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CHAPTER 5

The Developmental Psychobiology of Stress and Emotion in Childhood

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There is increasing evidence that childhood adversity exposes individuals to an elevated risk of physical and mental health conditions and that these deleterious effects are mediated, at least in part, by the activity of biological stress systems (Shonkoff, Boyce, & McEwen, 2009). Thus, there are important societal and public policy implications for studying stress and emotion in childhood with the goal of ultimately promoting stress resilience through well-designed interventions (Gunnar, Fisher, & The Early Experience, Stress, and Prevention Network, 2006). Advancing this goal requires moving beyond correlational studies of early life stress and maladaptive biobehavioral outcomes in adulthood. For instance, findings in human epigenetics have begun to shed light on some of the mechanisms through which early life experiences become biologically embedded (Meaney, 2010). Discovering evidence that early caregiving experience is associated with the epigenetic regulation of gene expression provides support for the hypothesis that early life stress has programming effects on the organism, shaping its future psychological and physiological reactivity, and thus its vulnerability to physical and mental illness.

While these advances brought about by the genomic era have suggested new biological mechanisms for the interplay between genes and environmental inputs, stress research has yet to fully explain pervasive individual differences in stress reactivity (Gunnar & Quevedo, 2007). It is an empirical reality that some individuals succumb while others thrive when confronted with similar challenges. Explaining these individual differences forms the core of developmental research on stress. The previous edition of this chapter (Gunnar & Davis, 2003) reviewed research that attempted to explain these individual differences by studying temperament (constitutional differences in stress reactivity) or the role of early experience (e.g., attachment history), as well as studies that were beginning to examine the interaction between the two (Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996). In the past decade, the focus on temperament as a set of behavioral predispositions with putative constitutional bases has morphed to include an increased attention to genetic polymorphisms that may confer heightened susceptibility to developmental context resulting in increased vulnerability in harsh contexts (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010) or better functioning in supportive ones (Belsky & Pluess, 2009). Research on the relationship between the quality of early care and later stress reactivity has continued to grow, garnering an ever-growing evidence base from animal models (Sanchez, 2006) as well as from human studies (van der Vegt, van der Ende, Kirschbaum, Verhulst, & Tiemeier, 2009). Newer investigations are also beginning to examine the interactions between genetic variants and early caregiving experience that may predict later stress reactivity (e.g., Luijk et al., 2010).

Gene-by-environment studies often point to *statistical* interactions, but the challenge for the field will be to create developmental models that incorporate the functional activity of genes and deconstruct environmental influences into their relevant components in order to capture bidirectional *causal* interactions between genes and environment. The developmental psychobiological systems perspective (Gottlieb, Wahlsten, & Lickliter, 1998)

outlined in the previous edition of this chapter remains pertinent; indeed, it is the only framework that accurately captures the dynamic, self-organizing nature of biological systems. Stress neurobiology is a prime example of these constant self-organizational efforts that aim to maintain ~~the~~ homeostasis and sustain life by mobilizing resources to respond to acute challenges (Dallman, 2007). The functioning of stress systems also illustrates the principle that the history of the organism constantly impinges on its current ability to function and adapt.

However, past exposure to stress has complex, nonlinear relationships with current responses (Sapolsky, 2003), which makes predictions based on the organism's history a challenge. On one hand, chronic exposure to stress has deleterious consequences at multiple levels of functioning that result in wear and tear across biological systems–a phenomenon called "allostatic load" (McEwen, 2008). On the other hand, ever since Levine's landmark studies of early handling in rat pups (Levine, 1957), it has also become evident that exposure to mild stress can enhance regulation of stress-sensitive physiological systems and decrease fearfulness. The question thus becomes: Under what conditions (intrinsic or extrinsic to the organism) does stress exposure induce vulnerability, and when does it promote resilience? The developmental timing and the duration of stress exposure, as well as the interactions between experience and the genetic characteristics of the organism are likely to be equally important determinants of an individual's stress response (Lupien, McEwen, Gunnar, & Heim, 2009). Context and the availability of coping resources (whether internal or external –e.g., social support) are also likely to play a decisive role in determining the magnitude and nature of the current stress response, as well as recovery from it.

In this chapter we review what is known about the developmental neurobiology of stress systems, aiming to articulate the current state of our knowledge on some of the factors that foster stress vulnerability or resilience. We begin with an overview of the anatomy and physiology of stress systems and some of their complex interconnections. This is followed by a discussion of what is known about the ontogeny of these systems and about the way individual differences in the activity of these systems might emerge. We will review research findings related to temperamental, genetic, and caregiving factors that have been associated with stress indices. We conclude with some thoughts about the need for basic research examining the development of stress systems at multiple levels of analysis, hopefully informing a comprehensive, biologically plausible model of stress and emotion across the lifespan. We begin, however, with a general discussion of the concept of stress as it is used in the psychobiological literature.

THE PSYCHOBIOLOGY OF STRESS

Stress is sometimes defined as a "real or interpreted threat to the physiological or psychological integrity of an individual that results in physiological and/or behavioral responses" (McEwen, 2000, p. 508), while others use the term to refer to the subjective experience or biological responses to the threatening situation. As Levine (2005) eloquently discussed, there are three types of constructs that are usually subsumed by the concept: the inputs (i.e., the challenges), the systems that process them, and the outputs or responses. To distinguish between these three potential connotations of the term, we will refer to events that trigger stress reactions as stressors (similar to Selye, 1975), and the outputs of this cascade will be called stress responses. We will refer to the biological and psychological systems that process the challenging inputs as stress mediators or simply stress systems.

Stress results when the demands of internal or external events exceed immediately available resources. These demands can be very diverse, ranging from temperature challenges, to infections, to real or perceived psychological threats. Despite the nonspecific nature of agents that can trigger a stress response (Selye, 1936), different biological pathways have been identified for two major classes of stressors: *Systemic stressors* involve a physical change in functioning that threatens viability and activates stress biology via spinal cord or brainstem reflexes, whereas *processive/psychogenic stressors* recruit forebrain processing and elaboration (Herman et al., 2003). Within each major class of stressors, different pathways converging on the paraventricular nucleus of the hypothalamus can be further differentiated. Despite these recent nuances, Hans Selye's first description of the General Adaptation Syndrome (Selye, 1936) is still relevant, postulating three stages to each stress response: alarm, resistance, and exhaustion. It must be emphasized that acute stressors which challenge the organism but do not persist sufficiently to cause exhaustion can sometimes be beneficial. The relationship between stress level and overall functioning has been described as an inverted U-shape curve, where medium-level stimulation is optimal (Sapolsky, 2003). These nonlinear effects are rooted in the neurobiology of stress and its control and feedback systems, which will be described in more detail below.

The stress response is multifaceted, encompassing neuroendocrine, autonomic, immune, and metabolic changes (Lupien et al., 2009). Stress responses executed by each of these systems interact in a dynamic fashion, allowing the organism to adapt to challenges and restore homeostasis. However, the integrated nature of these systems also guarantees that chronic challenges to the organism will have widespread effects across multiple domains, making it difficult to isolate any single causal process. The challenge of understanding the interactions between neuroendocrine, autonomic, immune, and metabolic systems will only be met by adopting a systems framework (Gottlieb, Wahlsten, & Lickliter, 1998) that acknowledges the complex, nonlinear, and self-organizing nature of biological systems. However, complex multicausal models will not be possible without a deeper understanding of the role played by each system in the stress response. Thus, in this section we review the anatomy and physiology of the limbic-hypothalamic-pituitary-adrenocortical (L-HPA) axis and the sympathetic-adrenomedullary (SAM) system, as the primary orchestrators of the mammalian stress response, followed by a discussion of the impact of limbic and frontal brain regions on the activity of these systems. We will not review the immune and metabolic changes associated with psychological stress here, as they are beyond the scope of this chapter, but recent reviews provide a useful introduction to these topics (for relationships between stress, immunity and health, see Glaser & Kiecolt-Glaser, 2005; Miller, Chen, & Cole, 2009; for links between stress and metabolism, see Dallman, 2010; Holmes, Ekkekakis, & Eisenmann, 2010).

The Limbic-Hypothalamic-Pituitary-Adrenocortical (L-HPA) System

The detection of threat triggers a neurohormonal cascade that results in the secretion of glucocorticoids (GCs; cortisol in humans, corticosterone in rodents) through the activation of the limbic-hypothalamic-pituitary-adrenal axis. Neurons in the medial parvocellular region of the paraventricular nuclei of the hypothalamus (PVN) secrete corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) into the hypophyseal portal system, traveling to the anterior pituitary and causing the release of adrenocorticotropic hormone (ACTH) into the general circulation (Gunnar & Vazquez, 2006). ACTH subsequently binds to its receptors in the cortex of the adrenal glands, leading to the release of GCs. Circulating hormones bind to receptors distributed throughout the brain and the body and also exert negative feedback inhibition at multiple levels of the hypothalamic-pituitary-adrenocortical (HPA) axis (Cone, Low, Elmquist, & Cameron, 2003). Additionally, current evidence also suggests that negative feedback involves GC receptors in other areas outside the HPA axis, including but not limited to the prefrontal cortex and limbic structures like the hippocampus and amygdala (Oitzl, Champagne, van der Veen, & de Kloet, 2009). We will discuss the role of these limbic and cortical areas in more detail in a subsequent section on Limbic and Cortical Regulation. The interconnections between limbic regions and the hypothalamic-pituitary-adrenal axis are what led the field to sometimes refer to it as the "limbic-hypothalamic-pituitary-adrenal axis" to emphasize the important role played by these structures in its activation or inhibition. We preserve this nomenclature here.

Once the GCs bind to their receptors, the activated receptors then enter the nucleus of the cell, where they regulate the transcription of genes with GC-responsive regions, ultimately leading to protein synthesis (Sapolsky, Romero, & Munck, 2000). This genomic pathway adds a significant lag to the effects of glucocorticoids, ranging from 20 minutes to hours and days, but recent evidence shows that GCs can also exert rapid nongenomic effects—e.g., increasing the cellular excitability in some hippocampal cells (Joëls, 2008). Furthermore, some studies indicate that GCs can exert fast negative feedback on the HPA axis through nongenomic mechanisms, which can occur instantaneously or with a very short latency after endogenous GC exposure (Evanson, Tasker, Hill, Hillard, & Herman, 2010). This is likely mediated by endocannabinoid signaling at the level of the PVN (Evanson et al., 2010).

Activating the HPA axis has widespread effects throughout the body, including a mobilization of energy to muscles, enhanced cardiovascular tone, a stimulation of immune function, inhibition of reproductive physiology, decreased feeding and appetite, sharpened cognition, and increased local cerebral glucose utilization (Sapolsky, Romero, & Munck, 2000).

It must be noted that GCs are not *only* produced in response to stressors, but are released in pulses across the day to ensure basal levels of hormones that are necessary for energy, motivation, and optimal functioning overall. Both excessive and deficient basal levels of glucocorticoids can impair behavioral and physical functions, potentially leading to pathological conditions (Chrousos, 2009). The release of basal GCs follows a circadian clock, with higher levels in the morning for humans (approximately 30 minutes after wake-up, which has been named the cortisol awakening response and has been associated with numerous psychological and physical health outcomes—for a

review, see Fries, Dettenborn & Kirschbaum, 2009) and decreasing production throughout the day, reaching minimum levels at night.

Glucocorticoids bind to glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) differentially when they are released in response to a stressor versus their basal circadian release. GCs have 10 times higher affinity to MRs and occupy them first before acting on the GRs (Oitzl et al., 2009). Thus, MRs are almost entirely occupied when GCs are in the basal ranges, and GRs only become occupied when stressors elevate GC concentration above basal levels. Evidence is accumulating for the hypothesis that the balance of MR:GR is crucial for an effective regulation of the stress response and for resilience to psychiatric disorders (Oitzl et al., 2009).

Recent research has shown that individual differences in the expression of MR and GR are not entirely due to genetic diversity, but their distribution is also affected by environmental factors, through epigenetic mechanisms. Recent work shows epigenetic modifications associated with early life abuse in rodents, for instance the increased methylation of glucocorticoid receptor (GR) genes which are associated with enhanced stress reactivity in adulthood (Kaffman & Meaney, 2007). Furthermore, childhood abuse has been associated with epigenetic alterations in genes regulating GR expression in the hippocampus of human suicide victims (McGowan et al., 2009) and depressed maternal mood during pregnancy is also associated with methylation patterns that correlate with heightened stress reactivity in the newborn (Oberlander et al., 2008). Future research will likely continue to explore the epigenetic mechanisms involved in the transduction of early life experiences into long-lasting patterns of stress reactivity.

The Sympathetic-Adrenomedullary System

Although the L-HPA system now figures prominently in research on stress, the older focus on the SAM system has not been lost in developmental research (Gunnar & Quevedo, 2007). The catecholamines epinephrine (EPI) and norepinephrine (NE) are the major outputs of the SAM system. EPI is produced by the adrenal medulla and then released into general circulation. EPI acts as a stress hormone, whereas NE produced at synapses is a neurotransmitter. Both EPI and NE act to energize and mobilize the organism for what has been termed the fight/flight responses. Neurons of the hypothalamus and other cell groups within the brain stem are the central coordinators of the sympathetic nervous system (SNS). In the brain, NE-producing neurons originating in the locus coeruleus (LC) and in other cell groups in the medulla and pons project widely throughout the cortex. Animal studies suggest that NE release in limbic forebrain regions (central and medial amygdala, lateral bed nucleus of the stria terminalis, medial prefrontal cortex, and lateral septum) mediate anxiety-like behaviors (Morilak et al., 2005). It must be noted that NE has modulatory effects at the synapse, operating on both excitatory and inhibitory inputs that the target cells receive (Morilak et al., 2005). In addition, LC neurons project to the CRH-producing cells in the hypothalamus, serving as a primary stimulus of increased CRH production and sensitization in response to emotional stressors.

Although the SAM system has long been associated with stress, its activity is not specific to threatening or aversive events. Instead, because of the role of the sympathetic system in supporting rapid energy mobilization, its activity tends to track conditions requiring effort and information processing more generally, rather than those involving distress and uncertainty about outcomes more specifically (e.g., Frankenhaeuser, 1979). Despite this, frequent mobilization of the sympathetic system, particularly in the presence of elevated cortisol, can threaten physical health.

The SAM system forms one arm of the autonomic nervous system (ANS). The other arm of this system is the parasympathetic nervous system (PNS). Unlike the SAM system, which is sometimes referred to as a diffuse or mass-discharge system, the PNS tends to be more fine-tuned, having discrete effects on the organ systems that it innervates (Hugdahl, 1995). Similar to the health-promotive effects of MRs for the L-HPA system, the PNS primarily promotes anabolic activities concerned with the conservation and restoration of energy (Porges, 1995). The presence of PNS terminals on most organs and tissues innervated by the SAM system allows the PNS to serve as a major regulator of sympathetic effects. Although both the PNS and SAM systems have been viewed as efferent systems that carry out work dictated by the brain, both systems also have afferent projections to the brain. These afferent projections not only inform the brain about the status of organs and tissues in the periphery, but also allow autonomic regulation of the central nervous system.

Parasympathetic neuronal projections leave the brain through several cranial nerves, including the 10th cranial, or vagus, nerve, which has been the focus of most of the psychophysiological research relating activity of the PNS to stress and emotion (Porges, 2009). The primary fibers of the vagus nerve originate in two nuclei in the medulla: the dorsal motor nucleus of the vagus, which regulates

visceral functions, and the nucleus ambiguus, which regulates functions associated with communication and emotion. In addition, a third medullary nucleus, the nucleus tractus solitarius, receives many of the afferent projections traveling through the vagus from peripheral organs. In his polyvagal theory, Porges (2009) argues that these three nuclei (and their corresponding vagal branches) serve distinct evolutionary functions: social communication, mobilization (e.g., fight/flight) and immobilization. The myelinated vagus, originating in the nucleus ambiguus, inhibits sympathetic input to the heart and fosters calm states, also decreasing the activity of the HPA axis (Porges, 2009). This state of physiological calm is theorized to facilitate social interaction and attention. Higher baseline vagal tone has sometimes been considered to be reflective of effective stress regulation, as it allows for a dampening of stress responses or a swift sympathetic activation when the vagal input is suspended.

Limbic and Cortical Regulation

The L-HPA and SAM systems do not operate in isolation. Rather, their activation is the result of a fine-tuned cascade of neural events that involve a large number of brain regions and neurotransmitters, creating a true "neurosymphony of stress" (Joëls & Baram, 2009). Limbic and cortical regions (e.g., the amygdala, hippocampus, the prefrontal cortex) relay information about threats that can activate or terminate stress responses. In this section we review some of the major limbic and cortical structures that modulate stress responses, and what is currently known about the circuitry that integrates this diversity of inputs.

The amygdala is one of the most important limbic structures modulating neuroendocrine and autonomic functions. Animal models have established its role in emotional learning and conditioning, particularly fear learning. Research has dedicated special attention to the central nucleus of the amygdala (CEA) as a principal orchestrator of fear behaviors (Ulrich-Lai & Herman, 2009). In this regard, it is noteworthy that CRH-producing cells do not reside exclusively in the hypothalamus but are also present in many brain structures that are involved in associating fear and anxiety with activation of the stress system, including the CEA and the prefrontal cortex (Bale & Vale, 2004). CRH acts on two types of receptors, which have different regional distributions and functional properties, with CRF1 mediating acute stress reactions via the activation of the HPA axis and CRF2 being involved in poststressor recovery and dampening of the HPA response (Korosi & Baram, 2008).

Evidence from rodent research suggests that the CEA activates the HPA axis in response to systemic stressors and integrates autonomic responses to psychogenic stressors, whereas the basolateral and the medial nuclei of the amygdala play a preferential role in activating the HPA axis in response to psychological stressors (Ulrich-Lai & Herman, 2009). The amygdala not only acts on the HPA axis but is itself influenced by glucocorticoid release. In rodents, stress-induced glucocorticoid release permits amygdala activation and facilitates fear learning (Moriceau, Roth, & Sullivan, 2010). Fear learning is central for adaptation, as the activation of stress circuitry is energetically demanding, and thus the ability to distinguish threatening from harmless stimuli is essential for survival.

The bed nucleus of the stria terminalis (BNST) is another structure that is important in modulating HPA axis responses, though different subdivisions of the BNST seem to have contrary effects: anteroventral regions seem to have excitatory effects on the axis, whereas posterior regions may be inhibitory (Choi et al., 2007).

The hippocampus is another major limbic structure that has inhibitory control of the HPA axis, through projections to the PVN, and it also influences the ANS (decreasing heart rate, blood pressure, etc.), most likely through indirect medial prefrontal cortex projections (Ulrich-Lai & Herman, 2009). GR and MR expressed in the hippocampus play a crucial role in negative feedback of the HPA axis, and it is likely due to changes in the activity of these receptors that chronically elevated circulating GCs have been linked to deficits in hippocampally-based abilities, such as declarative memory (Sapolsky, 2003).

Limbic structures are regulated by and communicate with frontal cortical regions, and their bidirectional connections impinge on the activity of the HPA and SAM systems. For instance, the degree and breadth of interconnectivity between the amygdala and frontal cortex in primates have been one of the surprising findings of the last two decades (Emery & Amaral, 2000). Perhaps especially in primates, the frontal cortex appears to play a central role in stress reactivity and regulation.

The prefrontal cortex (PFC) plays a crucial role in what has been termed *executive function*, or the top-down control of thought and action that includes working memory, inhibitory control, rule shifting, and executive attention (Zelazo, Carlson, & Kesek, 2008). These higher-order processes are crucial for the development of emotion regulation, compliance with norms, as well as intelligent planning of behavior. The PFC is organized into distinct topographical regions, which serve divergent and

specialized regulatory functions. Ventral and medial areas are thought to primarily regulate emotions, having extensive connections with the amygdala, the nucleus accumbens, and the hypothalamus, whereas regions located more dorsally and laterally are thought to regulate thoughts, attention, and actions and have important projections to sensory and motor areas (Arnsten, 2009).

The prefrontal cortex not only plays a role in regulating the activity of stress systems, but it also receives bottom-up inputs from them, and its activity can be impaired by acute or chronic stress exposure (Arnsten, 2009). Even though some experimental studies with squirrel monkeys suggest that stress-inoculating experiences (i.e., stressors that are not overwhelming in either duration of magnitude) can enhance prefrontally mediated cognitive skills that are instrumental for emotion and stress regulation (Lyons & Parker, 2007), multiple studies in humans show that both acute and chronic exposure to stressors can actually impair these higher order processes that rely on the PFC (Arnsten, 2009).

Indeed, chronic stress induces alterations in both cortical and limbic regions, such as dendritic atrophy and decreased GR expression in the medial PFC and the hippocampus (which typically have inhibitory control over the HPA axis) and increased dendritic branching in the basolateral amygdala and enhanced CRH expression in the CEA (Ulrich-Lai & Herman, 2009). Over time, these alterations are likely to impair the capacity for negative feedback of the HPA axis, as well as to decrease the available PFC-based cognitive resources for coping with stressors. The effects of stress on brain development and the sculpting of cortico-limbic circuits across the lifespan are likely mediated by both circulating GCs and by the extra-hypothalamic CRH system (Korosi & Baram, 2008).

Summary

The neurobiology of stress and emotions is extremely complex. While the field is beginning to develop a much deeper understanding of the neurobiological bases of both emotions and stress, most of the work has yet to be conducted with humans. Furthermore, we know the least about infants and young children. Animal models have the advantage of increased experimental control and the ability to use more invasive procedures (e.g., to examine molecular processes that underlie neural function), but the challenge of translating findings across species is not negligible. Nonetheless, combining information from animal and human studies is likely to yield more nuanced and plausible models, which can explain human developmental processes and serve as a starting point for interventions. In the next section, we discuss major findings relating to the early development of stress and emotion systems in humans.

PSYCHOBIOLOGICAL STUDIES OF STRESS AND EMOTION IN CHILDREN

Research incorporating biomarkers of stress and emotion has burgeoned in the past decade due to an increased recognition of the dynamic interplay between psychological functioning and biology. Since the 1980s, technological advances that allowed the salivary assay of cortisol (Kirschbaum & Hellhammer, 1989), electrophysiological measures of the autonomic nervous system (Porges, 1995), or neuroimaging (Nelson, de Haan, & Thomas, 2006) have also expanded the opportunities to study the neurobiology of stress and emotion at multiple levels of analysis. Despite these advances, ethical and practical constraints have limited the ability to probe at some levels of analysis and to have a high degree of experimental control in studies with children. Thus, animal research remains important for the development and testing of theoretical models that can then be translated to humans. In this section, we review the current state of human research studies that have investigated the early development of stress reactivity, addressing major developmental periods in chronological order, but we will also refer to animal studies to draw inferences or in areas where human research is entirely absent.

Developmental Periods of Stress Reactivity and Regulation

Stress reactivity and regulation undergo marked changes from the prenatal period through adolescence. Although there are no agreed-upon divisions of development in which to consider these changes, in this section we identify six periods to analyze: prenatal, early postnatal, toddler, preschool, middle childhood, and adolescence. These periods take us from the emergence of an HPA response to stressors during the fetal period through to increases in stress reactivity and basal levels that are observed in early adolescence. Our analysis also raises questions about the calibration and recalibration of stress responses during development, in accord with the stresses and challenges experienced by different children at different points in their ontogeny.

Prenatal Origins

Prenatal development is a period of great plasticity. The developing fetus receives nutrients and biochemical signals from the mother and, through her, from the environment. These signals are theorized to have long-lasting programming effects that may translate into risk factors for later disease (Barker, 1998). Furthermore, fetal HPA axis activity is important in its own right, impacting the future development of the organism. By gestational week 8, fetal adrenal glands have developed into morphologically distinct zones, and pituitary cells that produce ACTH can be identified (Kempna & Fluck, 2008). Furthermore, the fetus mounts a cortisol response to painful stimuli (e.g., intrauterine transfusion) beginning around week 20 and this response is independent from maternal cortisol levels or her responses to the medical procedure, supporting the idea of an endogenous fetal stress response (Gitau, Fisk, Teixeira, Cameron, & Glover, 2001).

Maternal stress has been the focus of many studies of fetal programming (Gunnar & Davis, under review). There is convincing evidence from both animal models (Kapoor, Dunn, Kostaki, Andrews, & Matthews, 2006) and human studies (reviewed in Talge, Neal, Glover, & the Early Stress Translational Research Prevention Science Network, 2007) that exposure to maternal stress is associated with altered biobehavioral outcomes in the offspring, including heightened stress reactivity.

One pathway through which maternal cortisol may influence the fetus's developing stress system is via effects on placental CRH production (Wadhwa, Sandman, & Garite, 2001). During gestation, the placenta produces a large number of hormones and peptides, including CRH, which maintain the integrity of the fetal-maternal-placental unit. As the placenta enlarges during pregnancy, CRH levels increase. Placental CRH binding protein (a molecule that traps CRH) and the anticortisol effects of rising estrogen levels protect both the mother and fetus from activation by stress hormones. CRH-binding protein during early pregnancy and the latter part of the third trimester stimulates fetal HPA maturation and contributes to the initiation of labor and delivery. Nonetheless, whereas the CRH molecule is necessary for healthy development of the fetus, it may also provide a mechanism through which maternal stress can influence the development of the infant's stress system. Another pathway that can mediate the relationship between maternal stress and infant reactivity involves the placental enzyme 11β-HSD2. The typical activity of this enzyme is to inactivate maternal cortisol, thus protecting the fetus during development. Rodent studies show that under conditions of experimentally-controlled maternal stress, the activity of 11β-HSD2 in the placenta is downregulated, thus failing to buffer the fetus from the potentially harmful levels of maternal cortisol (Mairesse et al., 2007). In addition, there is now evidence that maternal depression and anxiety during the third trimester is associated with increased methylation of fetal glucocorticoid receptor genes and elevated salivary cortisol responses in the infant at three months postnatal (Oberlander et al., 2008). Thus, epigenetic changes in stress-regulatory pathways provide yet another mechanism through which fetal programming of stress reactivity may take place.

These recent findings provide proof of principle for the fetal programming hypothesis and begin to dispel the objection that the fetus (or infant) and the mother both display heightened stress reactivity due to shared genetics, not due to prenatal processes such as maternal exposure to stress. While this is certainly a possibility, there are four lines of evidence supporting fetal programming effects. Animal models (Kapoor et al., 2006), where experimental control of the stressor and random assignment are possible, show elevated stress reactivity for dyads assigned to the stressful condition. Secondly, some studies in humans have been able to approximate random assignment by enrolling subjects exposed to random natural disasters—for instance, infants of mothers who were pregnant during the World Trade Center attacks on September 11 had smaller birth weights and more blunted cortisol profiles compared to controls (Yehuda et al., 2005). Thirdly, pharmacological exposure to stress hormones prenatally induces HPA-axis alterations in animals (Seckl & Meaney, 2004) and in preterm human infants—for example, prenatal treatment with betamethasone leads to a blunted cortisol response to a heel-stick blood draw stressor (Davis et al., 2004). Lastly and perhaps most convincingly, a recent human study involving in vitro fertilization showed similar effects of maternal stress, even when the mother and the baby were genetically unrelated (Rice et al., 2010).

Investigations of the biobehavioral outcomes of exposure to antenatal maternal stress have also accumulated, with several prospective studies documenting these effects across several domains of functioning (for reviews, see Talge et al., 2007, and Wadhwa, 2005). Notable outcomes include increased negative emotionality and fearfulness during infancy (Davis et al., 2007), attention and hyperactivity problems (O'Connor, Heron, Golding, Beveridge, & Glover, 2002), as well as deficits in general cognitive development (studies reviewed by Talge et al., 2007).

While the term *programming* suggests that effects are permanent, emerging evidence suggests that postnatal

experiences modify or ameliorate prenatal stress impacts. Some studies show that infant-mother attachment moderates the relationship between prenatal stress and negative cognitive and socioemotional outcomes (Bergman, Sarkar, Glover, & O'Connor, 2008, 2010), with securely attached infants being protected from some of these deleterious effects. Maternal sensitivity and responsiveness interacts with antenatal maternal psychiatric symptoms to predict infant cortisol levels, highlighting the crucial role of early social inputs as they may mitigate the effects of prenatal stress exposure (Kaplan, Evans, & Monk, 2008). We will discuss additional research involving the role of caregiving in shaping HPA axis reactivity in the section titled Stress and Caregiving Relationships, but these findings are important reminders that development is probabilistic and there is continuing plasticity during postnatal development.

Early Postnatal Development

Animal models (especially in rodents) have suggested the existence of a stress hyporesponsive period for the HPA axis in neonates (Rosenfeld, Suchecki, & Levine, 1992), when animals have lower basal corticosterone and respond minimally to stressors. In humans, however, for the first two to three postnatal months, the HPA system is highly reactive to stimulation; in addition, because the liver is immature the baby produces less cortisol-binding protein, thus even small increases in cortisol production result in greater circulating levels of the unbound and thus biologically active hormone (for a review, see Gunnar & Quevedo, 2007). During this early period, even seemingly small perturbations like a physical exam or being taken from a warm bath produce HPA stress responses in most healthy infants (see for review Gunnar, Talge, & Herrera, 2009).

The systems influencing stress reactivity and regulation undergo rapid maturation during the early months of life (see for review, Gunnar & Donzella, 2002; Gunnar & Quevedo, 2007). Three months of age has been described as a qualitative turning point in early infancy from which the infant emerges prepared to engage and sustain a broader range of interactions with the environment. By 3 months the elevations in cortisol that have characterized neonatal responses are no longer observed, on average, to handling stressors. Fussing and crying become increasingly dissociated from activity of the HPA system. Vagal tone increases, and some infants show increased competence in using vagal regulation to sustain attention and engagement during challenging stimulation. In addition, more clearly established day-night rhythms may facilitate the regulation of behavioral and physiological responses to potentially stressful stimulation. Unfortunately, we need to know much more about the integration of these various components of the stress system through this developmental period.

Beginning in the early postnatal period, there are a variety of biobehavioral regulatory mechanisms that modulate stress responding. Sleep is critical to stress regulation throughout life (Dahl, 2007). Quiet sleep appears to serve restorative functions in the newborn, similar to the restorative functions it serves at later stages of the life cycle. This has been equated with the concept of a stimulus barrier in early infancy that protects the newborn from overwhelming stimulation (e.g., Tennes, Emde, Kisley, & Metcalf, 1972). Indeed, stressors alter sleep in the newborn, increasing the ratio of quiet to active sleep (for discussion, see Gunnar, 1992). In animal models, the shift into sleep following stress has been shown to be facilitated by the rise in cortisol and other stress biochemical that increase in response to noxious stimulation (e.g., Born, de Kloet, Wenz, Kern, & Fehm, 1991). Thus it may be that stressors stimulate elevations in stress biochemicals that, in turn, facilitate the shift to quiet sleep supporting a return to homeostasis.

In addition to sleep, components of nursing serve stress-regulatory functions (e.g., Blass, 1996). Sucking, even when nonnutrient, produces calming through nonopioid pathways; pathways that may involve the vagal system (e.g., Porges, 1995). In contrast, the calming and analgesic effects of fats and sweet tastes appear to be opioid mediated. Thus, rat pups given a sucrose-flavored liquid are slower to remove their paws from a hot plate, and this effect is blocked if the pups are first pretreated with an opioid antagonist. Similar sucrose-mediated calming effects, even in the context of painful stimuli, have been demonstrated in human newborns (e.g. Stang et al., 1997). In addition, sweet tastes also produce facial expressions of positive affect and increase left-sided anterior EEG activity (Fox & Davidson, 1986). Although it is unlikely that this EEG activity reflects frontal lobe generators in the neonate, it may reflect activity of deeper structures such as the amygdala that also show asymmetric organization and are rich in opioid receptors (Pitkanen, Savander, & LeDoux, 1997). Finally, tactile stimulation (rubbing, patting, massaging) has a multitude of beneficial effects on infant development, including the facilitation of calm states as indicated by reductions in serum levels of norepinephrine and epinephrine, as well as in urinary cortisol levels, and the regulation of sleeping patterns through increases in levels of melatonin (for a review, see Underdown, Barlow, & Stewart-Brown, 2010).

The regulatory roles for feeding, sucking, and tactile stimulation have led some (e.g., Blass, 1996) to argue that the mother serves as a shield to buffer the infant from pain and facilitate the restoration of growth processes following periods of stress system activation. However, different components of parental stimulation may impact different aspects of the stress system (see Hofer, 1987). Those that impact crying (feeding, holding) seem less clearly capable of buffering heart rate responses to painful stimulation and have no apparent impact on cortisol responses to either painful or nonpainful stressors (Gunnar & Donzella, 1999). With development, however, the mother's presence and behavioral interventions become more potent buffers of multiple stress-mediating systems (Felt et al., 2000).

The Toddler Period

It has been suggested that there are two periods of marked change in biobehavioral organization during the first year of life (Emde, Gaensbauer, & Harmon, 1976). We have just discussed the first one, between birth and three months; the second is during the latter half of the first year, when the emergence of independent locomotion appears to produce dramatic neurobehavioral reorganization (e.g., Campos, Kermoian, & Witherington, 1996; Fox & Bell, 1993). This latter period is also associated with the emergence and organization of secure base behavior (e.g., Bowlby, 1969) and inhibition of approach to novel or strange events and people (e.g., Bronson, 1978). This period is also associated with marked changes in stress reactivity and regulation.

Elevations in cortisol to inoculation procedures are roughly comparable at 4 and 6 months of age; however, by the second year of life (i.e., 12, 15, 18 and 24 months), on average, infants do not exhibit elevations to these procedures (this point and others below are reviewed in Gunnar, 2000, Gunnar & Quevedo, 2007; see also a recent study by Davis & Granger, 2009). Similarly, maternal separation, stranger approach, unfamiliar and arousing events, and frustrating tasks do not readily provoke increases in cortisol in children older than 12 months. Whether this decrease in cortisol reactivity emerges gradually or abruptly has not been determined, nor have the processes accounting for this change been wholly identified. What has been shown is that there are individual differences in whether the infant exhibits an inhibition of the cortisol response to stressors by the end of the first year. Examination of cortisol increases at 6 and 15 months using the inoculation paradigm revealed that while most infants failed to elevate cortisol at 15 months, some showed increases that were as large or larger than those typically observed at 6 months.

These highly cortisol-reactive infants tended to be the ones with an insecure attachment relationship to the parent who accompanied them during the exam-inoculation procedure. The role of relationships in the development of individual differences in stress reactivity and regulation will be discussed more fully below. Here we only note that these data suggest that the organization of secure-base behavior in the latter part of the first year may play a significant role in the developmental changes in cortisol reactivity observed during this age period.

The Preschool Period

The development of frontal regions of the brain should allow increasing control over emotional behavior and physiological stress responses (Dawson, Panagiotides, Klinger, & Hill, 1992). Indeed, marked increases in self-control of negative emotionality develosp between 1 and 3 years (e.g., Kopp, 1989). Studies focusing on individual differences have shown correlations between expressive language development and regulation of negative emotions and social engagement and between both of these domains and cardiac vagal tone (e.g., Bornstein & Suess, 2000). The study of emotion regulation has dominated research on emotional development in the last decade, despite problems in definition and operationalization (Thompson, 1994). The research and theorizing of Posner and Rothbart (e.g., 2000) provided much needed focus in this area. They argued that maturation of the anterior attentional network permits effortful regulation of behavior, including emotional behavior. In line with these predictions, Kochanska, Murray, and Harlan (2000) have shown that children who perform better on tasks designed to assess effortful control also are better at suppressing both positive and negative emotional expressions.

Effortful regulation of behavior, nonetheless, undoubtedly involves multiple neural systems; thus, these studies provide only the first insights into the neural bases of self-regulation and its development. Presumably, as the child develops an increasing ability to regulate emotions, she should also become increasingly capable of regulating physiological stress reactions (Stansbury & Gunnar, 1994). This assumption is speculatively based on several arguments. First, with the development of the anterior attentional network, the child should be able to engage the cognitive component of the anterior cingulate cortex, thus suppressing activity of the emotional component (Bush, Luu, & Posner, 2000). This should help inhibit and constrain the reactivity of limbic components of the stress system. Second, to the extent that emotion regulation also involves increased activity in the left prefrontal

cortical regions, the child should become increasingly capable of using positive affect and approach-oriented behavioral strategies for managing potentially stressful situations (Davidson & Irwin, 1999). Third, the ability to regulate negative emotions should foster social competence and better social relationships with peers and adults. This ability, in turn, should enhance the child's opportunities to use positive and supportive social relationships to cope with stressful situations. Social competence should also reduce the likelihood that the child's behavior will create stressful interactions with others (for review, see Gunnar, 2000).

There is growing evidence in support of the above hypotheses in research involving preschool-aged children (for review, see Gunnar, 2000). However, consistent with the role of the HPA axis in energy mobilization, studies report both positive and negative associations between cortisol levels and reactivity as a function of the context of measurement. When cortisol is measured while children engage in challenging tasks that require effortful regulation of behavior, moderate increases in cortisol followed by a rapid return to baseline have been positively associated with measures of executive function and teacher reports of the child's self-regulatory competence (Blair, Granger, & Razza, 2006). In this study, executive functioning scores mediated the relation between cortisol reactivity and self-regulatory competence, and it was children who showed falling levels of cortisol over the assessment period who exhibited both poor self-regulatory competence and lower executive functioning scores. Similar positive correlations were obtained between parent reports of children's attention focusing and inhibitory control with preschoolers' cortisol responses to a frustrating task in which an adult fails to share candy equally with the child (Spinrad et al., 2009). On the other hand, there is also evidence that when acutely challenging tasks are not involved and predictions are to the regulation of cortisol under more chronic conditions, higher scores on measures of effortful control (i.e., attention focusing and inhibitory control) tend to be associated with a more modulated, less frequently activated HPA axis among preschoolers (e.g., Dettling, Gunnar, & Donzella, 1999) and a more mature diurnal cortisol rhythm (Watamura, Donzella, Kertes, & Gunnar, 2004). What we still need are studies examining developmental changes in cognitive and behavior regulatory processes and the young child's ability to modulate activity of stress-mediating systems under different conditions of challenge.

The prenatal period and early childhood years are critical in the organization of stress and emotion systems, as the organism is receiving a multiplicity of inputs from the environment, ranging from intrauterine exposure to glucocorticoids to complex social exchanges with caregivers. We have discussed evidence that some of these experiences may have programming effects and shape certain patterns of reactivity later in life. However, we must emphasize that the organization of stress and emotion systems does not end in early childhood. In the next two sections, we discuss the recalibration of stress and emotion systems during middle childhood and adolescence, under the influence of cortical and hormonal transformations. While these later developmental periods are not the main focus of this chapter, they are important to mention in order to maintain perspective on the massive opportunities for retuning stress and emotion systems later in life.

Middle Childhood

Based on evolutionary theory, Del Giudice, Ellis and Shirtcliff (2010) recently proposed the Adaptive Calibration Model of stress responsivity, according to which middle childhood should be a period during which the stress system is recalibrated in accordance to differential life history strategies for males and females. In part, the argument is based on the rise in adrenal androgens in middle childhood, which, they argue, underlies the increasing sexual differentiation of both the nature of what provokes stress responses and the physiological and behavioral systems that regulate stress-mediating systems. While set in place during middle childhood, they argue that puberty will further enhance these differences. This provocative theory promises to stimulate focus on middle childhood, adrenal androgens, and sex differences in stress reactivity and regulation. As yet, however, these studies await being conducted. Most of what we know about stress reactivity and regulation in middle childhood comes from studies examining relations between stress responding and children's behavioral and emotional problems.

Of particular note are an increasing number of studies examining both sympathetic and HPA activity. These studies suggest that by middle childhood these systems have become coordinated such that SNS activity serves to moderate relations between cortisol and behavior problems (see Bauer, Quas, & Boyce, 2002). For example, in one study of 8- and 9-year-old children (El-Sheikh, Erath, Buckhalt, Granger, & Mize, 2008), higher basal cortisol levels were associated with more internalizing and externalizing problems, but this was among children with higher but not lower SNS activity. Notably, no sex differences were noted along with this pattern.

Adolescence

Adolescence—and more specifically puberty—has been recognized as a period of radical social, emotional, and physical changes, which are also accompanied by an increased vulnerability to stress, mental disorders, and risk-taking behaviors (Dahl & Gunnar, 2009). Adolescence is also a sensitive period for brain development, when synaptic pruning occurs at a higher rate and cortico-limbic circuits reorganize, under the influence of gonadal and adrenal hormones, as well as that of psychosocial stressors (Andersen & Teicher, 2008). The protracted development of the PFC, which plays a key role in the regulation of emotion but which does not reach full maturity until mid-20s, combined with an increased emotional reactivity during adolescence, may lead to behavioral and mood dysregulation during this period. Specifically, the dramatic increase in the prevalence of depression, particularly in females, has drawn a lot of attention to the study of stress reactivity during this period (Andersen & Teicher, 2008).

Several studies have used experimental laboratory stressors to examine physiological reactivity during the pubertal transition, and they all provide evidence of increased stress reactivity from childhood to adolescence. Using a social-evaluative task (the Trier Social Stress Test for Children), Gunnar, Wewerka, Frenn, Long, and Griggs (2009) found an increase in cortisol output in response to social threat between the ages of 9 and 15, with cortisol increases being marginally correlated with sexual maturation. Furthermore, Stroud et al. (2009) also found an increase in cortisol responses to the same social stress task, but these responses were not reflected in the activity of the SAM system, as indexed by salivary alpha amylase. Despite a consistent pattern of results, the effects reported in these studies were relatively modest. Based on a similar study of 9- to 17-year-olds undergoing a public speaking task, Sumter, Bokhorst, Miers, Van Pelt, and Westenberg (2010) provided evidence that differences in cortisol production during the prestressor anticipatory period are stronger than differences in levels measured during the task. Stress reactivity during the anticipatory period increased with age and pubertal stage, as well. Future research should examine the meaning of these increased differences during the anticipation period. Researchers speculate that cognitive maturity may be an important component of the observed differences between children and adolescents. Furthermore, few studies have tried to disentangle age and puberty in the examination of stress and emotion during adolescence (for an exception, see Quevedo, Benning, Gunnar, & Dahl, 2009). Given the public health implications of adolescent behavioral and mental health problems, more research is needed to clarify the origins of these developmental changes in stress and emotional reactivity.

Individual Differences

Developmental research has made tremendous progress in moving beyond simple nature-versus-nurture conceptualizations of the origins of individual differences in stress reactivity. It is now recognized that temperamental predispositions, early experience, and genetic or epigenetic characteristics of the organism all interact dynamically with the current context, resulting in adaptation or maladaptation. This view regards differences not as entities that reside within individuals, but as differential patterns that emerge from the interaction between a person and the context. With respect to individual differences in stress reactivity, two recent theories—Biological Sensitivity to Context Theory and Differential Susceptibility Theory (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011)—converge on the argument that the valence of stress reactivity is not necessarily negative. Rather, different patterns of physiological responses to stressors are adaptive in different contexts. While empirical evidence for the fact that high stress reactivity can be beneficial in certain contexts still needs to be amassed, the theory does emphasize the importance of the match or mismatch between individual characteristics and context. In this section we discuss research addressing individual characteristics (e.g., temperamental predispositions or genetic makeup) and contextual factors such as caregiving relationships that may shape stress reactivity throughout development, with a special emphasis on studies that highlight person $\times$ context interactions.

Stress and Temperament

Studies of stress and temperament have often focused on behavioral inhibition (shyness) as a potential diathesis for anxiety disorders and overactive stress physiology. Behaviorally inhibited children display strong fear reactions to unfamiliar stimuli, and this has been hypothesized to be due to heightened excitability of limbic circuits, particularly the CEA (Kagan & Snidman, 1991). Recent evidence has provided support for this theory, with one study showing greater fMRI (functional magnetic resonance imaging) amygdala activation to novel versus familiar faces in adults who had been identified as behaviorally inhibited in infancy (Schwartz, Wright, Shin, Kagan, & Rauch, 2003). Nevertheless, given the integrated nature of cortico-limbic

circuits, it is not clear whether variations in amygdala function are necessarily causal to the behaviorally inhibited phenotype. For instance, one recent study has linked variations in the CRH gene to behavioral inhibition and risk for panic disorder in children (Smoller et al., 2005), suggesting that other brain regions containing CRH receptors may also function differently in behaviorally inhibited children and that amygdalar CRH may not be the only pathway to a fearful temperament.

Understanding the biological underpinnings of behavioral inhibition has benefited from studies incorporating measures of heart rate, cortisol, startle amplitude, and EEG in children displaying this behavioral profile (Fox, Henderson, Marshall, Nichols, & Ghera, 2005). Some studies show shorter heart periods (higher heart rate) and stronger heart rate acceleration in response to stressors in this population (Fox et al., 2005), but this profile is not always reliably found. It has been suggested that studies selecting the most extremely inhibited and uninhibited children may be more likely to show these effects (Fox et al., 2005).

With respect to cortisol levels, findings are also more nuanced and mixed than the straightforward prediction that behaviorally inhibited children would show higher cortisol reactivity. Some researchers found behavioral inhibition to be related to high basal cortisol (Kagan, Reznick, & Snidman, 1987), and social reticence at age 4 to be related to higher early morning cortisol (Schmidt et al., 1997), whereas others found that an increased cortisol response to starting preschool was associated with more assertive, angry, or aggressive behavior (de Haan, Gunnar, Tout, Hart, & Stansbury, 1998). These mixed findings could be understood by taking context and self-regulatory strategies into consideration: Children who are inhibited may disengage during activities that would elicit cortisol elevations (e.g., by withdrawing from social interactions), but show higher cortisol responses compared to their less fearful counterparts if they must participate (Gunnar, Tout, de Haan, Pierce, & Stansbury, 1998). Another pathway from temperamental predispositions to HPA axis activation has implicated peer relations, with evidence that exuberant and under-controlled children may be more likely to experience peer rejection and cortisol elevations (Gunnar, Sebanc, Tout, Donzella, & van Dulmen, 2003). Thus, behavioral inhibition is not necessarily in a linear relationship with HPA axis activation, as both fearful and exuberant children can reach the same physiological endpoint. Furthermore, a recent study showed that behavioral inhibition and cortisol elevations in day care interact to predict later internalizing symptoms in preschoolers, such that behaviorally inhibited children that exhibit cortisol elevations in day care express more internalizing symptoms over time, but decreasing levels of symptoms if they have lower cortisol activity (Gunnar, Kryzer, van Ryzin & Phillips, 2010).

In attempts to understand the underlying neurobiological differences between extremely inhibited and uninhibited children, researchers have also examined more direct indices of the forebrain systems presumably involved in fearfulness and negative emotionality. To this end, startle amplitude, a measure presumably mediated by the CEA, has been employed in several studies. At 9 months, infants selected at 4 months for extreme negative reactivity have been shown to exhibit larger startle reactions during stranger approach. Tested again at 4 years, however, larger startle amplitudes were not found for these children, although at this older age only baseline startle was examined, and this might not reflect the same underlying neural circuits (Schmidt et al., 1997).

Additionally, several studies have linked behavioral inhibition and negative emotionality to asymmetrical frontal EEG activation—specifically, to decreased alpha power in the right frontal region, which signifies increased activation of withdrawal systems (Fox et al., 2005). More broadly, individual differences in baseline asymmetry in activation have been linked to dispositional affective style (Davidson, 2002). It must also be noted that children who show longitudinal continuity in extreme behavioral inhibition are also the ones most likely to display and retain EEG asymmetry over time (Fox, Henderson, Rubin, Calkins, & Schmidt, 2001), whereas children who become less inhibited over time may not show this pattern.

Overall, none of the physiological biomarkers of stress reactivity discussed above bear one-to-one relationships with specific temperamental profiles or emotions. Often times, behavioral states and biological stress markers become dissociated (Quas, Hong, Alkon, & Boyce, 2000). We suggest that this is because context and the resources children need to cope with challenge are moderators of the relations between temperament and the activity of these stress-sensitive physiological systems. Furthermore, children who may look similar in terms of behavioral indices of temperament may differ dramatically in their genetic characteristics, which interact with environmental inputs to shape unique stress response profiles. In the next section, we discuss some of the recent findings examining candidate genes that may modulate stress reactivity, a line of research that has burgeoned in the past decade.

Genetic Polymorphisms and Stress Reactivity

The search for genes that may confer vulnerability for mental disorders in psychiatry has resulted in an increased

attention to genetic diversity in developmental science as well. Perhaps because main effects of genes have proven difficult to find, basic scientists have begun to explore gene-by-environment interactions and to envision developmental trajectories to maladaptive outcomes, rather that deterministic models of disorder. The activity of stress systems has long been associated with the development of psychopathology (e.g., a vast 40-year literature linking depression to altered HPA axis activity, reviewed in Pariante & Lightman, 2008). Thus, the search for genes that may influence stress reactivity has been a logical starting point for many gene-by-environment studies attempting to understand the development of psychopathology. However, the future challenge will be to integrate gene-environment studies with neuroscience and psychology (Caspi & Moffitt, 2006) and to create developmental theories of how specific environmental risk factors and genotype variations interact over time to produce alterations in brain and behavior function.

The most highly studied genetic polymorphisms purportedly associated with behavioral outcomes have been those linked to the gene coding for the serotonin transporter (5-hydroxytryptamine, 5-HT)—a protein that regulates the serotonin concentration in synaptic clefts and extrasynaptic sites, which was first linked to anxiety behaviors in humans by Lesch et al. (1996) and has since been associated with a wide variety of psychological outcomes, such as depression, anxiety, aggression, and the like. (Murphy et al., 2008). Caspi and associates' (2003) seminal findings (and similar results in Eley et al., 2004, Kaufman et al., 2004) that variations in the promoter region of the serotonin transporter gene moderate the relationship between stressful life events and adult depression have been revolutionary, but recent meta-analyses also highlight failures to replicate the initial findings (Munafo, Durrant, Lewis, & Flint, 2009; Risch et al., 2009). However, animal models suggest that the relationship between serotonergic function, early adversity, and maladaptive outcomes in adulthood should not yet be dismissed. Rhesus monkeys with a functionally equivalent version of the human short 5-HTTLPR allele who experience poor early care (peer rearing) have been shown to produce higher levels of ACTH in response to stress (Barr et al., 2004).

There are currently two competing theories of the role of the serotonin transporter gene. One theory views it as a vulnerability factor which acts by conferring altered sensitivity to stress (Caspi et al., 2010), whereas Way and Taylor (2010) have advanced the serotonergic social sensitivity hypothesis, suggesting that 5-HTT modulates receptivity to both positive and negative social experiences, since they showed that individuals with the short allele and positive social experiences were less likely to develop depressive symptomatology than individuals with the long/long combination. Few studies have tested these theories empirically, but one recent finding provided support for the vulnerability position, showing that children with at least one short allele were more likely to develop insecure attachment in an environment with low parental sensitivity, whereas children homozygous for the long allele seemed to develop secure attachment under both high and low sensitivity conditions (Barry, Kochanska, & Philibert, 2008). However, this was a small and low-risk sample, which also tended to have higher than average maternal sensitivity. No main effect of the 5-HTT gene on attachment security has been identified in studies thus far (Gervai, 2009), and future studies will be needed to begin to test these competing theories.

The serotonin transporter gene may interact not only with environmental factors, but also with other genes. It has also been suggested that the brain-derived neurotrophic factor (BDNF) gene may sensitize individuals to a risk for depression, if both maltreatment and at least one short copy of the serotonin transporter gene are also present (Kaufman et al., 2006). This finding has failed to replicate in a larger sample of adolescents (Nederhof, Bouma, Oldehinkel, & Ormel, 2010), suggesting caution in prematurely accepting G $\times$ E results.

Additionally, a functional polymorphism in the promoter region of the monoamine oxidase A (MAOA) gene, which results in low levels of the MAOA enzyme, has been shown to moderate the relationship between childhood maltreatment and the development of conduct disorder or antisocial personality disorder, providing an explanation for the diversity of outcomes observed in cases of childhood physical abuse (for a meta-analysis, see Kim-Cohen et al., 2006).

The genetic polymorphisms described above all interact with life stressors to predict negative outcomes, but the role of the HPA axis in the underlying pathways is not always clear, as these genes do not directly control the structure and function of the axis (though they shape neural circuitry that communicates with the axis). There is, however, a growing body of research that investigates genetic polymorphisms that directly affect components of the L-HPA axis. For instance, a recent study showed that the single-nucleotide polymorphism (SNP) FKBP5 rs1360780, which modulates GR sensitivity and plays an important role in negative feedback, interacts with insecure-resistant attachment to predict heightened cortisol reactivity in infants (Luijk et al., 2010). Furthermore,

Binder and associates (2008) found that this SNP moderated the relationship between childhood abuse and the development of adult posttraumatic stress disorder. Additionally, the CRH receptor gene (CRH-R1) moderates the relationship between childhood maltreatment and the development of adult depression (Grabe et al., 2010). The large number of genes regulating the activity of the HPA axis may all play a role in shaping psychological outcomes. Thus future studies will need to incorporate increasingly complex models that include interactions between several genes, as well as dynamic models of the activity of the axis under the genetic control of these diverse influences.

The G × E and G × G × E interaction effects discussed above are remarkable, but several questions remain to be answered by future research, such as a) what is the activity of these genes, and what are the specific mechanisms through which they influence brain function and structure? b) how do psychosocial factors like maltreatment infiltrate the body and interact with molecular processes? c) how do various genes operate in relation to each other? d) are there critical periods during which these genes–environment interactions trigger the maladaptive outcomes, or is the process not time- and development-sensitive? and finally, e) are the negative psychological outcomes investigated in these G × E studies reversible?

Stress and Caregiving Relationships

Animal models have shown that maternal caregiving behavior shapes the infant's stress reactivity by influencing the development of neural systems which underlie stress responses (Caldji et al., 1998; Meaney & Szyf, 2005). It is likely that early parental behavior influences stress reactivity through several mechanisms. One of these is that caregiving behavior seems to have direct stress-regulatory effects. In rodents, dams that show high levels of licking and grooming have rat pups which display fewer fearful behaviors in adulthood, compared to low-licking and grooming dams. A number of neurobiological changes accompany these differences in fear reactions, including more rapid containment of the HPA stress response, less evidence of CRH activity in the CEA, BNST, and LC, and decreased NE in response to psychosocial stressors (Caldji et al., 1998). At a molecular level of analysis, these changes have been linked to an increased methylation of GR genes in the hippocampus in pups with low-licking and grooming mothers (Meaney & Szyf, 2005). Methylation of GR genes in the hippocampus leads to a less efficient negative feedback of the HPA axis, as circulating glucocorticoids typically bind to these receptors in the hippocampus and trigger an inhibition of HPA axis activity. What is remarkable about these findings is that natural variations in maternal care seem to be sufficient to cause these alterations in stress reactivity.

There are many other pathways through which parental behavior impacts stress reactivity. For instance, it can be a source of chronic stress, as in the case of early abuse models. Thus, parents can potentially program stress neurobiology through more general mechanisms, such as exposing their offspring to repeated, uncontrollable stressors. Conversely, parental caregiving behavior can prevent infants from experiencing stressors in the first place, by providing contingent responses to their basic needs. The importance of this indirect buffering mechanism is evident in cases where it is absent—for example, chronic parental neglect, both in human and animal models. Before reviewing childhood studies of early caregiving and stress function, a brief glance at the adult literature is necessary to highlight some of the intriguing findings that will require a developmental explanation.

Social support has long been recognized as a moderator of life stress and a protective factor against physical and psychological illness in adulthood (Cobb, 1976; Taylor, 2007). Epidemiologists have acknowledged the crucial role of social and community ties in predicting longevity and overall health, above and beyond specific disease risk factors (Berkman & Syme, 1979). More recent research has started to investigate the psychological processes and neurobiological mechanisms that may underlie this social buffering effect in adults, with evidence that social support may protect individuals from the activation of stress systems (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Kirschbaum, Klauer, Filipp, & Hellhammer, 1995; Taylor et al., 2008). Experimental studies have shown that the presence of a supportive significant other can dampen the production of cortisol in response to a social-evaluative stressor (Kirschbaum et al., 1995), an effect that is amplified by the intranasal administration of oxytocin (Heinrichs et al., 2003). This effect has also been demonstrated in children, with one recent study showing that physical or phone contact with the mother increases oxytocin production and decreases cortisol reactivity to a similar laboratory stressor in girls aged 7–12 (Seltzer, Ziegler & Pollak, 2010). Social support seems to not only dampen neuroendocrine stress responses through the anxiolytic effects of oxytocin, but throughout development it may also become an internalized resource that promotes self-esteem and effective coping with stressors. In an MRI study of individuals undergoing a similar type of social-evaluative threat, psychosocial resources (defined

as positive self-esteem, optimism, and extraversion) predicted lower cortisol reactivity, which was mediated by lower amygdala activation during a different threat regulation task (Taylor et al., 2008). Furthermore, individuals high in psychosocial resources displayed greater right ventro-lateral PFC activation during this task. Future research will need to elucidate the relationship between social support, psychosocial resources, and the more effective containment of stress responses through increased PFC activity and decreased amygdala activation.

The social regulation of stress response systems more likely begins very early in life (Gunnar & Donzella, 2002). As early as 3 months after birth, maternal sensitivity and cooperation during a mild everyday stressor like a bathing routine predicts infants' poststressor cortisol recovery (Albers, Riksen-Walraven, Sweep, & de Weerth, 2008). In young children, studies of the quality of mother-infant attachment have yielded evidence that secure attachment relationships function to regulate the activity of stress-sensitive systems (see review by Gunnar, 2000). For instance, attachment security moderates the relationship between behavioral inhibition and cortisol responses to a novel stimulus in 18-month old infants (Nachmias et al., 1996). Furthermore, behavioral indices of distress or inhibition appear to be associated with heightened cortisol responses only when infants and toddlers are tested in the presence of a parent with whom they have an insecure attachment relationship (e.g., Spangler & Schieche, 1998). Other evidence indicates that securely attached children are buffered from cortisol elevations during an adaptation phase (having mother present) in the transition to child care (Ahnert, Gunnar, Lamb, & Barthel, 2004). Even though all children show elevations in cortisol when entering child care, it is informative that mother's presence has a protective role for the infant in the context of having a secure attachment history. It is important to note that attachment insecurity may interact with the genetic characteristics of the child to create an increased vulnerability to stress. For instance, having the short allele for the 5-HTT gene or the CC allele for the GABRA6 gene interacts with insecure attachment to predict higher salivary alpha amylase levels (an index of sympathetic nervous system activity) during a Strange Situation procedure (Frigerio et al., 2009).

Attachment insecurity is not the only variation in caregiving that is associated with less than optimal stress reactivity patterns. Recent evidence indicates that attachment disorganization is also associated with increased cortisol output during the Strange Situation compared to play episodes (Bernard & Dozier, 2010).

Assessing attachment beyond the infant and toddler years is challenging, but some studies suggest that the patterns observed in infancy continue later in childhood. For instance, 5-year-old children who experience negative parent-child interactions not only produce stories deemed "insecure" when using parent and child doll props, but they also show cortisol elevations during these tasks (Smeekens, Riksen-Walraven, Van Bakel, & de Weerth, 2010), suggesting that their symbolic play may recapitulate some of the stress they experience in the home due to parent unavailability and unresponsiveness.

The findings above illustrate the fact the normal variations in caregiving are sufficient to create differences in the regulation of stress systems. In addition to these findings, animal models of early adversity (Sanchez, 2006) and studies in humans (Cicchetti & Valentino, 2007) also show that neglect, deprivation or maltreatment influence the developing stress systems. We first review evidence from studies of children experiencing severe deprivation of adequate caregiving early in life, then discuss processes related to maltreatment.

The absence of adequate parental care early in life has been associated with atypical or dysregulated patterns of stress reactivity. Both institutionalized and foster care children have been shown to display disturbances in HPA axis function. Carlson & Earls (1997) were the first to report that toddlers living in an institution in Romania had exceptionally low early morning cortisol levels and a flatter cortisol slope across the day, which seemed counterintuitive at first. It is now understood that blunted cortisol patterns are often a signature of chronic stress, since chronic elevations in GCs lead to down-regulation over time. The same findings have also been observed for children in a Russian orphanage (Gunnar, 2001). However, by 6–7 years after being adopted into benevolent families, children from this population tend to exhibit elevated basal cortisol levels (Gunnar, Morison, Chisholm, & Schuder, 2001). It is not clear that the absence of adequate caregiving is the only operative factor, since early deprivation co-occurs with many other prenatal and postnatal risk factors. However, animal models discussed above can be used as converging evidence that caregiving is at least one of the factors that contribute to abnormal patterns of stress reactivity.

Similar disturbances in the cortisol rhythm have been reported in several recent studies of infants and preschoolers in foster care. Dozier et al. (2006a) found disturbances of basal cortisol rhythms in up to 65% of infants in foster care, with many of these children exhibiting abnormally low morning levels. Additionally, preschoolers entering a

new foster placement have been shown to exhibit similar patterns, with review of their records showing that the severity of experienced neglect predicts this atypical diurnal pattern (Bruce, Fisher, Pears, & Levine, 2009). In both instances, interventions designed to enhance parenting by foster parents appears to either normalize cortisol levels (Dozier et al., 2006b) or prevent the development of atypical diurnal patterns (Fisher, Stoolmiller, Gunnar, & Burraston, 2007).

Of course, the situations that result in maltreatment and foster placement are complex. Any of a number of factors beyond caregiver-infant interaction, including lack of adequate stimulation, malnutrition, and inadequate medical care might be involved in producing alterations in the development of the stress system. Nevertheless, research has begun to isolate and identify the dysregulating effects of different types of maltreatment on neuroendocrine and behavioral systems (Cicchetti & Valentino, 2007). Experiencing early physical and sexual abuse is associated with higher levels of internalizing symptoms, as well as flatter diurnal cortisol slopes (Cicchetti, Rogosch, Gunnar, & Toth, 2010). Furthermore, studies of adult international adoptees that have experienced early life neglect or abuse also show blunted levels of morning cortisol and flatter diurnal slopes (van der Vegt et al., 2009). These altered hormonal patterns, as well as the mood and anxiety symptoms present in this population have been theorized to be linked to alterations in CRH and GC activity (Heim & Nemeroff, 2001).

However, not all prior findings report evidence of blunted HPA axis activity. Several studies found evidence of elevated cortisol production in maltreated children who have developed posttraumatic stress disorder subsequent to their trauma (Carrion et al., 2002; De Bellis et al. 1999). It may be the case that concurrent trauma in childhood is associated with elevations in cortisol production, but with time and development, blunted patterns of reactivity may emerge due to down-regulation at several levels of the HPA axis, which would explain some of the patterns observed in adults who experienced early life abuse or neglect (e.g., van der Vegt et al., 2009 discussed above). Despite these speculations, there is a significant unexplained gap between the maladaptive patterns observed with maltreated/neglected children and those noted with adult survivors of these unfortunate experiences. Future work in this area will need to study children who experience abuse or neglect in a continuous longitudinal fashion, in order to clarify the development of these dysregulated neuroendocrine and biobehavioral patterns.

CONCLUSIONS

The last several decades have seen tremendous advances in our understanding of the neurobiology of the human stress system. Research on the development of stress reactivity and regulation in infants and children has burgeoned in recent years due largely to the development of noninvasive measurement techniques. However, we are still far from understanding the processes through which individual differences in stress responses become organized. Repeatedly throughout this review we have noted where basic information is lacking. Much of this information involves normative data on the organization of stress reactivity and regulation at different points during early development. As in the study of emotional development more generally, we have much more information about individual differences in stress reactivity than we do about normative patterns of development and change. However, unless we develop this latter body of knowledge, it will be difficult to explicate the origins of individual differences in stress reactivity and regulation.

Recent research investigating interactions between variations in genotype and environmental characteristics is beginning to shed light on some of the origins of individual differences in stress reactivity. Future work will need to use multiple levels of analysis (genetic, neuro-hormonal, behavioral, etc.) to elucidate the functional roles of genes and how they specifically impact neurobehavioral development. Meanwhile, studies of caregiver-child interactions indicate that qualities of care, including sensitivity and responsiveness, are related to reactivity and regulation of the stress system in infants and young children. Social support is a powerful natural stress buffer, and future interventions aiming to promote stress resilience or to reduce stress vulnerability will likely involve the effective deployment of social relationships, perhaps most effectively in early childhood. Understanding the underlying neurobiology of the stress-buffering effects of social support will be a powerful tool for advancing child welfare, as well as for promoting physical and mental health across the lifespan.

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