity) in biological relatives, especially first-degree relatives, than in control groups drawn from the general population, and 6) are quantitative traits that can be measured reliably and are associated more with the particular illness than they are with other disorders.

Braff and colleagues suggested that endophenotypes may represent a subset of a broader category of biological markers or vulnerability markers, largely associated with genes, whereas the broader category of markers can arise from the environment or some multifactorial process (Braff et al., 2007). Lenzenweger, in a review of similarities and differences between endophenotypes, intermediate phenotypes and biomarkers, emphasized this distinction as well, noting that biomarkers, unlike endophenotypes, need not be subject to genetic influences (Lenzenweger, 2013). Similarly, biomarkers need not co-segregate with the illness within families, which is another critical distinction with the endophenotype concept (Glahn et al., 2014; Lenzenweger, 2013). Definitions and uses of the term biomarker vary considerably, particularly compared with Gottesman and colleague's proposed definition of an endophenotype (Iacono, 1983; Miller & Rockstroh, 2013). Because biomarkers may not be subject to illness-related genetic influence, they may comprise a correlate of an illness-related process, rather than a mediator of an illness-related process (Kendler & Neale, 2010). Despite these differences, there is a general consensus that endophenotypes and biomarkers are related concepts, with endophenotypes forming a subset of biomarkers that are mediated by the same genetic etiologies that produce susceptibility to the illness (Glahn et al., 2012; Glahn et al., 2014; Lenzenweger, 2013; Miller & Rockstroh, 2013).

Intermediate phenotype (Meyer-Lindenberg & Wienberger, 2006; Rasetti & Weinberger, 2011) is another concept that is related to endophenotype. Weinberger and colleagues described intermediate phenotypes as heritable traits on a trajectory that extends from genetic etiology to clinical illness. The term has gained traction and is often used interchangeably with endophenotypes, if not as

frequently. Glahn et al. pointed out that a PubMed search using the term endophenotype listed 2111 publications between 1972 and August, 2013, while intermediate phenotype listed 700 (Glahn et al., 2014). As Lenzenweger and others (Miller & Rockstroh, 2013) have pointed out, however, the concept is ambiguous in several respects, such as the meaning of intermediate, and has been used in substantially different ways. For example, Insel and Cuthbert suggested that intermediate phenotypes were most appropriate for personality or other clinical clusters of symptoms (Insel & Cuthbert, 2009). Ambiguity in the concept is increased further by using a term that already has a formal meaning in genetics that is related to partial dominance (Lenzenweger, 2013). Notably, heritable intermediate phenotypes may be conceptually identical to endophenotypes (Lenzenweger, 2013; White & Gottesman, 2012).

A key issue related to the concepts of trait and stability is the role of development and age, and the impact of psychotropic medications. For example, with regard to the latter, neurocognitive measures can vary somewhat with illness exacerbations and remissions, as well as with medication status. Spohn and Strauss (1989) reviewed the literature and showed that neuroleptic treatment is associated with limited normalization on many psychological measures, whereas anticholinergic treatments appear to disrupt some aspects of memory. The core cognitive deficits remained, however, to greater or lesser degrees (Spohn & Strauss, 1989). Thus, stability is relative. Another issue, more related to the intrinsic development of the illness, is exemplified by the evolution of brain structural changes. In this situation, a preexisting deficit in the volume of prefrontal cortex (PFC), found in children at familial (genetic) high risk (FHR) for schizophrenia (Thermenos et al., 2013), shows further reduction in volume as the individual passes through a period of high risk into a first episode of schizophrenia (McIntosh et al., 2011). We will take up later what is known about the genetic basis of the PFC structural abnormality, but there is evidence for a genetic origin and evolution (Gulsuner et al., 2013). This changing picture poses many questions about the possibly varied genetic basis of different phases of illness, and whether PFC volume or thickness could be a useful endophenotype. In any case, age, development and stage of illness are important factors in considering the conceptualization and utility of endophenotypes.

Taking this conceptualization of endophenotypes as a starting point, we may now ask where they fit in an etiological model of schizophrenia. Figure 24.2 shows a model that helps to provide a context for the role of endophenotypes. We hypothesize that the combination of

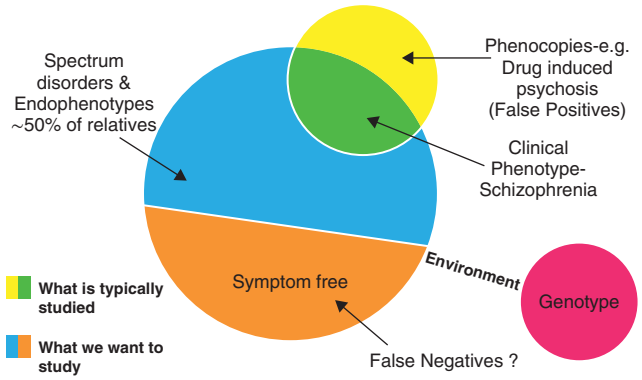


Figure 24.2 Model of genetic and phenotypic heterogeneity. See footnote 1. *Source:* Adapted with permission from Tsuang, Gilbertson and Faraone, 1991.

genotype (the circle to the right) and environment produces a range of possible outcomes (the large circle), only a small portion of which are captured by a clinical diagnosis of schizophrenia (the smaller circle intersecting with the larger one). Moreover, some portion of diagnosed individuals will be similar phenotypically, but will reflect false positive cases (e.g., people with schizophrenia-like brain disorders). The bottom portion of the larger circle contains unaffected individuals, which may also contain false negative cases, to an unknown extent. The upper portion of the larger circle contains the space between unaffected individuals and those with valid diagnoses of schizophrenia. This area contains individuals with less severe, schizophrenia spectrum diagnoses, and validly diagnosed schizophrenia itself. Endophenotypes are hypothesized to occur in this area, whether or not they occur in association with a recognized spectrum condition (e.g., schizotypal personality disorder). To the extent that new endophenotypes are identified, portions of the area at the bottom that are now classified as unaffected, may be reclassified into the area occupied by spectrum conditions/endophenotypes.

GENETICS OF SCHIZOPHRENIA: CURRENT STATUS AND APPLICATION TO ENDOPHENOTYPES

Although the idea of genetic contributions to schizophrenia is well-accepted and compelling (Allan et al., 2008; Craddock et al., 2009; Gottesman & Hanson, 2005; Harrison & Weinberger, 2005), until recently, the identity of genes that increase susceptibility to the disorder, and especially the biological mechanisms by which they act, have been largely unknown. Even with the recent flood of genetic associations with schizophrenia (Ruderfer et al.,

2013; Smoller et al., 2013) the findings only account for a small percentage of the etiological variance, which leaves mechanistic understanding in an early stage (Chen, 2013; Greenwood et al., 2011; Greenwood et al., 2013). Moreover, the genes being discovered as associated with schizophrenia may not be specific to schizophrenia, and may reflect susceptibilities to other disorders such as bipolar disorder or autism (Smoller et al., 2013). Nevertheless, the recent findings of 108 susceptibility loci in people with schizophrenia, including genes for brain development and immunity, has solidified the genetic foundation for schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

Understanding how genetic determinants of schizophrenia modulate liability for schizophrenia-spectrum conditions requires considering the idea that schizophrenia is broader than the DSM or ICD syndromes that are required for diagnosis (Tsuang et al., 2000). This can influence our thinking in a number of directions. On the one hand, it draws attention to the idea that schizophrenia and affective psychoses are on a continuum, and that this continuous dimension can be measured (Keshavan et al., 2011). On the other hand is the idea that conditions milder than schizophrenia such as schizotypal personality are on a continuum with schizophrenia, and manifest milder versions of some of the abnormal traits. The importance of identifying endophenotypes (Gottesman & Gould, 2003; White & Gottesman, 2012) reflects a growing awareness that multidimensional expressions of psychiatric disorders can advance the search for underlying etiological or modulatory factors (Allan et al., 2008; Allen et al., 2009; Chan & Gottesman, 2008; Eack et al., in press; Gottesman & Gould, 2003; Gur et al., 2007a; Turetsky et al., 2007). Moreover, endophenotypes may be more specific and amenable to objective measurement than diagnostic symptoms (Braff & Freedman, 2002; Braff et al., 2007; Gottesman & Gould, 2003), and are heritable, as noted above (Greenwood et al., 2007; Greenwood et al., 2013; Husted et al., 2009). While the underlying genetic etiology of many putative endophenotypes have turned out to be quite complex themselves (Flint & Munafo, 2007), these features all support the usefulness of endophenotypes in genetic studies (Braff & Freedman, 2002; Braff et al., 2007; Faraone et al., 1995a; Faraone et al., 2003; Faraone et al., 1995b; Gottesman & Gould, 2003; Gottesman & Shields, 1972; Seidman & Wencel, 2003; Tsuang, 1994; Tsuang et al., 2000; White & Gottesman, 2012).

At the time the concept of endophenotypes gained currency, the field of molecular genetics was in its infancy and the field of psychiatric genetics was based largely on the well-known genetic epidemiology that schizophrenia and other psychiatric disorders ran in families, and that the pattern of transmission was not consistent with a single major gene (Faraone & Tsuang, 1985; Gottesman & Shields, 1967). Family studies of parent-child and sib-pairs contributed to the well-known increase of a roughly 10-fold increase in the rate of schizophrenia when a first-degree relative had the illness (Gottesman, 1991; Tsuang et al., 1999a). This increased by an additional two or three fold with two first-degree relatives (such as a parent and a sibling with schizophrenia) or another 4–5 fold when a sibling was a monozygotic identical twin, sharing identical DNA. Schizophrenia was known to be highly heritable (approximately 81% on average) (Sullivan et al., 2003) and a genetically heterogeneous disorder (McClellan & King, 2010). This state of affairs existed mainly into the 1990s, when it became clear that a sole focus on DNA was insufficient to explain the role of genetics, and a focus on RNA and proteins was emerging (Glatt et al., 2011). More recently, as very large samples have begun to demonstrate as many as 100+ genes (of small effect) to be associated with schizophrenia (Ruderfer et al., 2013), the field has become much more complex. For example, a recent development is the identification of rare gene-disrupting copy number variants (CNVs) that contribute significantly to schizophrenia (Walsh et al., 2008), as well as other neurodevelopmental illnesses like autistic spectrum disorder. CNVs that disrupt genes involved with signaling, synaptic plasticity, and neurodevelopmental processes may be especially important for schizophrenia (Gulsuner et al., 2013; Kirov et al., 2012; Walsh et al., 2008).

These latter findings on brain neurodevelopment are consistent with the longstanding belief that endophenotypes for schizophrenia are presumed to derive mainly from the central nervous system (CNS). This is a very large terrain and thus we limit our scope in this chapter to focus on two important classes of endophenotypes that reflect the CNS: neuropsychological and structural neuroimaging endophenotypes. Even within the world of neuroimaging, which is quite broad, this review will focus on structural neuroimaging using magnetic resonance imaging (MRI). In addition to their relationships to underlying neurobiological etiologies, neuropsychological and structural neuroimaging share other common features. Both, for example, involve measures that are amenable to objective definition and measurement, both have been studied intensively and are amenable to quantitative analyses such as meta-analyses, and both have been discussed conceptually as furthering our understanding of the liability to develop schizophrenia (Fusar-Poli et al., 2011; Seidman et al., 2004;

Stone & Giuliano, 2013; Thermenos et al., 2013; White & Gottesman, 2012). This review will highlight representative findings in both of these areas. We will emphasize the utility of proposed MRI and neuropsychological endophenotypes in the context of key conceptual features that includes their association with schizophrenia, their appearance in unaffected biological relatives, their heritability and their trait-like characteristics—that is, their relatively stable appearance during all phases of the illness. By stability we do not mean that a characteristic is invariant. Rather, we mean that the characteristic is always present to some extent, and that the influence of clinical state on the trait is relatively modest compared with its typical appearance during more clinically quiescent periods.

NEUROPSYCHOLOGICAL ENDOPHENOTYPES

Are Cognitive Deficits a Central Part of the Disorder?

Some investigators proposed that cognition should be added to the diagnostic criteria for schizophrenia (Kahn & Keefe, 2013), although this option has critics (Heckers, 2013) and was not heeded in the recent deliberations by the Psychosis subcommittee of the DSM-V revision (American Psychiatric Association, 2013). Nevertheless, there is a broad consensus that cognition, including neurocognition and social cognition, is one of the key elements of the illness (Elvevåg & Goldberg, 2000; Seidman, 1983). This recognition, and the need to have a standardized neurocognitive assessment for treatment trials of cognition, led directly to the development of the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MATRICS–CCB) (Kern et al., 2008; Nuechterlein et al., 2008) and other brief, standardized batteries. Moreover, quantitative studies over the last 15 years demonstrate significant cognitive impairment across a broad range of cognitive domains (Aleman et al., 1999; Heinrichs, 2005; Heinrichs & Zakzanis, 1998). Cognitive deficits are associated with both impaired quality of life and with poor functional outcomes (Green, 1996; Green & Braff, 2001; Green et al., 2000; Mesholam-Gately et al., 2009; Nuechterlein et al., 2012). They are largely stable and severe from the first episode of psychosis to the chronic period and present in all phases of the illness (Heinrichs & Zakzanis, 1998; Mesholam-Gately et al., 2009). Thus, we share the belief of many in the field, that neuropsychological deficits are both hallmarks and core features of dysfunction in schizophrenia (Heinrichs, 2005). Nevertheless, several unresolved issues are also discussed below.

Are Cognitive Deficits Found in All Persons with Schizophrenia?

A separate but related question, and one that is more difficult to answer, is whether all individuals with schizophrenia have a neurocognitive disorder. All of the studies in this area, including those studying high IQ individuals with schizophrenia (Gray et al., 2013; Kremen et al., 2001; MacCabe et al., 2012), conclude that either the vast majority have neurocognitive deficits (Allen et al., 2003; Kremen et al., 2000; Kremen et al., 2001; Palmer et al., 1997) or that all do (Keefe et al., 2005; Wilk et al., 2005). Nevertheless, there are some methodological constraints that lead to caution about concluding this: while some of these studies find a modest subgroup of 25% or fewer of the sample that seem unimpaired, most of the samples are drawn from chronically ill patients who are more likely to be impaired, and none of these studies has assessed individuals at multiple time points to clarify whether the deficits are present at all time points. Despite these caveats, it appears that the vast majority has some form of cognitive impairment, which may vary by severity and type (Kremen et al., 2004; Seidman et al., 1992). Thus, from the point of view of endophenotype criteria (Gottesman & Gould, 2003), neurocognitive deficit meets the first criteria for an endophenotype—it is a core part of the illness.

Is There One Central Cognitive Deficit or Multiple Deficits?

This issue has been an area of debate for 20 years since Blanchard and Neale's paper describing a generalized cognitive deficit in schizophrenia (Blanchard & Neale, 1994). This point of view challenges the idea of deficits in many neurocognitive areas proposed by some (Seidman et al., 1992), or the primacy of executive function (prefrontal) deficits suggested by others (Goldberg et al., 1987; Levin, 1984; Seidman, 1983). This issue has been studied from a number of perspectives, and we will conclude that the answer is both—that there is evidence for a generalized deficit and that this cuts across many domains of cognition. On the other hand, there is also evidence that some deficits cannot solely be explained by the generalized deficit and thus, there are specific as well as generalized deficits.

This section focuses on general neuropsychological deficits first, and then takes up particular cognitive domains. We will focus on representative areas that are both impaired and well studied: overall cognitive abilities, learning and memory, attention, and executive functions (EFs). We will also emphasize specific representative tests/variables within each domain to identify the most valid endophenotype candidates.

Broad/Generalized Deficits

The notion of broad or more generalized deficits can be viewed in at least two ways. One is to consider single measures that are presumed to assess generalized functioning, such as Full Scale IQ scores derived from Wechsler intelligence tests. Impairments in broad measures of cognition, however, occur often in the context of broad neuropsychological impairments across many domains in schizophrenia (Hill et al., 2013; Seidman, 1997; Seidman et al., 1992). A recent meta-analysis that included 100 studies published between 2006 and 2011 showed, for example, that patients with schizophrenia performed worse than controls on all cognitive tests and domains assessed, though particularly in processing speed and episodic memory (Schaefer et al., 2013). This raises the question of whether separable cognitive deficits really occur, or whether they reflect a more generalized deficit that is evident in whichever cognitive domain is assessed. These choices are not mutually exclusive, however, as recent studies reveal both general and more specific cognitive deficits in schizophrenia (Dickinson et al., 2004; Nuechterlein et al., 2004; Wang et al., 2010). We will focus on IQ scores as a general measure of overall cognitive function because they are relatively discrete measures that can be assessed and compared more easily across studies.

Aylward et al. showed in a 1984 meta-analysis that overall cognitive ability as measured by IQ scores in subjects who subsequently developed schizophrenia or related disorders, was lower than in comparison samples. The effect size (Cohen's *d*) was small to medium (–0.43). Later, Woodberry et al. (2008) performed a meta-analysis on 18 studies in which children or teenagers subsequently developed schizophrenia, schizoaffective disorder, or schizophreniform disorder, using more recent diagnostic criteria. Consistent with Aylward et al., these subjects showed lower overall cognitive abilities, as measured by IQ scores in the premorbid period, with a moderate effect size relative to healthy controls ($d = -0.54$). This effect size is about half the magnitude of the IQ deficit in schizophrenia (Heinrichs & Zakzanis, 1998), which shows that a substantial portion of the deficit appears premorbidly. Sorenson et al. (2010) also showed that children 10–13 years old who later developed a disorder in the schizophrenia spectrum had lower IQ scores compared with a group who did not develop a psychiatric disorder. Clearly, IQ is affected premorbidly.

Mesholam-Gately et al. (2009) included data from 47 studies in a meta-analysis of first-episode schizophrenia. They showed medium to large deficits across 10 neuropsychological domains (effect sizes from $d = -0.64$ to -1.20), including an overall cognitive domain ($d = -0.91$) that was composed mainly of IQ tests. They also found that the magnitude and extent of cognitive deficits at the first episode was similar to the level of deficits observed in chronic schizophrenia (Heinrichs, 2005; Heinrichs & Zakzanis, 1998), further demonstrating the stability of these deficits.

Nonpsychotic relatives of patients with schizophrenia also show stable, cognitive deficits (Faraone et al., 1999; Kremen & Hoff, 2004; Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004; Snitz, MacDonald, & Carter, 2006). A meta-analysis that assessed 43 neuropsychological test scores from 58 studies showed smaller differences from control subjects than generally occur with patients (Snitz et al., 2006). Differences in overall cognitive ability, using the Wechsler Adult Intelligence Scale-Revised (WAIS-R), however, were significant, with a small effect size ($d = 0.31$). Consistent with the studies of adults is the result from a recent quantitative review of 28 studies of young nonpsychotic relatives under the age of 30 (and as young as age 7) that demonstrated that the largest impairment (presumably associated with genetic risk) was in IQ (Agnew-Blais & Seidman, 2013). While this could be a function of better psychometric features (e.g., higher reliability of IQ than other tests) and larger subject samples, which yielded more reliable estimates than many individual tests, it still supports the general deficit idea. Thus, this general impairment is found at all ages studied so far, in the premorbid period and in those at genetic risk for schizophrenia based on family history. It is also observed in the so-called prodromal, clinical high risk period (Giuliano et al., 2012) in which IQ deficits were again prominent.

A meta-analysis of IQ showed moderate levels of heritability (0.48) (Devlin et al., 1997). A few studies that assessed the heritability of IQ in schizophrenia also showed significant findings. One of these demonstrated small to moderate heritabilities (0.31–0.62) for neuropsychological measures in 17 multiplex Canadian families, with the highest heritability shown by IQ (0.64–0.74; the estimates varied slightly depending on which statistical model was used) (Husted et al., 2009). The concurrent and significant heritabilities for IQ and for other neuropsychological measures raise a question about whether broader measures such as IQ are independent from cognitive abilities that are conceptualized more narrowly (e.g., working memory or mental flexibility). Relevant to this point, Aukes and colleagues studied schizophrenia patients and their relatives in 25 multigenerational Dutch families and showed, for example, that a significant genetic correlation accounted for 76% of the variance between measures of spatial working memory and IQ (Aukes et al.,

2009). Owens et al. showed significant genetic correlations between measures of semantic and phonemic fluency, initiation and mental flexibility (i.e., EFs) and IQ (Owens et al., 2011), and Goldberg et al. showed significant genetic correlations between the Letter-Number Sequencing Test (i.e., working memory) and IQ (Goldberg et al., 2013). Toulopoulou et al. used twin and family data to show that shared genetic effects accounted for most of the variance in significant phenotypic correlations obtained between measures of intelligence and schizophrenia (89%), and between measures of immediate and delayed recall and schizophrenia (72% and 86%, respectively) (Toulopoulou et al., 2010). These findings provide support for the view that the same genes that contribute to the phenotypic expression of intelligence also contribute to the phenotypic expression of measures in other cognitive domains. For comparison, representative heritability scores are listed in Table 24.2 for IQ and other cognitive domains. Representative studies included in the table were published in the last 20 years, and included both twin and family studies. In addition, reviews or meta-analyses were included, with multiple results listed as ranges of heritabilities. PubMed search terms included heritability, schizophrenia, neurocognition, cognition, neuropsychology, memory, attention, executive function, and intelligence.

Although in one sense, these genetic correlations provide support for the use of these cognitive domains as endophenotypes, they also raise the question of the extent to which separable cognitive deficits actually occur in schizophrenia. An alternative possibility is that cognitive deficits reflect more generalized or widespread deficits that become salient in whichever cognitive domain is assessed (Goldberg et al., 2011). In a series of studies that assessed the issue, Dickinson and colleagues showed that much of the variance in cognitive performances that were attributable to diagnoses of schizophrenia were related to a single, common factor. In one of these studies, 47% of the variance in cognitive performance was attributable to a schizophrenia diagnosis, and 65% of that was attributable to a single, common factor (Dickinson et al., 2004). They showed in a subsequent study that 63.6% of the diagnosis-related variance derived from a common factor, with much smaller percentages attributable to performance in other cognitive domains, such as verbal memory (13.8%) and processing speed (9.1%) (Dickinson et al., 2008). Moreover, the same group demonstrated that schizophrenia patients showed higher correlations between composite scores of neuropsychological functions in a study of confirmatory factor analysis compared with healthy controls, consistent with the hypothesis that

TABLE 24.2 Heritabilities of Selected Neuropsychological Functions in Healthy Subjects and in Subjects with Schizophrenia

Study	Cognitive Domain	Subjects		Heritability (h^2 Intraclass Correlation or Risch's Lambda)
		Healthy	Schizophrenia	
Devlin, Daniel, and Roeder, 1997	Overall cognitive ability (IQ)	Meta-analysis Twin designs		0.48
Hermo et al., 2014		Review		0.66–0.82
Husted et al., 2009			Family design	0.64–0.74
Aukes et al., 2009			Family design	0.39
Toulopoulou, 2007			Twin design	0.70
Papassotiropoulos and de Quervain, 2011	Declarative memory	Review		0.30–0.60
Hermo et al., 2014		Review		0.43–0.63
Calkins et al., 2010			Family design	0.50
Husted et al., 2009			Family design	0.40–0.49
Gur et al., 2007b			Family design	0.66
Greenwood et al., 2007			Family design	0.25–0.27
Cornblatt et al., 1988	Attention	Family design		0.39–0.49
Hermo et al., 2014		Review		0.27–0.66
Calkins et al., 2010			Family design	0.40
Gur et al., 2007b			Family design	0.50
Greenwood et al., 2007			Family design	0.38–0.39
Ando et al., 2001	Executive function	Twin design		0.43
Husted et al., 2009			Family design	0.14–0.32
Tuulio-Henriksson et al., 2002			Family design	0.36–0.42
Greenwood et al., 2007			Family design	0.28

patients demonstrated a more generalized cognitive ability (or deficit) than controls (Dickinson et al., 2006). Consistent with these findings, a more recent study demonstrated both common and specific variance in a cognitive test battery that was related to functional deficits in schizophrenia (Sheffield et al., 2013).

Nevertheless, evidence for broad generalized deficits and evidence for more specific cognitive deficits do not necessarily conflict with each other, as both general and more specific cognitive deficits in schizophrenia occur simultaneously (Dickinson et al., 2004; Nuechterlein et al., 2004; Wang et al., 2010). Moreover, significant and even severe neuropsychological deficits can be shown in individuals with high IQ (Seidman, 1990), and thus the two levels of analysis are not isomorphic at the individual patient level. Similarly, the presence of one or more common cognitive factors does not mean that eventual treatments would affect all dimensions of cognition equally. Neuropsychological test performance in healthy control samples is often variable (Binder et al., 2009; Wechsler, 1997) and subject to dissociation in focal lesion cases (e.g., the patient H.M. developed profound temporal lobe amnesia following surgery for epilepsy, but retained intact immediate memory and above-average overall cognitive abilities (Squire & Shimamura, 1996)). Similarly, cognitive dysfunction is also likely to be dissociable, with potential treatments for schizophrenia influencing some dimensions of cognition more effectively than others.

In the effort to develop the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Cognitive Consensus Battery (MCCB), evidence for separable cognitive factors was obtained through factor analytic and other empirical studies (Nuechterlein et al., 2004). Seven distinct, replicated dimensions of cognitive dysfunction in schizophrenia were identified, including: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning and Memory, Visual Learning and Memory, Reasoning and Problem Solving, and Verbal Comprehension. Verbal Comprehension was excluded because it was considered less likely than the other dimensions to change with treatment, while Social Cognition was added because of growing interest in it, and because of a more general interest in understanding how changes in cognition affect other functional domains. We discuss some of these specific domains below.

Narrower/More Specific Deficits

Learning and Memory. Deficits in memory are among the most consistent and severe neuropsychological deficits in schizophrenia (Aleman et al., 1999; Cirillo & Seidman, 2003; Heinrichs, 2005; Heinrichs & Zakzanis, 1998; Seidman et al., 1992). Performance on learning and memory endophenotypes usually refer to performance on tests of learning and memory that assess the abilities to learn, retain and retrieve specified information. Most studies focus on the retention of facts or conscious, personally-experienced episodes, often called 'declarative' memory (Squire & Zola-Morgan, 1991). Its association with the illness is robust. Effect sizes versus appropriate comparison populations are typically large, in the 1.0–1.5 standard deviations range (Aleman et al., 1999; Cirillo & Seidman, 2003; Gold, 2004; Heinrichs, 2005; Heinrichs & Zakzanis, 1998; Stone & Hsi, 2011). Deficits in declarative (DM) are thus associated closely with schizophrenia spectrum conditions.

Deficits in DM are also stable. They occur at different phases of the disorder, including prior to the prodrome and prior to frank psychosis, and after remission from psychotic symptoms (Cirillo & Seidman, 2003; Hill et al., 2004; Joyce, 2005; Kravariti et al., 2003; Roofeh et al., 2006; Turetsky et al., 2002; Tuulio-Henriksson et al., 2004; Woodberry et al., 2008). Mesholam-Gately et al. showed a large effect size ($d = -1.20$) for an Immediate Verbal Memory composite score in their meta-analysis at the time of the first episode, and even larger effect sizes for specific test measures (Mesholam-Gately et al., 2009). These included $d = -1.47$ for immediate recall of short stories on the Wechsler Memory Scale (WMS) Logical Memory Test, and $d = -1.34$ for the total number of words recalled correctly over the course of learning 5 trials on the California Verbal Learning Test (CVLT). One of the largest evaluations of this same measure of learning on the CVLT-II was performed at seven sites as part of the first phase of the Consortium on the Genetics of Schizophrenia (COGS-1), with 509 control subjects, 309 subjects with schizophrenia, 449 sibling relatives and 232 parent relatives (Stone et al., 2011). The effect size for subjects with schizophrenia was again large (e.g., $d = -1.20$ for controls versus schizophrenia probands on the total correct responses for the 5 learning trials), consistent with the results obtained by Mesholam-Gately et al. in 2009.

Deficits in DM occur independently of deficits in overall cognitive ability (Tuulio-Henriksson et al., 2004), are mainly independent of clinical state (Cirillo & Seidman, 2003), and are largest in the learning/encoding stage (Cirillo & Seidman, 2003; Stone & Hsi, 2011), with milder deficits evident in rates of forgetting and in recognition, similar quantitatively to that observed in other conditions with mild medial temporal lobe damage (Gold et al., 1995;

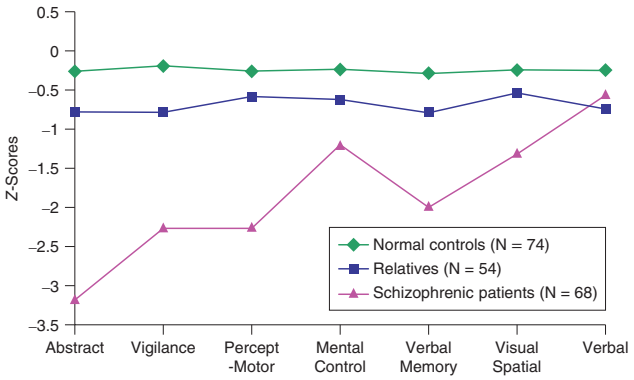


Figure 24.3 Neuropsychological profiles in patients with schizophrenia, first-degree relatives, and normal controls with a mean age in their early 40s. See footnote 1. *Source:* Adapted from Faraone et al., 1995. Reprinted with permission.

Seidman et al., 1998). Moreover, DM deficits prior to treatment show they were not produced by antipsychotic medications, which, in fact, may improve them modestly (Keefe et al., 2006b; Thornton et al., 2006).

Non-psychotic biological relatives of individuals with schizophrenia also show impaired encoding on DM, but the deficits are milder (no more than half of the effect observed in patients), and most often, do not involve abnormally high rates of forgetting (Agnew-Blais & Seidman, 2013; Faraone et al., 1995b; Faraone et al., 1999; Faraone et al., 2000; Gur et al., 2007a; Kremen & Hoff, 2004; Skelley et al., 2008; Stone et al., 2011; Stone & Hsi, 2011) (see Figure 24.3). The qualitative similarity of DM deficits in relatives to those that occur in patients adds to the view that impairments in DM reflect intrinsic features of the disorder (i.e., endophenotypes) rather than secondary phenomena related to effects of medication, psychosis, or other cognitive dysfunctions.

Until recently, most studies of DM in schizophrenia focused on verbal memory. Earlier (Seidman et al., 2003a; Tracy et al., 2001; Tuulio-Henriksson et al., 2003) and more recent studies (Cestari et al., 2013; Scala et al., 2013), however, show visual memory deficits in both schizophrenia patients and in non-psychotic relatives that are similar to those observed in verbal declarative memory. There is too limited a database to conclude that the deficits are equivalent in the two modalities, and such a conclusion would also require tests matched on difficulty to be equivalently impaired, a standard not yet observed. Nevertheless, visual memory deficit is present and significant.

Memory in healthy adults is moderately heritable (Bouchard, 1998; Finkel et al., 1995a), with heritability estimates that range generally between 30% and 60% (Papassotiropoulos & de Quervain, 2011). Deficits in DM in schizophrenia are similarly heritable. As noted above, for example, Husted et al., assessed heritability of several neuropsychological functions, and IQ (Husted et al., 2009). Immediate recall on the WMS Logical Memory Test was among the measures that showed significant heritability (0.40–0.49). Wang et al. showed that performance on the Logical Memory Test was the most heritable neuropsychological measure assessed (0.34) in a sample of first-episode, drug naïve, Han Chinese patients with schizophrenia and their siblings and parents, in relation to controls (Wang et al., 2010). Calkins et al. assessed the heritability of several neuropsychological functions in African-American probands with schizophrenia or schizoaffective disorder, their biological relatives, and in control subjects (Calkins et al., 2010). They showed significant heritability for several composite neuropsychological functions, including verbal memory (about 0.50). Performance on this verbal memory composite also showed significant heritability (0.66) in a previous multiplex, family study of schizophrenia from the same group (Gur et al., 2007b). Greenwood et al. demonstrated significant heritability for CVLT-II performance (0.25) in the COGS study, which included subjects with schizophrenia or schizoaffective disorder, depressed, and their biological siblings and parents (Greenwood et al., 2007; Greenwood et al., 2011).

Attention. Deficits in attention have long been considered central features of schizophrenia, and are among the most extensively studied (Calkins et al., 2010; Cornblatt & Keilp, 1994; Gur et al., 2007b; Kraepelin, 1919; Kremen et al., 1992; Nuechterlein, 1983; Nuechterlein & Dawson, 1984; Seidman et al., 2012). Several overlapping dimensions of attention are impaired. These include, among others: 1) attention span, which refers to the extent of information that can be held in mind; 2) selective attention, which refers to an ability to focus on particular stimuli; 3) cognitive control of attention, which refers to the abilities to organize and direct attention in relation to task demands; and 4) sustained attention and concentration, which refer to the abilities to sustain focus over time, sometimes in the presence of interfering or prepotent stimuli. Many of these aspects of attention are impaired in schizophrenia. Heinrichs and Zakzanis showed medium to large deficits in their meta-analysis of 22 measures derived from 204 studies (Heinrichs & Zakzanis, 1998), for example, including medium-sized deficits in auditory attention span (d = 0.62) and large deficits in measures of sustained attention (d = 1.18). More recently, Heinrichs also showed a large effect size (of over 1.0) for deficits in sustained attention (Heinrichs, 2005).

In their meta-analysis of first-episode psychosis in schizophrenia, Mesholam-Gately et al. (2009) organized putative attention measures into three composite subdomains. In the first of these, tests of attention also emphasized processing speed and produced an Attention: Processing Speed composite score that showed a large deficit compared with controls ($d = -0.96$). A second dimension of attention was assessed with an Attention: Vigilance subdomain that included scores from computerized continuous performance tests (e.g., omission errors, commission errors, and d'). This composite demonstrated a medium effect size versus control subjects ($d = -0.72$). The third subdomain emphasized working memory, which refers to the abilities to both hold information in mind consciously and manipulate it to solve problems or make decisions. The type of tests that comprise the Attention: Working Memory subdomain, which will also be considered in the next section (EFs), showed a medium to large effect sized deficit relative to control subjects (−0.79). The division of attentional components was based on cognitive science (Posner & Petersen, 1990), as well as factor analytic studies of clinical neuropsychological measures of attention (Kremen et al., 1992; Mirsky et al., 1991).

Different dimensions of attention overlap with each other to varying degrees, and with other neuropsychological deficits. Cohen et al., for example, showed that cognitive control of attention was closely related to mechanisms involved in the representation and maintenance of contextual information needed for the efficient selection of task-appropriate actions (i.e., working memory) (Cohen et al., 1999). The overlap between cognitive dimensions of function or dysfunction again raise questions about the prominence of general cognitive deficits in schizophrenia, as opposed to more specific deficits. Consistent with other recent findings, however (Dickinson et al., 2004; Wang et al., 2010), Nuechterlein et al., in their review of 13 factor analytic studies, also demonstrated support for separate cognitive deficits, including a separate attention/vigilance factor that focused on sustained, focused attention (Gur et al., 2007a; Nuechterlein et al., 2004).

Progress in defining and validating deficits in sustained attention separate from other, related cognitive dysfunction, together with consistent evidence of medium to large deficits, has contributed to a focus on sustained attention or vigilance as an endophenotype in schizophrenia (Chen & Faraone, 2000; Cornblatt & Keilp, 1994). Continuous performance tests (CPT) (Rosvold et al., 1956), a family of adaptable procedures, are the most widely utilized measures to assess sustained attention (Gur et al., 2007a). While different versions of the test are differentially sensitive to related cognitive dysfunctions (e.g., in working memory or perceptual processing) in schizophrenia, even simpler versions show consistent, medium to large deficits in vigilance, in most studies (Birkett et al., 2007; Mesholam-Gately et al., 2009; Pukrop & Klosterkotter, 2010). In a recent study, Seidman et al., developed an auditory CPT battery that allowed for manipulations of cognitive load and level of interference (Seidman et al., 2012), and showed substantially larger effect sizes for schizophrenia patient versus control comparisons on auditory working memory + interference ($d = 1.5$) than simple auditory vigilance ($d = 1.1$).

Performance stability has been demonstrated for several versions of CPTs. Among these, the degraded stimulus CPT and the CPT, Identical Pairs (CPT-IP) version, showed good reliability across sites, nationally and internationally (Cornblatt et al., 1988; Gur et al., 2007a). Deficits in these tests occur in medication naive subjects and in subjects taking antipsychotic medications (Finkelstein et al., 1997; Keefe et al., 2007b), and they occur in different stages of illness (Bhojraj et al., 2010a; Keefe et al., 2006a; Nuechterlein et al., 1992).

Like their ill relatives, nonpsychotic biological relatives of individuals with schizophrenia also show deficits in CPTs (Gur et al., 2007a; Kremen & Hoff, 2004). Snitz et al. showed small to medium effect sizes for several variables (Snitz et al., 2006). Among these, a quantitative measure of the ability to distinguish target from nontarget stimuli (d') showed a medium deficit in the CPT., Identical Pairs version ($d = -0.53$), as did false alarm responses ($d = -0.54$). Recent large studies using the Penn Battery version of the CPT have also demonstrated significant deficits in nonpsychotic relatives (Calkins et al., 2010; Gur et al., 2007b). Nonpsychotic relatives show smaller deficits on simpler versions of CPTs, rather than on more complex versions that contain higher loads of working memory, interference and/or perceptual processing (Kremen & Hoff, 2004), but still show significant impairments in vigilance with minimal working memory and perceptual processing loads (Birkett et al., 2007). In Seidman's auditory CPT study described earlier, relatives showed deficits in the small to medium range ($d = 0.4$ to 0.5) when interference was maximized (Seidman et al., 2012).

A growing literature shows that performance deficits in attention are significantly heritable. Cornblatt et al. showed heritabilities for the CPT, Identical Pairs version, of 0.39 (using digits as verbal stimuli) and 0.49 (using shapes as visual, nonverbal stimuli) in healthy families (Cornblatt et al., 1988). Chen et al. showed heritabilities of 0.48 to 0.62 in relatives of patients with schizophrenia

(Chen et al., 1998). Greenwood demonstrated a significant level of heritability for the degraded stimulus version of the CPT (0.38) in the COGS-1 study (Greenwood et al., 2007), while Gur et al. and Calkins et al. showed significant heritability using the Penn Battery CPT (0.50 and 0.40, respectively) (Calkins et al., 2010; Gur et al., 2007b). Interestingly, a recent study that assessed heritability for performance in tests of attention that did not utilize CPT tests did not show significant levels of heritability (Wang et al., 2010), which further validates the use of CPTs as endophenotypes.

Executive Function. Executive functions (EFs) refer to a family of cognitive abilities that include, among others, the acquisition, organization, maintenance, transformation, updating and retrieval of information, and also its protection from interference. These properties underlie and contribute to many adaptive cognitive and functional activities, such as learning, problem solving, fluency, processing speed, mental persistence, and resistance to interference. Like the other cognitive domains reviewed in this discussion, EFs are involved in the normal performance of many cognitive tasks. Also similar to the other cognitive domains reviewed in this section, EFs are often robustly impaired in schizophrenia (Bhojraj et al., 2010a; Egan et al., 2001; Gur et al., 2007a; Gur et al., 2007b; Kremen & Hoff, 2004; Seidman et al., 1992; Seidman et al., 1995), but separable from other cognitive abilities (Nuechterlein et al., 2004) in at least some dimensions.

Many studies documented deficits in EF in schizophrenia. Among several that quantified the magnitude of the dysfunctions, Heinrichs et al. used an EF composite score based on performance on the Wisconsin Card Sorting Test (WCST), which showed a large deficit ($d = 0.95$) compared with control subjects. Heinrichs also showed deficits with large effect sizes in a 2005 meta-analysis for performance on the WCST and on tests of verbal fluency (both > 1.0). Mesholam-Gately et al. also used an EF composite based on WCST function in their meta-analysis of first episode schizophrenia and showed a large deficit ($d = -0.83$). Other aspects of EF have also shown significant deficits. Lee and Park, for example, showed small to medium deficits in visual-nonverbal ($d = -0.46$) and in verbal ($d = -0.45$) working memory tasks. Wang et al. showed medium to large effect-sized deficits ($d = -0.73$ to -1.33) for prospective memory tasks (i.e., remembering to carry out intended actions) (Wang et al., 2009).

Despite the large deficits shown in individuals with schizophrenia for several measures of EF, some do not have equal potential as endophenotypes. Deficits on the WCST, for example, though large and studied extensively, may have limited value as an endophenotype. Heritability studies for WCST performance have been inconsistent, with several studies failing to show significant heritability estimates in schizophrenia families (Gur et al., 2007b). Kremen et al. performed the largest adult twin study to date on the heritability of the WCST., using the Vietnam Era Twin Registry sample, and failed to show either significant heritability or monozygotic–dizygotic differences (Kremen et al., 2007). Several factors probably contribute to inconsistent WCST heritability levels in the context of large deficits in performance, including the multifactorial complexity of the test and a multitude of cognitive factors that contribute to performance (Kremen et al., 2007).

Working memory tests provide another paradigm that emphasizes EF, has been studied extensively in schizophrenia (Lee & Park, 2005), and are more promising as endophenotypes. There are two broad classes of working memory studies. As noted above, the first one emphasizes vigilance and the transient maintenance of information (e.g., WAIS-IV Digit Span Forward). The second class involves vigilance and maintenance of information as well, but it also involves the manipulation of information (e.g., WAIS IV Letter-Number Span). It is the second type of working memory task that emphasizes EFs, and which will be considered here in more detail as a putative endophenotype for schizophrenia. This paradigm also corresponds to the more complex working memory tasks referred to in the Attention section, above (Mesholam-Gately et al., 2009).

Effect sizes for all working memory paradigms considered together (Lee & Park, 2005) are smaller than they are for the cognitive endophenotypes reviewed above in overall cognitive ability, verbal declarative memory, and sustained attention. More complex paradigms with larger EF deficits, however, often demonstrate large effect sizes (Gur et al., 2007b). This point was demonstrated, for example, in a recent, large COGS study that compared performance on simple and more complex verbal working memory paradigms in schizophrenia probands, their relatives, and control subjects (Horan et al., 2008). Effect sizes for the probands versus controls were large ($d = -0.94$) for the more executive paradigm, and were medium ($d = -0.54$) for the simpler paradigm that emphasized maintenance.

Deficits in working memory show other features similar to the strong endophenotype candidates discussed above. These include stability. Deficits in working memory are present at all stages of the illness (Gur et al., 2007a; Heaton et al., 2001; Keefe et al., 2006a; Lee & Park, 2005; Mesholam-Gately et al., 2009), are present with and without antipsychotic medication (Barch et al., 2001; Keefe

et al., 2007a), and are not secondary to clinical symptoms of schizophrenia (Heaton et al., 2001).

Non-psychotic relatives of patients with schizophrenia show smaller but significant deficits in working memory. Snitz et al. showed, for example, small ($d = -0.27$, digit span, backward condition) to medium ($d = -0.55$, spatial delayed response tasks–accuracy) effects sizes (Snitz et al., 2006). Like patients with schizophrenia, working memory tasks that emphasize EFs show greater effect size decrements in relatives. Conklin et al. showed, for example, that effect size increased from a digit span forward ($d = -0.43$) to a digit span backward ($d = -0.56$) to a letter–number span ($d = -0.66$) paradigm (Conklin et al., 2005). Horan et al. showed similar findings, with a larger effect size in a letter–number span paradigm that required reordering ($d = -0.36$) than a letter–number span that did not require reordering ($d = -0.22$) (Horan et al., 2008).

Performance on working memory tasks shows significant heritability in both healthy subjects (0.43–0.49) (Ando et al., 2001; Hansell et al., 2005) and in families with schizophrenia (0.36–0.42) (Tuulio-Henriksson et al., 2002). Recent studies by Husted et al. (2009), Calkins et al. (2010), and Greenwood et al. (2007) provide additional evidence for heritability of working memory performance in schizophrenia families (0.32–0.50) (cf. Table 24.2).

Summary. Taken together, the studies in this section provide strong overall support for the view that both general and specific cognitive deficits are core features of schizophrenia that are significant in magnitude, occur in all phases of the illness to varying degrees, are evident to milder degrees in nonpsychotic relatives compared with controls, and are heritable. This evidence implicates overall general intellectual abilities, but also more specific abilities in attention, learning and memory, and executive function as endophenotypes for schizophrenia.

NEUROIMAGING OF BRAIN STRUCTURE ENDOPHENOTYPES

Schizophrenia was originally proposed as a neurobehavioral disorder over a century ago (Bleuler, 1911/1950; Kraepelin, 1919). The conceptualization has been confirmed through a massive neuroimaging and postmortem literature (Harrison, 1999; Shenton et al., 2001) that is well beyond the scope of the current chapter. Instead, we have chosen to limit the focus to structural neuroimaging, and thus to exclude functional neuroimaging, in part because a structural magnetic resonance imaging (MRI) scan does not involve a task that could be subject to many confounds. It does not exclude the possibility of confounds or moderators to structural scans, such as type of magnet, field strength, technician reliability, head position, software used to measure structural features such as freesurfer, voxel-based morphometry, or manual segmentation and parcellation, reliability of measurement, etc. All of these are indeed factors that can create noise that could interfere with the signal of brain abnormality and yield differences across studies. Nevertheless, given these caveats, structural scans by their nature are more likely to measure trait characteristics. Moreover, there is now enough of a literature on brain structure in first-degree relatives of persons with schizophrenia, and in individuals at clinical high risk (CHR) or prodromal periods, that we concluded that the best MRI yield for this review would come from structural studies.

Brain Abnormalities in Patients with Schizophrenia and Their Relatives: Structural Magnetic Resonance Imaging (sMRI)

The study of abnormal psychobiological endophenotypes in patients with schizophrenia and their unaffected (nonpsychotic) first degree relatives has developed considerably over the past 40 years since the initial computer tomography (CT) scans were introduced (Johnstone et al., 1976). These include, among others, psychophysiological endophenotypes such as P50, prepulse inhibition, oculomotor abnormalities and other sensory gating paradigms (Turetsky et al., 2007), and a variety of structural, functional, and metabolic neuroimaging paradigms.

A vast literature of in vivo neuroimaging studies beginning in the late 1970s with CT scans (Johnstone et al., 1976; Weinberger et al., 1979a, 1979b) show compelling evidence for structural brain abnormalities in schizophrenia (Bogerts, 1993; Harrison, 1999; McCarley et al., 1999; Ren et al., 2013; Roiz-Santianez et al., 2013; Seidman et al., 2004; Shenton et al., 1997; Thermenos et al., 2013). Despite heterogeneous patient samples, methodologies, and imaging technologies, neuroimaging studies consistently implicate a variety of abnormalities in brain structure. Moreover, meta-analyses (Boos et al., 2007) and reviews comprised primarily of adult relatives indicate that these nonpsychotic and unmedicated siblings, offspring, and parents had elevated rates of brain structural abnormalities (Seidman et al., 2003b; Seidman et al., 2004). Moreover, these findings are consistent with and extend the much older pneumoencephalography and CT studies that demonstrated brain structural abnormalities in schizophrenia (Seidman, 1983).

The effects are generally milder in relatives than in patients, and less widespread than in the patients where the abnormalities had a more diffuse nature. Similar to the case for cognitive abnormalities, neuroimaging abnormalities do not occur in all relatives. Also similar to the case for many psychiatric and neurological disorders and syndromes, there is no one discrete brain region or circuit that is consistently abnormal in schizophrenia. Nevertheless, abnormalities such as ventricular enlargement (especially including the third and lateral ventricles) are among the most robust and extensively replicated findings in any domain of biological research on schizophrenia (Seidman et al., 2003b; Shenton et al., 2001). While structural abnormalities are widespread (Fusar-Poli et al., 2011; Honea et al., 2005; Ren et al., 2013; Thermenos et al., 2013), it is of considerable interest that many brain structures that show abnormalities in schizophrenia include or are related to limbic system structures that are involved in the regulation of emotion and declarative memory, which are often markedly impaired in schizophrenia (Cirillo & Seidman, 2003; Papez, 1937; Stone & Hsi, 2011).

Structural brain abnormalities share other important endophenotypic features with cognition that facilitates the study of critical questions related to the development and expression of schizophrenia, as noted earlier in this chapter. One of these is that like cognition in typically developing individuals and in schizophrenia, brain structure in typically developing individuals (Peper et al., 2007) and in schizophrenia (Boos et al., 2007; Moran et al., 2013) reflects significant genetic influence.

Another similarity is a shared notion of stability, which, as we noted above, is used here to refer to the invariance of the presence of the abnormality, rather than to an invariance of its particular expression. This is important conceptually and clinically because different brain abnormalities may be related to different features of the illness, may develop in different brain regions at different times, and may change in expression over time (Olabi et al., 2011; Seidman et al., 2003b; Vita et al., 2012). These features are thus relevant to the question of which brain abnormalities are necessary or specific for the development of psychosis, which may be addressed, in part, through cross sectional studies of nonpsychotic relatives of patients with schizophrenia (Seidman et al., 2003b, 2004; Thermenos et al., 2013). Related to this point is the question of when structural brain changes develop and under what specifiable environmental conditions? This point also underlies a growing number of recent prodromal studies that seeks to identify changes in brain structure or function in high-risk (HR) subjects that are proximal to the development of psychosis (Borgwardt et al., 2008; Fusar-Poli et al., 2011, 2012). Moreover, recent evidence of continued changes in brain structure following the development of psychosis suggests that brain changes in schizophrenia may be progressive (Olabi et al., 2011; Vita et al., 2012).

One recent trend has been to study younger relatives up to about age 30. This has the advantage of being able to assess whether brain abnormalities are present in childhood, and whether they evolve over time, particularly during the HR period of adolescence, and whether they might be useful for prediction of psychosis. In part this focus has been spurred by the same reasoning that motivates CHR studies of youth, which is the goal of understanding the pathophysiology of psychosis and its prediction. In a recent review, we found that many neuroimaging studies of young relatives reported findings in multiple brain regions (Thermenos et al., 2013). In that paper, we abbreviated the names of the 12 research groups that produced structural MRI data to make them easier to refer to (on p. 609). We will use the same convention here for simplicity. They are named along with the author most often identified with their papers: Canada High Risk Study (Canada HRS; Tibbo/Allen), Edinburgh High Risk Study (Edinburgh HRS; Lawrie/Johnstone), German High Risk Study (German HRS; Schreiber), Harvard Adolescent High Risk Study (Harvard Adolescent HRS; Seidman), Harvard Language and Risk High Risk Study (Harvard Language HRS; DeLisi), India High Risk Study (India HRS; Venkatasubramanian), Iowa High Risk Study (Iowa HRS; Ho), Korea High Risk Study (Korea HRS; Kwon), New York University High Risk Study (NYU HRS; DeLisi), NIMH High Risk Study (NIMH HRS; Gogtay/Rapoport), Pittsburgh/Detroit High Risk Study (Pittsburgh/Detroit HRS; Keshavan), University of North Carolina High Risk Study (UNC HRS; Belger), Turkey High Risk Study (Turkey HRS; Sismanlar), and the Washington University of St. Louis High Risk Study (Washington University HRS; Csernansky). Note that the evolving phases of the NIMH study lead us to incorporate two data sets (first authors were Gogtay/Mattai).

This review demonstrated that most of the studies were cross sectional, with only a few using longitudinal designs. When multiple studies were published by the same group at different time points. Thermenos et al. (2013) emphasized the conclusions from the studies with the larger and later samples. It should be noted that studies vary considerably in their method of MRI analysis, with a diversity of methods and software used for morphometry (e.g., manual vs. automatic segmentation, manual parcellation, voxel-based morphometry [VBM]) and statistical

analysis (e.g., corrections for multiple comparisons across the whole brain vs. regions of interest [ROI], multivariate pattern analyses at the level of single subjects; Zarogianni et al., 2013). Thus, the conclusions drawn may be less robust than those for neuropsychological measures that are standardized and, in essence, simpler to measure.

Brain Morphology (Gray Matter: Volume, Cortical Thickness, and Shape) as Depicted in Cross Sectional Studies

Overall Brain Size

This measure is often unreported in schizophrenia patients and in relatives, yet it could be a good general measure, similar to overall IQ. Smaller overall brain volumes in schizophrenia than matched controls but not in bipolar disorder vs. controls was first reported by Ward et al. (1996) and Hoge et al. (1999). The reductions in schizophrenia were modest, roughly 1–2%. A recent study that assessed patients with either schizophrenia or schizophreniform disorder, showed significant decreases of 1.30% and 1.12% respectively (Crespo-Facorro et al., 2009). A recent meta-analysis also showed smaller whole brain volumes (De Peri et al., 2012), thus it appears that a small but reliable difference exists in patients with schizophrenia. The picture in nonpsychotic relatives is mixed and based on far fewer studies. The Pittsburgh/Detroit HRS (Keshavan et al., 2002b; Rajarethinam et al., 2007) and the NIMH HRS (Gogtay et al., 2003) reported lower intracranial volumes, while the Edinburgh HRS., Turkey HRS., and Harvard Adolescent HRS did not.

Total Cortex

Similar to overall brain size, measures of total cortex are often not the focus of sMRI investigations, mainly for the same reason—the focus has been on identifying specific, abnormal neural circuits. Nevertheless, numerous studies reported reductions in particular regions make clear that cortical reductions occur in schizophrenia (Bora et al., 2011; Crespo-Facorro et al., 2009; Honea et al., 2005; Palaniyappan et al., 2012; Ren et al., 2013). Recently, the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP), a large consortium study reported widespread cortical reductions in subjects with either *DSM-IV* (American Psychiatric Association, 1994) schizophrenia or schizoaffective disorder compared with healthy controls, and were also more substantial than those observed in subjects with bipolar I disorder with psychosis (Ivleva et al., 2013). A selective review of papers published between 2001 and 2008 showed reductions in cortical gray matter volumes in all regions of interest except for the caudate nucleus, which often enlarges due to effects of antipsychotic medications (Levitt et al., 2010). The same review concluded that these cortical decreases did not differ between first-episode and chronic samples, indicating that they were largely present at the onset of psychosis rather than mainly occurring secondary to chronicity. Moreover, reductions were particularly prominent in cortical regions (e.g., frontal and temporal lobes) that are related to higher cognitive and to emotional processing.

In addition to reduced cortical volumes, subjects with schizophrenia show widespread cortical thinning compared with controls and to patients with bipolar I disorder (Jung et al., 2011; Rimol et al., 2010). In one study that reported simultaneous analyses of cortical volume, thickness and area, most volume reductions were associated with cortical thinning, with more circumscribed reductions in cortical areas (Rimol et al., 2012).

Compared with healthy control subjects, a prodromal group showed significant cortical thinning as well, though not as extensive as that demonstrated by a schizophrenia sample (Jung et al., 2011). Similarly, a study from the Edinburgh HRS showed multiple areas of cortical thinning in first episode patients, including the superior frontal, medial parietal, and lateral occipital regions, but only showed thinning in the left middle temporal gyrus in the HR group (Sprooten et al., 2013). This HR sample included 17 subjects who later developed schizophrenia. Notably, the observed thinning in the left middle temporal gyrus in these subjects was not predictive of their later conversion to psychosis. In this regard, these HR subjects who later developed psychosis did not differ from HR subjects who did not develop psychosis. However, a separate study of this group over the course of 8 years showed that as they became prodromal and developed increasing symptom severity, they showed additional volume reductions (McIntosh et al., 2011), as reported earlier. Taken together, these findings underscore the point that some volume abnormalities are evident earlier in development than others and are less predictive of clinical outcome, while others develop in closer association to the onset of schizophrenia, and are more closely related to its development.

Other findings with nonpsychotic relatives are mixed. In the B-SNIP study, nonpsychotic relatives of subjects with schizophrenia or schizoaffective disorder did not show total cortex gray matter volume reductions. Similarly, the Pittsburgh/Detroit HRS did not report overall differences in total cortical thickness or surface area (Prasad et al., 2010a). In contrast, the Washington University HRS

(Calabrese et al., 2008) and the NIMH HRS (Gogtay et al., 2003) reported an overall smaller total cerebral volume in HR compared with controls.

Lobes in the Cortex

Prefrontal (PFC). Smaller PFC volumes, thickness or surface areas are well-replicated in schizophrenia, and often show relatively significant cortical volume reductions in superior, middle, or inferior frontal regions (Bora et al., 2011; Honea et al., 2005; Ivleva et al., 2013; Levitt et al., 2010; Ohtani et al., 2013; Palaniyappan et al., 2012; Ren et al., 2013; Xiao et al., 2013). Cortical thinning is also evident in these regions (Jung et al., 2011; Rimol et al., 2010; Schultz et al., 2010), as is other diverse cellular pathology involving both neurons and glia (Goldman-Rakic, 1994; Selemon & Rajkowska, 2003). Nevertheless, the large size of the PFC, coupled with its dense networks of connections and functional and anatomical heterogeneity, also contributes to conflicting sMRI findings. A recent study that used 3T imaging and reliable manual parcellation in an attempt to improve the accuracy of PFC volume measurements confirmed reductions in chronic schizophrenia patients in the left superior frontal, bilateral middle frontal and bilateral inferior frontal gyri (Ohtani et al., 2013).

A recent meta-analysis that included clinical HR (i.e., prodromal) subjects showed reductions in the left medial and the right middle frontal gyrus, and in the right inferior frontal gyrus in subjects who developed psychosis subsequently (Fusar-Poli et al., 2011). Frontal regions were also smaller bilaterally in a recent prodromal sample ($n = 182$) compared with control subjects, and did not show additional changes in a subgroup ($n = 48$) that subsequently developed psychosis (Mechelli et al., 2011). More studies are needed to determine the central changes in the CHR phase of illness.

A study from the Washington University HRS that also used a manual parcellation procedure showed smaller middle and inferior frontal gyri in schizophrenia subjects, but only smaller inferior gyri in the nonpsychotic HR subjects (Harms et al., 2010). This finding thus showed an intermediate level of abnormality in the HR group. Similarly, the Harvard Adolescent HRS reported smaller medial frontal gyri and frontal poles (Rosso et al., 2010), and the NYU HRS showed smaller right inferior frontal gyri in the HR subjects (Li et al., 2012a). The Turkey HRS showed only a nonsignificant reduction in PFC volume, but also reported on a relatively small sample (23 HR and 26 control subjects) and restricted age range (8 to 15 years old) (Sismanlar et al., 2010).

A few HR studies reported language-related cortical abnormalities. The Pittsburgh/Detroit HRS reported a smaller left pars triangularis, a reversal of pars triangularis asymmetry (Bhojraj et al., 2009), and smaller areas in the frontal-parietal lobes (Prasad et al., 2009). The Harvard Language HRS reported a smaller left pars triangularis and right pars orbitalis, and a reversal of orbitalis lateralization (Francis et al., 2012). The NYU HRS study did not find significant changes in the laterality index in language areas in the HR group (Li et al., 2012b).

Multiple HR studies demonstrated differences in cortical thinning from controls, though they varied somewhat in the nature and extent of the abnormalities. Among these, the Korea HRS showed significant thinning bilaterally in the ventromedial PFC and frontal poles (Byun et al., 2012). The NIMH HRS showed significant thinning in the left PFC in the HR group (Gogtay et al., 2007), in a larger follow-up study of an earlier report (Gogtay et al., 2003). An independent study from the same group using the same procedures as they did in their 2007 study showed bilateral PFC (and left temporal) thinning in a sample of HR subjects who were 5 to 26 years old (Mattai et al., 2011b). It should be noted that brain abnormalities in subjects in this sample, however, normalized with age, with few abnormalities remaining by the age of 17. In this context, a recent report from the Edinburgh HRS that showed superior gyrus frontal lobe thinning in first-episode subjects with schizophrenia showed thinning only in the left middle temporal gyrus in the HR group (Sprooten et al., 2013). Other studies that have shown widespread decreases in cortical thickness in schizophrenia patients in frontal and temporal cortices have not found any significant differences from controls in nonpsychotic relatives (Borgwardt et al., 2008; Goldman et al., 2009). While the great majority of studies showing abnormalities in cortical area or thickness report thinning in schizophrenia, one HRS (NYU) showed increased cortical thickness and cortical areas in the HR group (Li et al., 2012a).

These studies of PFC abnormalities in cortical volumes or cortical thinning thus show a range of relationships between subjects with schizophrenia and relatives, including milder or more restricted PFC abnormalities in relatives (Harms et al., 2010), different abnormalities in nonpsychotic relatives compared with schizophrenia patients (Sprooten et al., 2013) and a lack of abnormalities in relatives compared with patients, at least at certain developmental stages (Mattai et al., 2011b). These similarities in patterns show support for alterations in brain regions as endophenotypes, but the differences between patients and relatives are consistent with patterns reported

in other brain regions (Xiao et al., 2013), and with the view that brain abnormalities in schizophrenia subjects at least partly reflect the expression of illness rather than only the liability to develop it (Goldman et al., 2009). Nevertheless, PFC reductions in clinical HR subjects who are not yet psychotic (Fusar-Poli et al., 2011; Mechelli et al., 2011) highlight a need to integrate findings among different types of HR subjects.

Temporal Cortex. Structural abnormalities in temporal cortex are well established in schizophrenia (Bogerts, 1993; McCarley et al., 1999; Seidman et al., 2003b; Shenton et al., 2001). Similar to findings obtained in studies of PFC, they are also frequently prominent (Bora et al., 2011; Honea et al., 2005; Ivleva et al., 2013; Levitt et al., 2010; Palaniyappan et al., 2012) and conceptualized as key areas in the etiology of schizophrenia (Bogerts, 1993, 1997; Crow, 1990). Earlier reports of abnormalities focused on the superior temporal gyrus (McCarley et al., 1999; Shenton et al., 2001), but now include the middle and inferior temporal gyri as well (Hu et al., 2013; Kuroki et al., 2006; Tang et al., 2012; Xiao et al., 2013). Cortical thinning is also evident in these regions (Jung et al., 2011; Ratnanather et al., 2013; Rimol et al., 2010; Schultz et al., 2010), including in the planum temporale (Ratnanather et al., 2013), and also abnormal lateralization (Hu et al., 2013; Ratnanather et al., 2013).

In a recent study that examined both first-episode subjects with schizophrenia and their unaffected siblings (Hu et al., 2013), the schizophrenia subjects showed bilaterally lower volumes in the middle and superior temporal gyri. The unaffected siblings showed a subset of these abnormalities, with smaller volumes in the left middle temporal gyrus. The Pittsburgh/Detroit HRS reported bilaterally smaller superior temporal gyri in nonpsychotic relatives (Rajarethinam et al., 2004), that were not observed in the Harvard Language HRS (Francis et al., 2012). In a subsequent larger study, the Pittsburgh/Detroit HRS showed a smaller right Heschl's gyrus, and increased Heschl's gyrus L>R asymmetry in the HR group (Bhojraj et al., 2009). Subsequent studies also showed bilaterally smaller temporal cortices in a study of default mode processing (Bhojraj et al., 2010b), and smaller, thinner superior temporal gyri (in auditory association cortex), especially in males (Bhojraj et al., 2011).

The Korea HRS and the NIMH HRS both demonstrated bilateral temporal lobe cortical thinning in the HR groups (Byun et al., 2012; Gogtay et al., 2007). A subsequent NIMH study showed reduced cortical thickness in the left temporal lobe in HR (Mattai et al., 2011b), replicating their earlier study (Gogtay et al., 2007). The Turkey HRS study reported a nonsignificant reduction in whole temporal lobe volume (Sismanlar et al., 2010), while the NYU HRS study found increased cortical thickness in the right superior temporal gyrus (Li et al., 2012a).

Fusar-Poli et al. reported reduced volumes in the superior temporal gyrus in their meta-analysis that remained significant following the development of psychosis in a subgroup of subjects (Fusar-Poli et al., 2011). A recent study of preprodromal children aged 9 to 12 years old who showed multiple antecedents of schizophrenia (including psychotic-like experiences in some of the children) reported decreased volumes in the right middle temporal gyrus and increased volumes in the left superior-middle temporal gyri (Cullen et al., 2013). These temporal lobe abnormalities were evident whether or not the children endorsed symptoms of psychosis.

Parietal Cortex. Volume reductions in parietal cortices are reported in schizophrenia frequently (Borgwardt et al., 2008; Honea et al., 2005; Ivleva et al., 2013; Levitt et al., 2010; Olabi et al., 2011; Palaniyappan & Liddle, 2012; Sprooten et al., 2013; Yildiz et al., 2011), though abnormalities do not appear as prominent as those in frontal or temporal lobes (Honea et al., 2005; Ivleva et al., 2013). Nevertheless, similar types of neuropathology in parietal cortex, such as cortical thinning, occur in schizophrenia (Palaniyappan & Liddle, 2012; Rimol et al., 2010) and in prodromal subjects (Jung et al., 2011). Moreover the supramarginal gyrus, which is one of two subregions of the inferior parietal lobule, showed morphometric abnormalities compared with controls that were not evident in the angular gyrus, which is the other subregion. The abnormalities included reduced gyrification (especially in the left hemisphere) and cortical thinning (Palaniyappan & Liddle, 2012). Both subregions showed reduced volumes. Evidence of parietal volume reductions in early onset schizophrenia and significant correlations between right superior parietal volume and age of illness onset (Burke et al., 2008) contribute to the view that some forms of schizophrenia may start in the parietal lobe and then progress to the temporal and frontal lobes (Yildiz et al., 2011).

HR studies have also implicated the parietal lobes. Among these, in the Pittsburgh/Detroit HRS, HR subjects had smaller right supramarginal and angular gyri than controls (Bhojraj et al., 2009). They also showed attenuation of supramarginal and angular gyrus asymmetries, (Bhojraj et al., 2009), and increases in curvature and parietal cortical thinning (Prasad et al., 2010a). The NIMH HRS also reported parietal volume reductions

(Gogtay et al., 2003, 2007). A second, independent NIMH HRS also reported parietal cortical thinning although these findings lost statistical significance as the subjects reached adolescence (Mattai et al., 2011b). The NYU HRS study was the only study to reveal statistically larger cortical thickness in HR, in the right angular gyrus (Li et al., 2012a). Abnormalities in the supramarginal and the angular gyri were not obtained in the Harvard Language HRS (Francis et al., 2012).

Occipital Cortex. Lowered occipital cortical volumes have been shown in schizophrenia (Ivleva et al., 2013), as has cortical thinning (Rimol et al., 2010). Moreover, a recent multivariate study of gray matter abnormalities in schizophrenia identified one of two components as including the posterior occipital lobe (Turner et al., 2012).

The Korea HRS reported cortical thinning in the occipital cortex (Byun et al., 2012). In contrast, the NYU HRS study reported increased occipital cortical thickness in HR (Li et al., 2012a). Occipital differences in cortical volume, surface area, or thickness were not observed in the Pittsburgh/Detroit, Edinburgh, NIMH, Iowa, or Harvard Adolescent HRS.

Ventricles

Ventricular enlargement is prominent in schizophrenia, as demonstrated by several meta-analyses (Arnone et al., 2009; De Peri et al., 2012; Sayo et al., 2012; Wright et al., 2000) and many previous CT and pneumoencephalographic studies (Johnstone et al., 1976; Weinberger et al., 1979a, 1981). One recent meta-analysis included 72 MRI studies (Sayo et al., 2012) that showed a significantly increased ventricular brain ratio with a mean effect size of 0.65. Another recent study that evaluated brain abnormalities in first-episode schizophrenia and bipolar disorder showed lateral ventricular enlargement in 45 studies compared with controls (De Peri et al., 2012).

Somewhat in contrast, effects in nonpsychotic relatives are mixed. The Pittsburgh/Detroit HRS reported an enlarged third ventricle (Keshavan et al., 1997a), as did the Edinburgh HRS (Lawrie et al., 2001). However, neither the Edinburgh nor the NYU HRS (DeLisi et al., 2006) showed significant differences from controls in lateral ventricular volumes. In general, similarities and differences in brain volumes between patients and relatives at least partially reflect the influence of psychosis (Palaniyappan et al., 2012).

Cingulate Cortex

Anterior. Several studies show abnormalities in the anterior cingulate cortex (ACC). A meta-analysis of seven MRI studies showed significantly reduced volumes in patients with schizophrenia, compared with healthy control subjects (Baiano et al., 2007). A meta-regression analysis in the same study showed that reductions in volume were related to slice thickness but not to age or gender. Another meta-analysis using 31 studies also showed significantly reduced volumes in the ACC compared with healthy control subjects (Glahn et al., 2008). Bora et al. showed reduced volumes in the ACC that were related particularly to chronicity, negative symptoms and male sex (Bora et al., 2011). By contrast, Calabrese et al. did not find volume reductions in the ACC (Calabrese et al., 2008). Another study that did find volume reductions, however, also showed that greater duration of illness and severity of positive symptoms correlated significantly with reduced ACC volumes, but not with posterior cingulate volumes (Wang et al., 2007).

Findings from family HR studies are mixed. Smaller ACC density reductions in nonpsychotic relatives were reported by the Edinburgh HRS (Job et al., 2003) using VBM, but not more recently when the same group used a more surface-based analysis (FreeSurfer) (Sprooten et al., 2013). The Pittsburgh/Detroit HRS (Diwadkar et al., 2006) reported reduced ACC volumes, although the subjects had schizotypal features that may have made them more like a prodromal group. Cortical thinning was reported by the Korea HRS in the right anterior cingulate and the left paracingulate cortices (Byun et al., 2012). As noted already for schizophrenia patients, the Washington University HRS did not find significant differences in volume, surface area, or thickness (Calabrese et al., 2008).

A recent study of 14 prodromal subjects, 34 first-episode subjects, and 51 healthy controls showed significant gray matter reductions in the left ACC in the first-episode subjects compared with the healthy controls (Nakamura et al., 2013). The prodromal group did not differ significantly from either of the other groups, however. These findings may reflect the small sample size to some extent or the method of ascertainment, as several (though not all) HR studies also reported volume reductions. Results from another study of prodromal subjects showed reduced cortical thickness in the ACC (and other regions) compared with healthy controls (Jung et al., 2011). They showed less severe reductions in thickness, which were also less widespread, than those observed in patients with schizophrenia.

Posterior. Jung et al. (2011) showed reductions in cortical thickness in the posterior cingulate. The Washington University HRS reported reductions in the posterior cingulate

in schizophrenia patients (Calabrese et al., 2008), but the significance of the finding was related to whole cerebral volume reductions, and was lost when cerebral volume was utilized as a covariate. In a larger study by the same group (Wang et al., 2007), significant reductions in posterior (and anterior) cingulate volumes remained after effects of whole cerebral volumes were accounted for.

The Washington HRS reported decreased volumes in the posterior cingulate in nonpsychotic siblings that were of similar magnitudes to the reductions they reported for patients with schizophrenia (Calabrese et al., 2008), but which also reflected the effects of cerebral volume, as noted. The Korea HRS reported significant cortical thinning in the left posterior cingulate (Byun et al., 2012).

Hippocampus

As described previously, medial temporal lobe abnormalities occur frequently in schizophrenia (Glahn et al., 2008; Honea et al., 2005, 2008; Ivleva et al., 2013; Nelson et al., 1998; Seidman et al., 2003b; Stone & Seidman, 2008; Wright et al., 2000), which often include the hippocampus. One of the relatively few studies that did not show reduced hippocampal volumes in patients attributed their findings to methodological limitations (Honea et al., 2008), as the same group showed hippocampal volume decreases in another analysis that utilized subcortical segmentation (Goldman et al., 2008). More recently, a study that compared manual tracing methods with a semiautomated parcellation method (FreeSurfer) in schizophrenia and schizoaffective subjects showed bilateral reductions in hippocampal volumes using both methods (Arnold et al., 2014). Another recent study that also showed bilateral reductions in hippocampal volumes demonstrated further that smaller volumes were related to poorer cognitive performance after controlling for age, gender, education, and Positive and Negative Syndrome Scale (PANSS) scores (Guo et al., 2014). Notably, a longitudinal study of child-onset schizophrenia showed stable reductions of hippocampal volume between the ages of 10 and 29 compared with control subjects, while the trajectories of the volumes did not change (Mattai et al., 2011a).

Numerous studies show smaller hippocampal volumes in nonpsychotic relatives of patients with schizophrenia (Boos et al., 2007; Moran et al., 2013), though not all show it (Boos et al., 2012; Honea et al., 2008). Several early HR studies that assessed the amygdala-hippocampal complex prior to the development of segmentation procedures that could differentiate the hippocampus and amygdala, showed smaller volumes in HR youth (Keshavan et al., 1997b, 2002a; Lawrie et al., 1999; Schreiber et al., 1999). Similarly, recent studies also showed bilaterally smaller hippocampal volumes (Ho & Magnotta, 2010; Sismanlar et al., 2010), and shape differences (Ho & Magnotta, 2010). In contrast, the UNC HRS reported smaller hippocampal volumes but the findings did not remain significant when they were corrected for brain volume (Dougherty et al., 2012). Moreover, the NIMH study that reported stable volume reductions in childhood-onset schizophrenia did not show differences between nonpsychotic siblings and controls (Mattai et al., 2011a).

Summary of Representative Cross Sectional Studies

At the broadest level, we can conclude that brain structure is an endophenotype for schizophrenia. Structural deficits are associated with schizophrenia, are state independent, and are generally more prevalent among the relatives than in healthy controls. Many structures have been found to be abnormal but the consistency of findings and the relatively small number of studies suggests to us that currently the most robust findings are for PFC and hippocampus across patients and relatives. Although there are fewer studies, a growing literature highlights the importance of cortical thinning in both patients and relatives.

Longitudinal Studies

There is substantial evidence of longitudinal brain structure alterations in schizophrenia, usually demonstrated from the first episode of psychosis onward throughout the first 5 years of illness (Asami et al., 2012; Hulshoff Pol & Kahn, 2008; Olabi et al., 2011; Vita et al., 2012). It is now also apparent that the structural alterations become progressively more pronounced over time even earlier, in the prodromal, CHR period, thus beginning before the first episode of psychosis has been initiated. Comparisons of structural brain alterations in CHR compared with controls have shown progressive loss of gray matter in orbital PFC (Borgwardt et al., 2008; Pantelis et al., 2003), superior temporal cortex (Borgwardt et al., 2008; Takahashi et al., 2009), ACC, parahippocampus, fusiform cortex (Pantelis et al., 2003), and insula (Takahashi et al., 2009). Moreover, structural changes in CHR who convert to psychosis compared with those who do not demonstrate evidence for significantly greater reductions over time in PFC (Dazzan et al., 2012) and temporal cortex (Takahashi et al., 2009).

The literature is more limited and a bit mixed in the family HR studies that evaluated change in brain structure over time. Three studies have carried out longitudinal analyses: the Edinburgh, Pittsburgh/Detroit and the NIMH HRS. The Edinburgh HRS is the one completed study that has a large enough sample size followed

longitudinally, including a relatively large sample of HR who later developed schizophrenia, to begin to hypothesize a pattern (McIntosh et al., 2011). The HR group when taken together showed significant reductions over time compared with controls in whole brain volume, left and right temporal lobe, and left frontal lobe volume. Over time, the left and right PFC showed significant reduction in those who developed schizophrenia, and this tissue loss was significantly greater than in the other HR groups who did not go on to develop schizophrenia. These data, as well as the aforementioned observation that PFC volume is smaller at the baseline assessment, indicates that it is a risk factor for schizophrenia, and is a central focus of brain changes as the illness develops.

In the Pittsburgh/Detroit HRS, while longitudinal one year follow-up scans of HR showed reductions in surface area in the total cortex, bilateral inferior frontal cortex and occipital cortex (Prasad et al., 2010b), the small number of individuals who transitioned to psychosis thus far is too small to draw any conclusions. In the NIMH study headed by Gogtay and Rapoport, a number of baseline differences were observed, consistent with other studies (i.e., smaller cortex including PFC, temporal and parietal cortices in two independent samples (Gogtay et al., 2007; Mattai et al., 2011b). However, there were trajectory differences compared with the other studies, in that most differences between controls and HR siblings normalized by ages 17–20, and no differences between groups remained significant at the last assessment point in both samples. The differences across these three studies highlight sampling differences in their designs. For example, the Edinburgh HRS sampled teenagers from families with at least two ill cases, the Pittsburgh/Detroit HRS sampled offspring, and the NIMH study sampled well siblings of cases of childhood schizophrenia.

The longitudinal studies highlight the challenge of using imaging measures as endophenotypes, especially based on data from HR studies. Nevertheless, perhaps the most robust measures to date are PFC volume or thickness, followed by hippocampal volume, and it is likely that this active area of research will yield more findings in the coming years.

Heritability of and Susceptibility Genes in Neuropsychological and Structural Brain Traits

Heritability in Brain Abnormalities

Our review confirms the familial nature of abnormalities in brain volumes in schizophrenia families. While not all abnormalities in relatives are identical to those in patients, owing to effects of psychosis (Palaniyappan et al., 2012), stage of development, environmental factors and gender, among other factors (Geoffroy et al., 2013; Kaymaz & van Os, 2009), volume abnormalities in specific brain regions in patients with schizophrenia are accompanied frequently by reductions in the same regions in their biological relatives. Moreover, similar to the case for cognitive abilities in healthy individuals (Bouchard, 1998; Finkel et al., 1995a, 1995b; Papassotiropoulos & de Quervain, 2011), brain volumes in healthy individuals are heritable (Kaymaz & van Os, 2009; Peper et al., 2007). This discussion focuses somewhat more on heritability of brain abnormalities than on heritability of cognitive functions, which were reviewed above in relation to a more discrete number of cognitive domains. Representative heritabilities in schizophrenia are shown in Table 24.3. As with the representative heritabilities for selected cognitive domains listed in Table 24.2, heritabilities for selected brain regions are listed in Table 24.3. Studies listed in the table were published in the last 20 years, and focused on twins or families with schizophrenia. PubMed search terms again included schizophrenia and heritability, and brain volume, and MRI.

Similar brain abnormalities in nonpsychotic relatives provide evidence for co-segregation of the abnormalities in schizophrenia families (Seidman et al., 2002). From an endophenotype perspective, however, it is also important to demonstrate that abnormalities are related to the risk for schizophrenia (i.e., they share genetic variance with the disorder and show a genetic, also called a phenotypic, correlation). Family and especially twin studies have been particularly useful in this regard, both in assessing heritability (and in estimating the extent of shared and unique environmental factors), and in showing the extent to which they are related to overlapping genetic effects. Representative family and twin studies show that group differences in brain volume are often, though not always, associated with evidence for heritability. Family studies include Honea et al. (2008), for example, who showed gray matter volume reductions in schizophrenia patients in temporal, frontal and parietal cortices but did not show significant genetic correlations (using intraclass correlations, ICC) between patients and siblings in left medial frontal gyrus, left superior temporal gyrus, and left insula. Patients and their siblings did show significant ICCs (and heritability) for hippocampal volumes, however, which did not show group differences between patients and either controls or siblings. Goldman et al. (2008) also used a family design and showed widespread subcortical and cortical reductions or increases in patients, including the hippocampus. Although nonpsychotic relatives did not show significant volume differences compared with controls for any region, strong

TABLE 24.3 Heritabilities of Selected Brain Regions in Healthy Subjects and in Subjects with Schizophrenia[1]

Study	Brain Region	Subjects		Heritability (h^2, intraclass correlation, or Risch's lambda)
		Healthy	Schizophrenia	
Barre et al., 2001	Total brain volume	Twins		0.90
White et al., 2002		Twins		0.99
Hulshoff Pol et al., 2012			Twins	0.65
Kaymaz and van Os, 2009			Review	0.70–0.95
Brans et al., 2008			Twins	0.66[1]
Rijsdijk et al., 2005			Twins	0.94
Hulshoff Pol et al., 2012	Third ventricle		Twins	0.61
van Haren et al., 2012			Twins	0.64
van Haren et al., 2012	Frontal lobe (cortical gray)		Twins	0.43
Kaymaz and van Os, 2009	Frontal lobe		Review	0.40–0.70
van Haren et al., 2012	Temporal lobe		Twins	0.52
Turner et al., 2012	Temporal-frontal cluster		Twins	0.43
Kaymaz and van Os, 2009	Temporal lobe		Review	0.40–0.70
Kaymaz and van Os, 2009	Hippocampus		Review	0.40–0.70
Roalf et al., 2014			Family	0.56 (left) 0.33 (right)

[1]Refers to heritable influence on volume loss in a 5-year longitudinal design.

evidence for genetic influence on volume reductions was obtained for the cortex and the hippocampus, as measured by ICCs and Risch's lambda. Turner et al. (2012) analyzed two separate datasets with patients and controls, one of which also included nonpsychotic siblings. Evidence for schizophrenia-related genetic influence was obtained for volumetric abnormalities in medial and inferior frontal lobe, temporal lobe, and posterior occipital lobe.

Several twin studies also show evidence of heritability in brain volume abnormalities, which is related to schizophrenia. Consistent with other family study findings, twin pairs who are discordant for schizophrenia often show greater volume abnormalities in the affected member of the pair (Rijsdijk et al., 2005). In one study that compared monozygotic and dizygotic twin pairs who were discordant for schizophrenia (or for bipolar disorder) with healthy control twin pairs, significant genetic correlations were obtained between schizophrenia and thinner parahippocampus, thinner right orbitofrontal cortex, thicker right parietal cortex, thicker temporoparietal cortex, and thicker superior motor cortex (Hulshoff Pol et al., 2012). Notably, greater environmental liability was associated with thinner right medial occipital cortex. The same group followed brain volume changes in monozygotic and dizygotic twins who were discordant for schizophrenia, in comparison to healthy controls, for 5 years (Brans et al., 2008). In that period, significant decreases in volume occurred in whole brain and in the frontal and temporal lobes in patients and in their nonpsychotic twins. Significant genetic correlations between liability for schizophrenia and changes in brain volume reflected significant genetic effects on these correlations, as shown by heritabilities of 66% for whole brain, 76% for frontal lobe, and 79% for temporal lobe.

Van Haren et al. (2012) reported findings from the largest twin study to date to relate brain volumes in schizophrenia to their relative genetic and environmental contributions. This study included 684 subjects, including concordant and discordant monozygotic and dizygotic twin pairs, and control twins. Data were collected at five sites by the Schizophrenia Twins and Relatives (STAR) consortium. The results showed smaller volumes for several brain regions in subjects with schizophrenia, and also smaller white matter and a larger third ventricle. Significant heritabilities were obtained for most of the brain volumes assessed. In one instance, 77% of the smaller cerebral volume in schizophrenia subjects was attributable to genetic factors that contributed to both the smaller volume and to the liability for developing schizophrenia. Similarly, 94% of the reduction in cerebral white matter was attributable to genetic factors, and 83% of the enlargement of the third ventricle was attributable to genetic factors. It is important to note, however, that these large heritabilities do not mean, for example, that 77% of the variability in cerebral volume is accounted for by genetic factors that increase liability for schizophrenia. The actual correlation between schizophrenia and volume size was −.22, which explains 4.8% of the total variance in cerebral volume. This is still a significant portion of the variance, and one

that highlights the importance of genetic factors in the neurodevelopmental factors underlying brain development and function.

Heritabilities for brain abnormalities are often comparable to heritabilities for cognitive functions, though both vary considerably depending on the particular brain region or cognitive function. The study by Husted et al. (2009), for example, assessed heritability for 13 cognitive measures in a multiplex family design and found intelligence (IQ) to have the highest value (64–74%). Heritabilities of the other measures ranged from 31 to 62%. In another example, Toulopoulou et al. (2007) used a twin design to assess heritabilities of intelligence, working memory, processing speed, perceptual organization, and verbal comprehension (Toulopoulou et al., 2007). Significant genetic influences affected all cognitive domains, but shared genetic variance accounted for 92% of the covariance between liability to schizophrenia, and intelligence. In the COGS heritability study described earlier (Greenwood et al., 2007), all cognitive measures proposed as endophenotypes showed significant heritabilities that ranged from 25% (California Verbal Learning Test–Second Edition) to 55% (Spatial Processing, from the Penn Battery).

Schizophrenia Susceptibility Genes

The demonstration that at least some disease-related changes in cognition and in brain structure are influenced by common genetic processes is a step closer to understanding both the genetic etiology of schizophrenia, and the biological trajectories involved that create the liability. In parallel with attempts to identify possible endophenotypes that are associated with the illness, appear in nonpsychotic relatives, show stability and are heritable are attempts to identify their underlying genetic architecture. This includes the identification of chromosomal regions that may harbor individual genes, and attempts to identify candidate genes themselves.

Models of the genetic transmission of schizophrenia have long emphasized the importance of additive genetic effects of genes that individually exert small or moderate effects (Faraone & Tsuang, 1985; Gottesman & Shields, 1967; Tsuang et al., 1999a). These small effects contributed to the difficulties in the late 1980s and early 1990s in replicating findings in genetic linkage studies (Tsuang et al., 1999a). The situation improved somewhat with the development of large and often international collaborative studies to increase sample size and statistical power, which, in turn, increased positive findings and replications of those findings (Baron, 2001). The search for susceptibility genes still remained mired, however, by a variety of factors such as continued difficulties in finding pleiotropic genes of small effect, polygenic inheritance, environmental factors, and heterogeneity, among others. The increasing utilization of putative endophenotypes and the decreasing reliance on clinical symptoms alone improved the situation further by identifying potential biological substrates that underlie schizophrenia. These developments influenced a movement toward studies to identify or test candidate genes, including genome-wide association studies (GWAS), which are useful in detecting associations to common alleles (Greenwood et al., 2013).

Several recent studies reported associations of single nucleotide polymorphisms (SNPs) with measures of cognition. Simons et al. (2013) studied 152 SNPs in 43 candidate genes in patients with schizophrenia and healthy comparison subjects. The patients showed 13 significant associations between the SNPs and cognitive functions assessed with a battery of tests, which were located in DRD1, DRD3, SLC6A3, BDNF, FGF2, SLC18A2, FKBP5, and DNMT3B. Greenwood et al. (2013) reported a genome-wide linkage analysis that included 10 cognitive endophenotypes (including an antisaccade task, which has a cognitive component) that they already showed to be heritable (Greenwood et al., 2007). One region showed genome-wide significance (antisaccade task) on chromosome 3p14, and another region almost showed genome-wide significance on 1p36 (Emotion Recognition from the Penn battery). Nine other regions showed suggestive linkage. In a separate study, Greenwood et al. related these endophenotypes to 94 functionally relevant candidate genes for schizophrenia and found that 38 of them were associated with at least one endophenotype to schizophrenia (Greenwood et al., 2012). Moreover, 11 genes showed evidence of pleiotropy, with associations to three or more endophenotypes (including ERBB4 and NRG1).

Walters et al. (2013) used six SNPs to represent significant genome-wide loci obtained from three GWAS using patients with schizophrenia and healthy controls. Five of the six loci were not associated with any cognitive measures. One of them, however, rs6904071, was associated with both delayed episodic memory and with decreased hippocampal volume. Similarly, Bakken et al. (2011) showed that two SNPs on the Prader-Willi and Angelman syndrome region of chromosome 15q12 (i.e., rs4906844 and rs11633924) showed a genome-wide association with both cognition and cortical thickness in schizophrenia. These findings underscore the point that many genes associated with impaired cognition may also be associated with abnormal brain structure. Consistent with this observation, a recent

review of candidate genes for abnormal brain structure in schizophrenia, (for example Kaymaz & van Os, 2009) included additional candidates genes/alleles for which this may be the case, including COMT Val58Met (Egan et al., 2001), DISC1 (Nicodemus et al., 2014), and BDNF (Simons et al., 2013).

One recent study compared nine putative susceptibility genes for schizophrenia that have been the subject of neuroimaging studies (all kinds, not just structural) and of cognitive investigations (Rose & Donohoe, 2013). A meta-analysis was performed to compare the effects of study methodology on effect size. The results demonstrated greater percentages of cognitive findings with small or medium effect sizes, and greater percentages of imaging studies with medium or large effect sizes. As a group, these genes thus show greater effects on brain structure or function than they do on cognition, though these findings do not apply to individual genes, cognitive functions, and brain regions or brain functions. As important, however, is the point that these genes appear to exert pleiotropic effects and may contribute to the genetic effects in heritability studies.

Nonpsychotic relatives also show many of the same relationships as patients. The Iowa HRS showed, for example, that NRG1 SNPs were associated with total cerebral gray matter volumes (Ho et al., 2008). The NIMH HRS also related a NRG1 risk allele (420M9–1395) to changes in total gray and white matter volumes (Addington et al., 2007), and related COMT Val158Met to cortical thinning (Raznahan et al., 2011). The Edinburgh HRS reported that COMT Val158Met was related to bilateral reductions in anterior cingulate gray matter density (McIntosh et al., 2007). Simons et al. (2013) showed that one of the SNPs associated with cognition in schizophrenia patients was also associated with their nonpsychotic siblings.

CURRENT AND FUTURE DIRECTIONS

This foray into even a limited number of schizophrenia related neuropsychological and structural neuroimaging endophenotypes yielded an almost overwhelming number of studies. This attests to the degree to which this construct has gained high levels of interest in schizophrenia, and in psychiatry in general. Moreover, the endophenotype concept is a foundation of the NIMH RDoC initiative, which underscores its growing importance as a window into psychopathology research (Casey et al., 2014; Cuthbert & Insel, 2010).

We present the schizophrenia endophenotype story as an exemplar of endophenotypes in psychiatry and hope that the readers will delve into other disorders based on this work. At this point, extensive investigations of neuropsychological deficits and structural brain abnormalities provide compelling evidence that specific measures in both domains meet proposed criteria for classification as endophenotypes for schizophrenia. Taking Gottesman's proposed criteria for endophenotypes as a starting point (Gottesman & Gould, 2003), multiple deficits in each broad domain have been associated with schizophrenia. Strong associations with schizophrenia were evident within these domains as well, in neuropsychological subdomains such as attention/working memory, declarative memory, executive functions, and intelligence. Similarly, abnormalities in a variety of brain regions were associated with the illness, such as whole brain and each lobe of the brain, but particularly in the frontal and temporal lobes. Moreover, structural abnormalities were evident cortically and subcortically (i.e., hippocampus).

Both neuropsychological measures and abnormal volumes in brain regions occur frequently in relatives, though they are often milder, and some that are more related to psychosis than to the underlying liability to schizophrenia may not be present in relatives. In both domains, the deficits that are associated with schizophrenia persist through all stages of the illness, though their expression may vary at different stages, or as a result of treatment or other environmental or epigenetic factors. Moreover, neuropsychological functions and brain structures are under significant genetic control in healthy individuals, and in schizophrenia. An extensive literature shows significant heritability for many neuropsychological deficits, and for many brain volumes. Increasingly, linkage and association studies, as well as other genetic strategies aimed at identifying susceptibility genes, such as gene expression (Glatt et al., 2011) and copy number variation (Addington & Rapoport, 2012) studies, show that genetic correlations between schizophrenia and expressions of these endophenotypes often reflect significant genetic influence. Consequently, these strategies have implicated individual genes to an extent that would have seemed unlikely as recently as a decade ago. With this foundation, we may look forward to the continued identification of genes and genetic mechanisms that underlie the liability to schizophrenia.

More specifically, the fulfillment of Gottesman's proposed criteria for neuropsychological and brain structure endophenotypes helps to validate the endophenotype concept in identifying disease-related abnormalities that may provide clues to the identification of underlying pleiotropic genes that contribute to both the observed endophenotype

and to the liability for schizophrenia. It is significant that many genetic studies linked neuropsychological and structural neuroimaging endophenotypes to each other, as well as to schizophrenia. These relationships may have been even more salient had we not limited this review to structural brain endophenotypes assessed through MRIs, but their relationships with each other were robust nevertheless. The relationships observed between the neuropsychological measures and structural neuroimaging variables raise the important question of how to utilize and conceptualize multiple endophenotypes.

The question may be considered in at least two broad dimensions. One of these is clinical. Do some relationships between endophenotypes have greater clinical significance than others, for example, in assessing liability to schizophrenia? We proposed preliminary steps toward a provisional liability syndrome in nonpsychotic relatives of schizophrenia subjects using neuropsychological measures and negative symptoms (Faraone et al., 2001; Tsuang et al., 1999b) and showed preliminary evidence of validation for the concept (Stone et al., 2001, 2012). Consistent with the view that endophenotypes could help define and characterize a significant portion of the schizophrenia spectrum (Figure 24.2), we hypothesized that a combination of genetic liability and the biological consequences of early adverse environmental factors (e.g., preeclampsia or other pregnancy or delivery complications) could create a liability syndrome for schizophrenia (schizotaxia). This syndrome, which was adapted from a concept proposed by Paul Meehl (Faraone et al., 2001; Meehl, 1962; Stone & Giuliano, 2013), in interactions with later environmental factors (e.g., stress, substance use), could result in a range of outcomes (depicted by Thermenos et al., 2013; Figure 24.4), including stable schizotaxia, schizophrenia spectrum disorder, the development of a prodromal high risk phase, and a conversion to psychosis/schizophrenia (Thermenos et al., 2013). Investigations such as these are promising; however, such syndromes will likely remain in the early stages of development, at least until strategies can be developed to select the most useful endophenotypes to include in them, and the most useful syndromes, themselves. Nevertheless, the field will need to continue to develop them if we are ever to identify the individuals most at risk for developing schizophrenia.

The second way to conceptualize the importance of multiple endophenotypes is related to their utility in leading to the clearest genetic etiologies in areas of interest. This pathway, in turn, may then lead to the identification of biological mechanisms of action influenced by the genes involved. Despite the recent progress in the field,

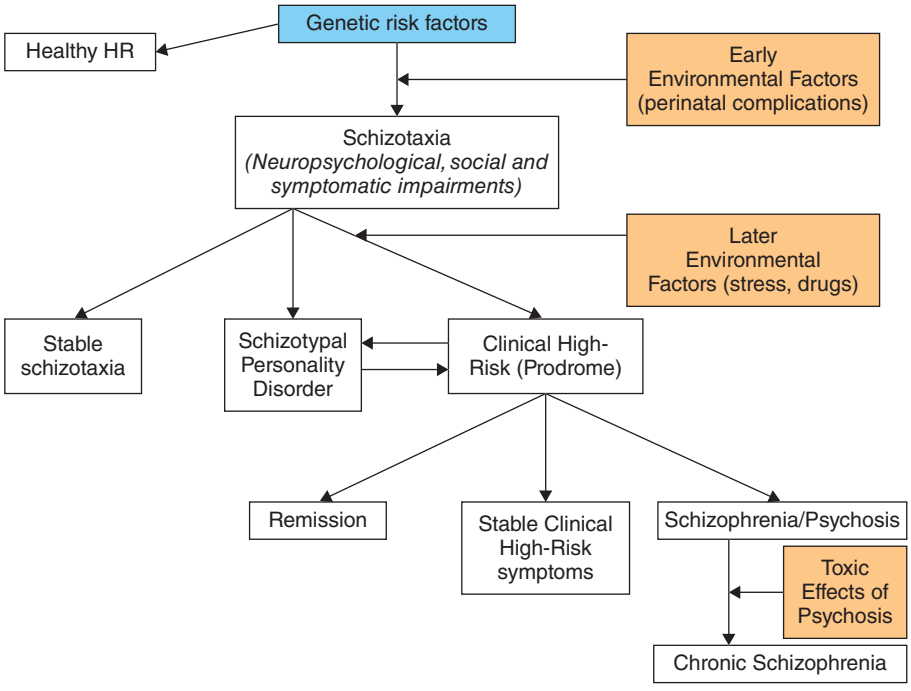


Figure 24.4 Developmental pathway of familial high risk for schizophrenia: Schizotaxia represents the syndrome associated with genetic risk. See footnote 1. *Source:* H. W. Thermenos, M. S. Keshavan, R. J. Juelich, E. Molokotos, S. Whitfield-Gabrieli, et al., A review of neuroimaging studies of young relatives of individuals with schizophrenia: A developmental perspective from schizotaxia to schizophrenia. *American Journal of Medical Geneicst B: Neuropsychiatric Genetics,* pp. 605, *162*, 2013. Used with permission.

the process of identifying valid endophenotypes among hundreds or thousands of candidates in the field, and then locating and testing candidate genes, is a slow and arduous one. Multiple factors contribute to this state-of-the-field, including the strong likelihood that most genes contribute small effect sizes that are difficult to detect. This point is magnified by the added complexity of detecting variants of genes, some of which are rare, that are actually etiological. Polygenic, epigenetic, gender, developmental, and environmental modulation of gene effects may increase complexity further.

We are, however, making progress. The recognition that many putative endophenotypes are heritable has allowed a database of these effects to emerge at the beginning of the twenty-first century. For example, in one of the largest and best known studies in identifying the genomic substrates of endophenotypes in schizophrenia, COGS investigators and their collaborators have identified common variant substrates from candidate gene (Greenwood et al., 2011) and linkage studies (Greenwood et al., 2013). Additional work has led to the detection of highly penetrant de novo events (Gulsuner et al., 2013) associated with schizophrenia endophenotypes. The identification of new biological anomalies (for example, through copy number variants and gene expression studies) has opened up new genetic fronts that likely will have relevance to the etiology of some endophenotypes. Unraveling the genomic and neurobiological substrates of schizophrenia will certainly be a time-consuming, but ultimately fruitful, task (Braff & Braff, 2013).

TRANSLATIONAL IMPLICATIONS

One of the first applications of endophenotype research in psychiatry was to identify disease-related abnormalities that could advance genetic research into complex disorders (such as schizophrenia) beyond the limits that were permitted by clinical diagnoses (Gottesman & Gould, 2003). In addition to the conceptual advances this perspective afforded, as discussed earlier in this chapter, the endophenotype perspective contributed to at least two other important developments.

One of these is the NIMH RDoC initiative, which is attempting to develop a classification system for psychopathology that is based on dimensions of behavior and its underlying neurobiology rather than on the formal clinical symptoms that are often more distal and less specific products of those processes (Casey et al., 2014; Cuthbert & Insel, 2010). The utilization of that strategy emphasizes a dimensional rather than a categorical or diagnostic approach that facilitates the study of how behaviors, neurobiological systems, and gene regulation change with time and in interaction with other biological and environmental events to facilitate or inhibit different outcomes (Casey et al., 2014). This perspective, which is multidisciplinary in nature, broadens the type of inquiries that may be posed through laboratory research, and encourages translational research, which is a second recent development related to endophenotype research. One of the goals of this approach is to identify and utilize laboratory-based discoveries in human clinical trials and other related studies (Rubio et al., 2010).

In looking to the future, whether the immediate focus is more clinical or more genetic, it will thus be essential to develop translational strategies to maximize the efficient use of endophenotypes. This is particularly true of many neuropsychological and structural neuroimaging endophenotypes, which are themselves complex etiologically (e.g., declarative memory, whole brain volumes). It is likely that one strategy will not fit all purposes. Conceptual considerations about the nature of liability to schizophrenia guided our initial attempts to define a liability syndrome, for example, as described above, but more objective, empirical strategies may be necessary to validate the syndrome and to increase its power. If it is true that endophenotypes show simpler genetic etiologies and more direct pathways to underlying gene identification, then one strategy may be to identify and use simpler, truer endophenotypes when possible, rather than more complex phenotypes whose heritabilities reflect a mixture of genetic etiologies. Another strategy might be to utilize an endophenotype ranking system that is based on differential genetic utility scores, as suggested recently (Glahn et al., 2012). Whichever endophenotype strategies are employed, it will be essential to increase our ability to capitalize on the opportunities they afford to identify genes that increase or decrease the risk for schizophrenia. The half-fulfilled promise of this approach remains particularly promising for neuropsychological and neuroimaging endophenotypes, in the hope of finding therapeutic interventions eventually to ameliorate or prevent these core features of the illness, and the illness itself.

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