CHAPTER 4

Psychoneuroendocrinology of Stress

Normative Development and Individual Differences

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Acknowledgments: This research was supported by Grants MH080905 and MH078105 to Megan R. Gunnar. Jenalee Doom is supported by NIMH Training Grant MH015755 and Elisa Esposito is supported by NICHD Training Grant HD00715.

CHAPTER OVERVIEW

Developmental psychology is rapidly becoming a neuropsychobiological field. No longer are we satisfied with documenting developmental trajectories of cognitions,

emotions, and social behaviors, nor are we satisfied with describing and theorizing about how children's transactions in the world influence development. To all of these still critical foci of developmental science, we have added goals of understanding how the genes we are born with, the experiences we have that overlay those genes with chemical marks that control their expression (epigenome), and the physiological responses in our brains and bodies all come together to write the story of our lives. Nowhere is the importance of a multilevel, multidisciplinary, genes-to-society perspective more apparent than in the study of stress and its role in development.

To be fair, the study of stress has always been a psychobiological field from the time Selye first used the term to refer to the body's response to threats to its viability (Selye, 1946). While Selye was focused on physical threats, it quickly became apparent that psychological threats were as potent and often more potent than physical damage to the body in activating stress responses (e.g., Dickerson & Kemeny, 2004). Nonetheless, in developmental psychology the study of the effects of stressful life conditions on children continued for many years as a purely psychological endeavor. An interest in biology and neurobiology entered this part of our field first from biological psychiatry and then in the then-emerging field of developmental psychopathology (see review, Gunnar & Vazquez, 2006). Temperament researchers also brought an interest in stress biology into the field somewhat indirectly through their interest in how mildly threatening events sorted children along a dimension of fearfulness or behavioral inhibition that was reflected in their autonomic and neuroendocrine reactions (e.g. Kagan, Reznick, & Snidman, 1987). However, it was the advent of noninvasive salivary assays for the key stress hormone cortisol that broadly opened the field to questions about the development and regulation of stress biology and how the biology of stress interacts with the child's genetic makeup and experiences to affect the development of our physical and psychological well-being (see review, Gunnar & Vazquez, 2006).

This chapter is about the state of the art in our understanding of the multilevel processes that are involved in how we deal with stressors, how these processes change with development, and how the activity of stress-mediating systems during childhood and adolescence affects our health and functioning. As discussed herein, there are multiple systems that mediate the impact of stress on development; however, the key system from a developmental perspective is the hypothalamic-pituitary-adrenocortical (HPA) system. The sympathetic-adrenomedullary (SAM) system undergirds the fight-or-flight response to threats, but its catecholamine products, epinephrine and norepinephrine (NE) do not cross the blood brain barrier. In contrast, cortisol, the HPA's product, is a steroid hormone that acts in all parts of the body, with the brain being a primary target for its actions. Cortisol is a gene transcription factor, meaning that it changes the expression of numerous genes. It plays a major role in early development, and the genes it regulates are critical to neural plasticity. Thus, this neuroendocrine system is a developmentalist's dream: not so much a window on what a person is thinking and feeling but a door through which experiences get under the skin and affect development. It is for this reason that, although we discuss both the sympathetic and parasympathetic nervous systems, this chapter is focused on the HPA system. Sadly, readers will find that although it is a developmentalist's dream, it is also a researcher's nightmare because like any neuroendocrine system, the system rapidly adjusts to conditions that provoke its activation. Therefore, as is explained herein, stress is associated with both high and low levels of cortisol production.

In addition, although stress is often construed as something bad, stress is a ubiquitous part of life. Thankfully, not all children experience unpredictable, uncontrollable, chronic stress, which can be toxic to development, but many do and we need to understand individual differences in the impact of this type of stress in order to promote greater resilience and recovery for its victims. All children, however, experience stress as part of their everyday existence. From the impact of infections or cuts and abrasions, which trigger immune reactions that activate the HPA axis, to the threat of social exclusion, failing a test, or flubbing one's lines in a play, there are numerous opportunities in every child's life for stressors to affect development and the effects are often positive. Learning to cope with mild threats to our physical and social selves is an aspect of development that is critical for resilient functioning. As we have known for a long time, it is not so much the actual event as an individual's construal of the event that determines how stressors affect that individual (Lazarus & Folkman, 1984). As we learn to cope with mild to moderate threats, both our bodies and our psyches perceive threats as more manageable and thus we become more resilient to life's hassles and roadblocks. What the field is beginning to show is that multiple neurobiological systems interact with the stress system at different points to mediate the effect of stressors on stress vulnerability and resilience. Understanding how these systems interact is critical to appreciating the role of stress in human development.

The complexity of the neurobiology and psychobiology of stress dictated the choice of topics and construction of this chapter. Nearly 20% of the chapter is devoted to anatomy and physiology, including genetics. Although much of the description is not developmental, our emphasis reflects the critical importance of understanding the physiology of stress in order to use its study to decipher the effects of stress on development. After this we take up a very brief discussion of normative development. Understanding normative processes as they are revealed in relatively low-stress developmental contexts is critical to interpretation of effects of stress in high-stress developmental contexts. We then turn to a discussion of theory. Until recently, there has been no theory devoted to a developmental analysis of stress, although nondevelopmental theories have been applied to children and adolescents. We consider what is currently available and argue that what we have is not yet adequate. The bulk of the chapter is devoted to a key issue in the study of stress and human development. Specifically, what evidence do we have that adversity during children's development affects the neurobiology of stress and stress-induced mental and physical health outcomes through stress-mediating systems? As our discussion of temperament reveals, an equally important question is whether individual differences in temperament are critical moderators of the effects of stress on developmental trajectories. The discussions of both adversity and individual differences lead to the final section on whether vulnerability to mental disorders is reflected in and/or created by aberrant activity in stress-mediating systems.

Throughout this review we were challenged by the fact that the field of stress and development has burgeoned in the past decade. Furthermore, our review crosses multiple fields: genetics, neurobiology, developmental psychology, biological psychiatry, and developmental psychopathology. Given limited room for references, we were forced to only provide examples of relevant research, relying on reviews whenever we could. We have tried, whenever possible, to acknowledge at least one paper from each of the active laboratories in hopes that readers can then track down other important work from these laboratories. It is a sign of the robustness of this research area, however, that in the past decade publications on stress biology and development have moved from specialty journals into journals that rarely used to publish papers with biological measures other than perhaps heart rate. As more readers encounter work on the biology of stress, it is essential that they have a reasonably sophisticated understanding of that biology. Thus, it is to the anatomy and physiology of stress that we now turn.

HYPOTHALAMIC-PITUITARY-ADRENAL ANATOMY AND PHYSIOLOGY

There are a number of reviews of HPA anatomy and physiology (e.g., Gunnar & Vazquez, 2006; Joëls & Baram, 2009; Levy & Tasker, 2012). Here, we briefly summarize.

The Hypothalamic-Pituitary-Adrenal Axis

Cortisol (CORT), a glucocorticoid hormone, is produced by the adrenal cortex following a signaling cascade initiated in the paraventricular nucleus (PVN) of the hypothalamus (see Figure 4.1). These cells release the neuropeptides corticotropin-releasing hormone (CRH) and arginine vasopressin. These releasing hormones travel to the anterior pituitary where they bind to corticotropic cells signaling the cleavage of a large pro-hormone into adrenocorticotropic hormone (ACTH) and several endorphins and melanin-stimulating hormones. ACTH is then released into circulation and binds to receptors in the cortex of the adrenal gland stimulating CORT production. Finally, CORT is secreted into the circulation, acting on its receptors throughout the body. The mature adrenal cortex consists of three regions: one producing aldosterone, a salt-water regulating hormone, one producing dehydroepiandrosterone (DHEA), an androgen with anabolic effects that increases in advance of puberty and also responds to ACTH, and the zone that produces CORT.

Mineralocorticoid Receptor and Glucocorticoid Receptor

Two receptor types, mineralo- and glucocorticoid receptors (MRs and GRs), bind CORT. CORT will bind first to MRs, unless, as is the case outside the brain, the MRs are protected from CORT by an enzyme barrier (11β-HSD2) that converts CORT into an inert substance (Wyrwoll, Homes, & Seckl, 2011). GRs are occupied as MRs become less available or where they are not present to compete with GR. Throughout the brain, GRs become involved at the peak of the circadian cycle or during stress responses. GRs mediate the genomic stress actions of CORT, while MRs in the brain mediate basal genomic actions (see for review, Gunnar & Vazquez, 2006).

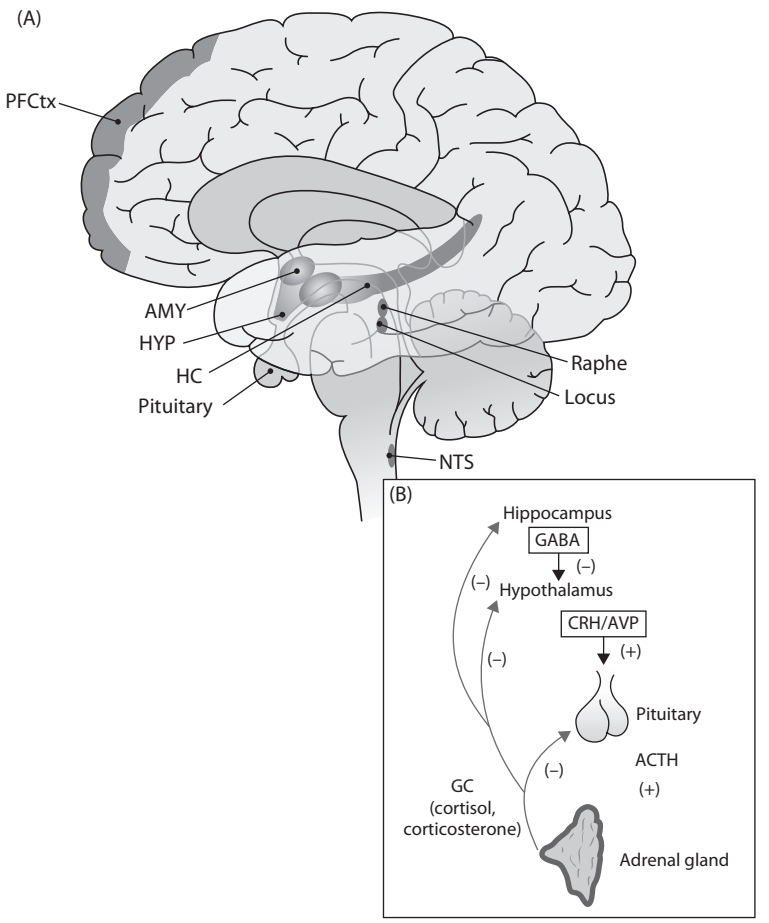

Figure 4.1 The HPA System. Panel A depicts the anatomy of the HPA system and structures important in its regulation. Panel B depicts the activation (+) and negative feedback inhibition (−) pathways of the HPA system.
Panel A: PFCtx = prefrontal cortex, AMY = amygdala, HYP = hypothalamus, HC = hippocampus, NTS = nucleus of the tractus solitarius.
Panel B: GCs = glucocorticoids, cortisol and corticosterone, GABA = gamma animobutyric acid, CRH = corticotropin-releasing hormone, AVP = arginine vasopressin, ACTH = adrenocorticotropic hormone.

Source: Reprinted with permission from Gunnar and Vazquez (2006).

Once released into circulation 80%–90% of CORT becomes bound to cortisol-binding globulin, which prevents it from interacting with its receptors. The unbound CORT, being lipid soluble, enters freely into all cells of the body. In the cell's cytoplasm, CORT binds to its receptors. Receptor binding is mediated by chaperones. Heat shock protein 90 (Hsp_{90}) facilitates CORT binding to its receptors, while a co-chaperone, FK506 binding protein 5 (FKBP5), decreases this affinity (Heim & Binder, 2012). As will be discussed, FKBP5 plays an important role in stress vulnerability and resilience. Once the hormone-receptor complex has been formed, it translocates to the nucleus where it interacts with glucocorticoid responsive elements to regulate gene transcription and protein synthesis.

The time from PVN-CRH stimulation to peak CORT levels in plasma is about 20–25 minutes and about 2 minutes longer for the transition to saliva. Genomic effects take minutes to hours and may last days. Thus, these genomic actions cannot be part of the fight-or-flight response. Indeed, a stress response of the HPA axis is generally considered to be essential to the later phases of coping with stress, rather than fight-or-flight, because it helps to increase energy for the long haul, reverse the effects of other stress mediators and, through effects on neural systems, alters the organism's responses to similar threats when they are next encountered (Sapolsky, Romero, & Munck, 2000).

The idea that CORT is not a part of fight-or-flight is now being qualified. It appears that CORT can produce

effects through rapid, nongenomic processes that take about 7 minutes to operate (Tasker & Herman, 2011). Nongenomic effects involve CORT receptors that with stress relocate to the cell membrane. These nongenomic mechanisms help explain fast negative feedback, which we have known for a while occurs before gene-mediated CORT effects could take effect. Nongenomic effects have so far have been noted in the PVN, pituitary, hippocampus, and amygdala. Several nongenomic mechanisms have been identified. One GR-mediated mechanism acts via the endocannabinoid system, and there is increasing evidence that this system plays a role in PVN-located negative feedback. In the amygdala, rapid CORT action operating through this system may contribute to the dampening of responses to repeated stressors (Hill & McEwen, 2010). It appears that many of CORT's nongenomic actions are permissive. That is, operating through these mechanisms, CORT supports and enhances the metabolic, cognitive, and/or emotional processes being used to manage threat.

Corticotropin-Releasing Hormone

CRH is not produced only in the PVN, but also in other brain regions, most prominently the central nucleus of the amygdala (Kovács, 2013). CRH operates by binding to two G-protein coupled receptors (CRHR1 and CHRR2) that are located in different brain regions and have opposing functions. CRHR1 mediates many of the behavioral, hormonal, and autonomic effects of stress. Outside the HPA axis, receptors for CRH (e.g., CRHR1) are located in the basolateral and medial nuclei of the amygdala, prefrontal cortex, hippocampus, cerebellum, and in the reticular formation. CRHR1 antagonists markedly reduce fear and thus are targets for drug treatment. Critically, while CORT acting in the PVN downregulates CRH, in the amygdala chronic elevations in CORT upregulates CRH, increasing fear behavior.

Diurnal Rhythm

CORT is released once per hour in pulses throughout the day. In diurnal animals, the largest pulses are in the early morning hours and smallest at the onset of nighttime sleep. Thus, CORT is high at awakening and near zero 30 minutes after nighttime sleep onset. Imposed on this rhythm is a surge in CORT 30–40 minutes after awakening, the CORT awakening response (CAR) (Fries, Dettenborn, & Kirschbaum, 2009). A robust rhythm of the HPA axis requires near zero levels of CORT around the nadir of the rhythm. Thus, a common stress signature is slightly elevated late afternoon and evening CORT levels with suppressed early morning levels. The normal CORT diurnal rhythm is regulated by the circadian CLOCK system, (e.g., Kino & Chrousos, 2011), while circadian CORT variation also serves as a peripheral clock that synchronizes other systems including the hepatic, circulatory, and respiratory systems. Consequently, a dysregulated CORT rhythm impairs the functioning of other critical systems.

Stress Response

In the face of threat we mount stress responses to cope and survive. Stress responses are stressor specific (Joëls & Baram, 2009); however, stressors can be grouped into two broad classes. Systemic stressors (e.g., blood volume loss, infection, heat and cold stress) can activate the HPA axis even in a comatose organism. Psychogenic stressors require forebrain processing and elaboration. Activation to psychogenic stressors involves the central nucleus of the amygdala. From the central nucleus of the amygdala, the pathway to HPA activation crosses several synapses and involves the bed nucleus of the stria terminalis. Signals then converge on the PVN to release CRH (Ulrich-Lai & Herman, 2009). Fear of bodily harm and death are highly potent triggers of the HPA response; however, in humans, threats to the social self, particularly if combined with lack of predictability and control, are also powerful activators of the HPA axis and other stress-mediating systems (Dickerson & Kemeny, 2004). The field's most reliable laboratory stressor task is the Trier Social Stress Test (TSST), which threatens the social self through combining public speaking and mental arithmetic while being filmed and judged by a panel (Kirschbaum, Pirke, & Hellhammer, 1993). There is a version for children and now several versions that do not require the large cast of experimenters (e.g., Yim, Quas, Cahill, & Hayakawa, 2010). The TSST can be used with children as young as 7, but becomes more reliable as children get older. Stressor tasks for younger children are more challenging to find and are affected by the child's relationship with the parent who accompanies them to the laboratory (Gunnar, Talge, & Herrera, 2009).

Feedback Mechanisms

CORT controls its own levels through negative feedback via GRs in the pituitary, hypothalamus, hippocampus, and medial PFC (mPFC) (Tasker & Herman, 2011). Mediated by $GABA_A$ receptors, GABA-producing cells surround the

PVN and provide tonic inhibition of the HPA axis. Chronic stress leads to significant downregulation of GABA-ergic synaptic input to the PVN, thus reducing the tonic brake on the system. Regulation of CORT by its own production (i.e., negative feedback) operates on several time scales (Joëls & Baram, 2009). Fast negative feedback occurs within minutes, and in the PVN involves the endocannabinoid system. In the CA1 region of the hippocampus, negative feedback involves cell-membrane MR. Negative feedback that involves genomic mechanisms is slower but critical to HPA regulation. This type of negative feedback involves the hippocampus and mPFC and is mediated by GR. Negative feedback is itself subject to regulation. In response to chronic stress, GR expression is reduced in the hippocampus and mPFC, which reduces negative feedback regulation, but also prevents GR-mediated effects on these brain regions, which can be damaging if prolonged.

Current Methods and Methodological Issues

In this section we focus on the two methods that are the most relevant for research on children and adolescents: salivary and hair cortisol. There are a number of recommended methodological reviews for salivary cortisol (Granger et al., 2007; Gunnar & Talge, 2007; Kudielka, Gierens, Hellhammer, Wüst, & Schlotz, 2012). Numerous substances need to be controlled or avoided in assessing the HPA axis, some general to any mode of sampling, others specific to saliva. Milk in the mouth is a problem somewhat particular to child studies. Milk contains cortisol so samples contaminated by milk tend to have elevated scores (Gunnar & Talge, 2007). Avoiding dairy products within 30 minutes of sampling, rinsing the mouth, and waiting 5 minutes is advised. Medication use is another problem for researchers, especially those studying children at risk for psychopathology. If possible, drug washout periods are advised, but this is not always possible or even advisable for children with serious emotional and behavioral problems. There are various pathways through which drugs affect the HPA system and at least one paper describes a template for using this information and statistical controls to minimize impact on the data (Granger, Hibel, Fortunato, & Kapelewski, 2009). There are challenges with the collection matrix, with passive drool being preferred but not always possible with infants and young children. When swabs are used, those made of synthetic substances are preferred. These have recently become available and are marketed for use in collection. For children, motivating them to mouth these swabs can be challenging.

Several laboratories have found that using small amounts of sweetened drink mix crystals with the swab to get the sweet taste works well. However, depending on what is in the crystals this can lower the pH of the saliva and affect assay dynamics. The solution is to use only a few grains, which have no measurable effects (Gunnar & Talge, 2007).

While cortisol is a stable molecule, it does break down over months and years even in very cold storage and does so more in some samples than others (Kudielka et al., 2012). In a longitudinal study, one would want to avoid shifting levels as assays shift antibody lots, but it is best to assay about every 6 to 12 months.

Timing is critical to any study of the HPA axis. Laboratory tests should take place at the same time for all participants. While late afternoon and evening times are preferred because the axis is more quiescent and elevations are easier to detect, this is unrealistic in studies of infants and young children. Testing all at the same time of day or in time blocks that can be used in the analysis is essential, however. Making sure that time since napping and/or morning awakening is entered into the analysis protocol is also important. A different problem, compliance to protocol, arises when parents take samples at home. Significant numbers of parents misreport when they sample, a problem that is worse for early morning sampling relative to when children awake (Smith & Dougherty, in press). Errors in timing in the early morning result in reports of absent or blunted CARs, which are inaccurate. Use of objective "track cap" monitoring where sampling materials are stored in a device that tracks the time the cap is opened is strongly advised. Recently, despite numerous studies showing that infants and young children lack a CAR, we now know from a study using actigraphy and track caps that the CAR is robust from as early as 2 weeks postnatal (Stalder et al., 2013).

Many times we are less interested in the momentary activity and regulation of the axis than in an overall cortisol production. In these instances, what is needed is a reliable integrated measure of cortisol production. Sometimes what we need is information on cortisol production prior to the onset of our study. We may need a measure of how the axis responded to an unpredictable stressful event that was the reason for the study, but happened before any data were collected. In the last decade, researchers have begun to examine cortisol levels in hair to obtain this type of integrated measure that can serve as a calendar of cortisol production over the past months and is free from problems of protocol adherence (Stalder & Kirschbaum, 2012).

While it is still not clear how cortisol gets into hair, hair serves as a reservoir of cortisol and other chemicals and

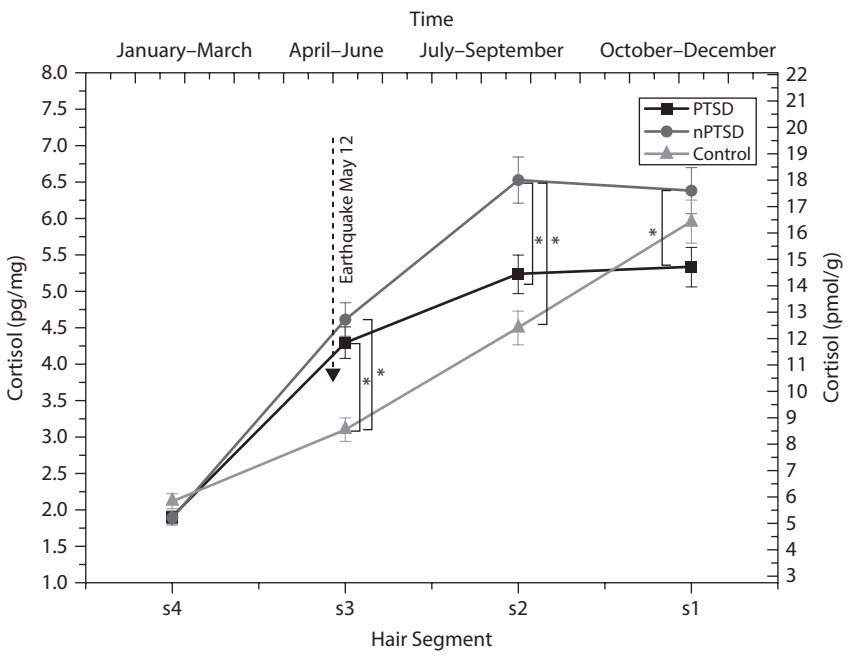

Figure 4.2 Hair cortisol levels in 64 adolescent girls following the Wenchuan earthquake on May 12, 2008.
Cortisol levels in 3-cm hair segments reflect time after and before the earthquake: S1 = 5 to 7 months, S2 = 2 to 4 months, S3 = 2 months before to 1 month after, and S4 = 3 months before the earthquake. The girls were divided into those who developed PTSD (n = 32), those who did not (nPTSD, n = 320 and nontraumatized controls (n = 20). These data show the utility of hair cortisol as a calendar for analyzing the effects of a traumatic event as well as the "washout" effect.

Source: Reprinted with permission from Luo et al., 2012.

hormones. Hair grows at roughly 1 cm/month, although there may be age and race differences in rates of hair growth. Counting back 1 cm from the scalp, hair provides a calendar. There are challenges to hair sampling, especially washout, or the decrease in cortisol from scalp to ends of the hair, which is possibly due to hair near the tips being washed more times than hair near the scalp. Both washout and the utility of hair sampling can be seen in Figure 4.2, which shows levels of hair cortisol in female adolescents from two towns who experienced the Wenchuan earthquake in 2008 (Luo et al., 2012). The far right side represents cortisol levels in the past month while the far left side represents levels 1 year before.

Examining cortisol levels in the controls, a washout effect is apparent. However, even with the washout, a strong effect of the earthquake is apparent as is the blunting of cortisol production among girls who developed PTSD. There is evidence that the washout effect may be avoided by changing the way the hair sample is processed (i.e., avoiding isopropanol) as washout may not be due to hair washing as much as to more damaged, older hair being open to the cortisol-leeching effects of isopropanol (Stalder & Kirschbaum, 2012). However, control groups are advised.

NEURO-SYMPHONY OF STRESS—HYPOTHALAMIC-PITUITARY-ADRENAL INTERACTIONS WITH OTHER STRESS MEDIATORS

CORT and CRH do not act alone. There are a number of stress mediators. These mediators all interact in what has been appropriately described as a "neuro-symphony of stress" (Joëls & Baram, 2009). Their interactions vary as a function of the type, duration, and characteristics of the stressor, the developmental stage of the organism, and characteristics unique to the individual, such as genetic background. These stress mediators execute essential functions in their own spatial and temporal niches. Overlap in these niches allows for interactions between them and studies describe direct interactions among individual mediators. We consider some of these other stress mediators next.

Sympathetic-Adrenomedullary and Parasympathetic Nervous System

The sympathetic adrenomedullary (SAM) system is the peripheral effector of the fight-or-flight response and is

critical to our ability to cope with threat. Milliseconds after the perception of threat, preganglionic sympathetic nerves in the spinal cord leading to end-organs are activated, the most important of these for the fight-or-flight response is the adrenal medulla with its production of epinephrine (Ulrich-Lai & Herman, 2009). Epinephrine (E) from the adrenal medulla travels throughout the body to have widespread effects on cardiovascular activity, blood pressure, and energy metabolism. These effects are enhanced by norepinephrine (NE) released from nerve terminals. E and NE effects are fast and short-lived. The half-life of E is 2 minutes. E and NE produced in the periphery do not enter the brain, but NE is produced in the central nervous system, often in coordination with increases in the periphery.

The SAM system is the hormonal component of the sympathetic nervous system (SNS), which, in turn, is one arm of the autonomic nervous system that serves many functions beyond fight-or-flight (ANS; McCorry, 2007). It supports arousal and attention in the central nervous system; thus we see increases in activity mediated by the ANS (i.e., heart rate, blood pressure) on effortful tasks, even if they do not threaten our social or physical selves. For example, effortful tasks like the Stroop or Mirror Drawing increase ANS activity but typically do not increase activity of the HPA axis, nor do they usually increase the production of E from the adrenal medulla. Rather they increase arousal through the release of NE from sympathetic nerve terminals and the production of NE in the brain from the locus coeruleus. These and other effortful cognitive tasks are *not* good tasks if the goal is to produce a fight-or-flight response of the SAM system and activation of the HPA axis.

There are numerous ways to measure activity in the SAM system. Galvanic skin response assesses peripheral NE activity. Salivary alpha amylase measures an enzyme regulated by NE and parasympathetic regulation of saliva flow. Finally, pre-ejection period (PEP), measured by impedance cardiography, is a relatively pure index of E produced from the adrenal gland.

The parasympathetic nervous system (PNS) plays a critical role in stress by helping to restore the conditions under which the body can rest and repair (Porges, 2009). The SAM system is organized for mass action, while the PNS is more targeted. The existence of both afferent and efferent projections from the brain also means that the PNS provides important information about the state of the body. Information travels to the brain along the nucleus tractus solitarius (NTS), which has inputs into the amygdala and neural systems involved in threat perception and response. Much of the focus on PNS innervation in relation to stress and emotion has focused on the activity of the 10th cranial, or vagus, nerve. The myelinated vagus provides tonic inhibitory input to the heart over the sinoatrial node (the heart's main pacemaker). Decreases in vagal input increase heart rate by *lifting the vagal brake*. Vagal tone is measured as respiratory sinus arrhythmia (RSA) or the variation in heart rate surrounding respiration. Changes in heart rate in response to negative emotional tasks in children are primarily due to changes in vagal tone rather than changes in sympathetic activity.

Central Norepinephrine

Because the enzyme that converts NE to E is present primarily in the adrenal medulla, there is little E in the brain. E and NE produced by the periphery do not enter the brain, although they affect the brain via the NTS (Porges, 2009). Instead, NE in the brain is produced principally by the locus coeruleus (LC) in the brainstem (Benarroch, 2009). Like the peripheral SAM system, the central NE system has many functions in arousal, attention, learning, and emotions. Like CRH, NE also mediates fear behaviors. Another critical role of the central NE system during stress is the formation of emotional memories that can alter future behavior (Roozendaal & McGaugh, 2011). NE acting in the basolateral amygdala (BLA) is essential for the consolidation of emotional memories, and these NE effects require the presence of CORT. Increasing CORT in the BLA during stress through both rapid nongenomic and slower genomic mechanisms enhances the effects of NE. In addition, CORT acting via GR located in the NTS increases NTS NE signals to the BLA, further enhancing the consolidation of emotional memories. These effects have been shown in children, adolescents and adults where individuals who showed both a large CORT and PEP (adrenal E) response to the TSST had better free-recall of the experience during a pop quiz 2 weeks later than did those who showed less of a CORT response and/or no PEP response (Quas, Yim, Rush, & Sumaroka, 2012). It should be noted that, in contrast to memory consolidation, elevated CORT impairs memory retrieval.

Dopamine

Dopamine (DA) is a major catecholamine neurotransmitter produced in several brain regions, including the ventral tegmental area, which projects to the nucleus accumbens

and PFC. Increases in CORT stimulate production of dopamine through GR receptors. During stress, activation of the ventral tegmental area by CORT results in excessive DA release into the PFC, leading to overstimulation of D1 receptors and impairments in working memory and other executive functions (Shansky & Lipps, 2013). Via GR in the PFC, CORT blocks catecholamine transporters located on glia, impairing their maintenance of DA and NE needed to support PFC-mediated learning, reasoning, and working memory. Via GRs in the PFC, CORT also alters DA cell firing rates. These mechanisms help explain the effect that stress has on self-regulation.

In addition, via interactions with DA, CORT affects activity of the nucleus accumbens allowing stress to modulate the circuits involved in reward (Mora, Segovia, Del Arco, de Blas, & Garrido, 2012). Through GR-mediated genomic mechanisms and membrane nongenomic pathways, rising levels of CORT during the initial phases of the stress response enhance dopamine activity in the accumbens. The behavioral effects of these increasing DA levels are dependent on interaction of the nucleus accumbens with the PFC. There is also evidence that the strengthening of glutamate synapses within the ventral tegmental area is dependent on CORT acting through GRs (Mora et al., 2012). Finally, chronic stress remodels and can impair the reward system, increasing susceptibility to addiction, and these changes involve CORT actions operating through GR.

Serotonin

Serotonin, a biogenic monoamine, plays a critical role in HPA activity. Serotonin is produced in the midbrain raphe nucleus, and one site for its terminals is the PVN, where it induces CRH expression (Chen & Miller, 2012). During development, serotonin is part of the biological pathway that decreases methylation of the GR gene in the hippocampus (Zhang, Labonté, Wen, Turecki, & Meaney, 2013). In turn, during stress, CRH and CORT modulate the synthesis and turnover of serotonin in the raphe (Chen & Miller, 2012).

Oxytocin

Oxytocin (OT) has been identified as a potential mediator of the ability of social support to buffer HPA reactivity. During stress, OT is released from cells in the PVN and from the central nucleus of the amygdala (Smith & Wang, 2012). Animal studies involving intraventricular administration of OT or human studies involving intranasal administration show reduced anxiety and HPA responses, as well as decreased heart rate and blood pressure responses to stressors. In children, having direct or even phone contact with mothers after the TSST elevated OT and lowered CORT (Seltzer, Ziegler, & Pollak, 2010). Early deprivation of parental care in monkeys impairs the development of the OT system and may reduce the animals' ability to use social support to regulate stress (Winslow, 2005).

Brain-Derived Neurotrophic Factor

Stress remodels the brain and one way this happens is the complex cross-talk between CORT and brain-derived neurotrophic factor (BDNF; Gray, Milner, & McEwen, 2013). BDNF is a neurotrophin that helps regulate nerve cell proliferation, differentiation, survival, and synaptic plasticity. Basal levels of CORT have neurotrophic/neuroprotective effects, enhancing BDNF activity through increasing levels of its receptor, TrkB. During stress, the relation between CORT and BDNF is dependent on timing, levels, and duration of CORT elevations and differs by brain region. In the hippocampus, there is some suggestion that increasing levels of CORT may facilitate BDNF expression until, at some point, excessive levels or levels that are elevated for too long suppress BDNF. Importantly, in the hippocampus, chronic stress produces hippocampal atrophy (which is reversible). Effects of stress in the basolateral amygdala are the opposite of those in the hippocampus and do not appear to reverse during recovery. In the basolateral amygdala, CORT induces increases in BDNF that, in turn, increase dendritic branching and spine density. Some of these effects on amygdalar BDNF are mediated by rapid, nongenomic mechanisms.

Immune System

There is a growing literature on the interaction between the HPA axis and the immune system, particularly with regards to explanations of early life stress and later life health (G. E. Miller, Chen, & Parker, 2011). These interactions are multiple and change across time following an acute stressor. Inflammatory immune cytokines activate the HPA axis, induce fever, and act in the brain to induce withdrawal and depression-like symptoms (e.g., sickness behavior). Elevated CORT and E/NE increase cytokines that have anti-inflammatory effects. Indeed, anti-inflammatory actions are a critical function of CORT. However, both hyperactivity and hypoactivity of the HPA

axis, through different mechanisms, are associated with chronic increases in inflammation and impairments in wound healing. Chronic elevations in CORT may down-regulate GR and produce glucocorticoid resistance, while chronic suppression of CORT levels may fail to restrain inflammatory responses. Stress effects on inflammatory cytokines are believed to be one pathway through which adversity increases the risk of affective disorders.

HERITABILITY AND GENETICS

There are marked individual differences in reactions to stressors. This has led to an interest in heritability of stress reactivity and a search for the polymorphisms that, in interaction with experience, contribute to individual differences in stress reactivity and regulation.

HERITABILITY

Although early heritability studies of the HPA axis were marked by considerable methodological limitations (Bartels, van den Berg, Sluyter, Boomsma, & de Geus, 2003), studies with appropriate sample sizes have begun to reveal the genetic underpinnings of both basal and stress regulation of the HPA axis. In adults, CORT levels shortly after waking show heritability estimates ranging from .34 to .69, whereas later in the day heritability estimates are lower to negligible. One interpretation of these findings is that reactions to experiences during each day mask the trait component of CORT production. This is consistent with evidence that heritability appears high in adults at all points in the cycle when CORT is assessed under laboratory conditions, but are much lower when samples are collected at home (Franz et al., 2010). Using statistical techniques that allow isolation of the trait component should reveal heritability as was shown in a large twin study of children (Van Hulle, Shirtcliff, Lemery-Chalfant, & Goldsmith, 2012). However, even using these techniques, the highest heritability estimates were found for samples taken 30 minutes after waking, and the diurnal rhythm itself showed heritability. For practical purposes, these findings suggest that the CAR may be a particularly useful tool for researchers interested in probing the HPA axis with candidate gene studies.

All studies mentioned above used individuals from low-risk backgrounds. Recently, researchers have examined the effects of adversity on heritability. For example, among 19-month-old twins, the heritability of HPA reactivity to novel stressors was lower among children reared under high-risk conditions for whom shared environment accounted for considerable variance, while heritability was relatively high among children reared under low-risk conditions (Ouellet-Morin et al., 2008). The utility of heritability studies is limited by their treatment of genetic and environmental factors as independent forces. In order to explore actions of particular genes or sets of genes within an environmental context, molecular genetics studies are necessary.

Molecular Genetics

Multiple genes regulate the HPA axis and its effects. Information about polymorphisms in these genes not only allows for examination of their effect on the axis, but also provides information about behavioral and health characteristics that are mediated by activity of CORT and CRH. Following is a discussion of some genes that appear promising. In some instances, researchers have focused on associations or interactions with individual single nucleotide polymorphisms (SNPs), but other research is considering the influence of haplotypes, or several variants in linkage disequilibrium that are inherited simultaneously.

Corticotropin-Releasing Hormone Receptor 1 (CRHR1)

There are a number of SNPs in the CRHR1 gene. Male carriers of GG genotype of rs110402 and rs242924 SNPs with a history of moderate to severe maltreatment demonstrated significantly higher plasma CORT in response to a DEX/CRH test while A-allele carrier females were the ones to produce larger CORT responses (Heim et al., 2009). (Note that the DEX/CRH test is considered a more sensitive and reliable pharmacological measure of the reactivity of the HPA axis than is obtained by simply administering CRH.) Sex differences in the type of abuse experienced make it difficult to interpret these findings. Measured during childhood, maltreated children homozygous for the TAT haplotype demonstrated significant flattening of the diurnal slope (which appeared to be driven by lower morning CORT levels) compared with children carrying at least one other allele (Cicchetti, Rogosch, & Oshri, 2011). Finally, several CRHR1 haplotypes were found to moderate CORT reactivity in preschoolers and more critically, these haplotypes interacted with other genes in the CRH system, highlighting the complex polygenic underpinnings of HPA reactivity (Sheikh, Kryski, Smith, Hayden, & Singh, 2013).

Given CRHR1 moderation of maltreatment effects on the HPA axis, researchers have also examined whether similar moderation is observed for depression. Particularly pertinent to this review, the CRHR1 TAT haplotype, consisting of SNPs rs7209436, rs110402, and rs242924, has been shown to significantly moderate the effect of childhood maltreatment on the development of depression in adulthood. Findings with the TAT haplotype, maltreatment, and depression, however, have been variable (e.g., Ressler et al., 2010).

Glucocorticoid Receptor (NR3C1)

Multiple polymorphisms in the GR gene have been investigated; only two are discussed here (for review, see Spijker & van Rossum, 2009). The ER22/23EK variant refers to G to A nucleotide changes in two SNPs (rs6189 and rs6190) in codons 22 and 23. This allele is associated with glucocorticoid resistance in response to dexamethasone, a synthetic CORT, but it has not been consistently demonstrated that this allele affects CORT secretion in response to a psychosocial stressor. The minor allele of the BclI variant (rs41423247) represents a C to G transformation that is associated with increased sensitivity to CORT (Spijker & van Rossum, 2009). Minor allele carriers show increased suppression of plasma CORT following administration of DEX and males show decreased HPA-axis responsivity following the TSST. The minor BclI allele may also increase children's susceptibility to maternal psychopathology as assessed using prenatal measures of psychopathology and child behavior at 14 and 36 months of age (Velders et al., 2012). The relatively high frequency of the minor allele (roughly 30%) makes this polymorphism of particular interest.

FKBP5

As noted, as part of the chaperone complex, FKBP5 acts to reduce the affinity of CORT for GR. Increases in CORT stimulate increases in FKBP5, which then decrease the ease with which CORT binds to GR, allowing a short-loop negative feedback mechanism. SNPs in this gene appear to confer differences in induction of FKBP5 in response to elevated CORT and GR activation, and subsequent GR resistance or sensitivity (as reviewed in Heim & Binder, 2012). In healthy adults, individuals homozygous for the T allele of rs1360780 exhibit significantly lower peripheral FKBP5 expression, and several SNPs (rs3800373, rs1360780, and rs4713916) have yielded evidence of exaggerated CORT response even in infants for individuals with at least one copy of the minor allele (Heim & Binder, 2012).

Associated Neurotransmitter Polymorphisms

As described above, the DA, central NE, and serotonin systems all interact bidirectionally with the HPA axis and CRH; thus, not surprisingly, genetic polymorphisms in genes that regulate these systems interact with the axis and CRH as well. For example, a meta-analysis reveals that homozygosity for the gene variant that produces the short version of the serotonin transporter gene (5-HTTLPR) reduces transcriptional efficiency of that gene and increases the CORT response to psychosocial stress (R. Miller, Wankerl, Stalder, Kirschbaum, & Alexander, 2012). Functional variants of the monoamine oxidase (MAOA) and catechol-o- methyltransferase (COMT) genes also affect CORT reactivity via their effects on NE and dopamine. The low-activity alleles of the MAOA gene, a 30-bp VNTR, and COMT gene (val158met SNP rs4680; met/met), in combination with each other, are associated with increased plasma ACTH and salivary CORT following a psychosocial stressor (e.g., Bouma, Riese, Doornbos, Ormel, & Oldehinkel, 2012). Variation in these systems, as well as others, may affect the HPA axis drive, produce elevated CRH and CORT effects on neural functioning, and influence the efficiency of social support as a stress buffer.

Epigenetics

The structural genome is overlaid by chemical marks, or epigenome, that regulate how the genetic material in each cell interacts with its transcription factors (Szyf, 2012). Epigenetic marks are passed on when the cell divides and, in some instances, from one generation to the next. The epigenome is tissue- and cell-specific, which allows for the tremendous variation in cell types throughout the body. Although much of the epigenome is determined before birth during morphogenesis, postnatal experiences driven by hormones, social experiences, nutrition, toxins, and stress continue to alter the epigenome throughout life.

Methylation is a principal, but not sole, mechanism of epigenesis. DNA methylation refers to the addition of a methyl group to the DNA, which then affects its interaction with transcription factors. DNA methylation occurs in regions where a cytosine is directly followed by a guanine (CpG, cytosine-phosphate-guanine sites or "islands"). Methylation is a bidirectional process, and genes can exist in a range of degrees of openness to transcriptional activity. This range reflects both methylation and histone acetylation and deacetylation (which relaxes or condenses chromatin). Epigenetics provides a powerful means whereby experience can alter developmental trajectories. Although the

epigenome does not alter the structural genome, relations between them are expected. That is, some gene by experience interactions may reflect mechanisms through which the structural genome influences experiential shaping of the epigenome.

As discussed in the section on childhood adversity, during sensitive periods of development, parental care programs the ease with which the GR gene in the hippocampus is transcribed (Szyf, 2012). In rodents, this period is during the first postnatal week when regulatory regions of the GR gene containing the NGF1-A binding, which are completely methylated after birth, are then demethylated as a function of maternal licking and grooming of the pups. Rodents who receive higher levels of maternal care exhibit less methylation at this site and are better able to regulate the HPA axis. It is unknown if there is an equivalent period in humans, but there is evidence that adversity in childhood is associated with differential methylation (see Childhood Adversity section).

There is a growing body of work examining the association between early life adversity and whole genome methylation patterns using either cheek cells or white blood cells, (e.g., Essex et al., 2013). Patterns on these cells will not necessarily correspond to methylation patterns in the brain, and methylation in one type of cell in one region of the brain will not necessarily reflect methylation in other types of cells in other brain regions. It is important to find evidence, using animal models, that stress affects methylation of genes regulating processes important in stress vulnerability and resilience. It appears to do so. For example, in addition to the GR gene, it is clear that early adverse care causes increased methylation of the BDNF gene in the PFC, reducing BDNF expression and contributing to stress-induced impairments in PFC functioning (Roth & Sweatt, 2011). Furthermore, during fetal development elevated CORT programs neural stem cells, upregulating cell cycle-related genes in a GR-dependent manner, and making resulting nerve cells more susceptible to oxidative stress and aging (Bose et al., 2010).

Summary and Future Directions

Several promising research trajectories should guide the study of HPA physiology and human development in the coming years. First, although much has been discovered about PFC regulation of HPA activity, further research is needed to address the development of this top-down regulation together with other stress-mediating systems, interacting in the "neuro-symphony of stress" (Joëls & Baram, 2009). Second, understanding monoamine, neuropeptide, and steroid hormone receptor systems will be vital to interpreting individual differences in responses to stressors. Physiological regulation is strongly influenced by the location, concentration, sensitivity, and function of receptors across tissues and organ systems. Research into how receptor systems develop and their subsequent effects on homeostatic regulation will be essential to understanding stress physiology, neural activity, and behavior. Finally, true developmental research must measure psychological and biological processes at multiple time points to understand the mechanisms involved at each stage of development and the factors contributing to maintenance or change in stress and emotion systems.

NORMATIVE DEVELOPMENT OF THE HPA SYSTEM

Using the HPA system to understand the effects of stress on development requires understanding normative changes in the system's activation and regulation. These have been described extensively (e.g., Hostinar & Gunnar, 2012) and are summarized here.

Prenatal Period

The HPA axis becomes stress-responsive by the 20th week of gestation. This is the case even though the fetal adrenal gland contains a large fetal zone that helps produce estrogens and involutes over the first 6 postnatal months. Not only does the fetus produce CORT, but maternal CORT can reach the fetus. This raises the question of whether and how CORT influences fetal development. CORT plays critical roles in advancing tissue development, which likely explains why CORT levels in mother and fetus rise toward the end of gestation. However, as in later development, CORT needs to be tightly regulated. Because the fetal liver is immature, its production of binding globulins is low; therefore, even small increases in CORT produce large increases unbound, biologically active CORT. Both MR and GR are present from early in gestation; thus, CORT likely has effects across much of fetal development.

There are numerous checks and balances, however. The enzyme 11β-HSD2, which converts CORT to an inert substance, is present at the blood-brain barrier, in the placenta, and in fetal tissues. It is highly expressed in the fetal brain between prenatal Weeks 19 through 26, when it is often seen colocalized with GR. As term approaches,

levels decrease. Thus, 11β-HSD2 likely serves the function of temporarily protecting rapidly developing brain regions from overexposure to CORT (Wyrwoll et al., 2011).

Infancy

Full-term healthy newborns elevate CORT to a variety of even mild stressors. This degree of reactivity remains during the first months of life, but by 3 to 4 months, the axis has become less responsive, perhaps reflecting the development of fast feedback mechanisms.

Events that provoke distress typically also activate the HPA axis; nevertheless, behavioral distress and HPA systems are differentially regulated. Thus, soothing techniques that reduce crying might have no effect on CORT levels, and CORT reactivity may be uncorrelated or only very slightly correlated with crying in many instances (Gunnar & Donzella, 1999).

Three months is an important turning point in development when the infant becomes better regulated and is able to socially engage for longer periods. The diurnal CORT rhythm becomes more stable around this time, although it is only the morning peak and evening nadir that are readily observable. Not until the child gives up the afternoon nap in the preschool years (approximately 3 to 5 years of age) are midafternoon levels predictably lower than mid-morning levels.

In the neonatal period, a variety of stimuli embedded in the caregiver–infant relationship begin to regulate the infant's HPA system. As reviewed in Hostinar and Gunnar (2012), there is some evidence that the more time the parent and infant spend in physical contact the shorter the bouts of crying and the smaller the CORT elevations to everyday stressors, like being removed from the bath. During these first months when the HPA axis is still highly reactive to stimulation, there is evidence that sensitive responses to infant distress regulate the axis, returning CORT levels more promptly to baseline (Albers, Riksen-Walraven, Sweep, & de Weerth, 2008). The regulatory roles of caregiving activities allow the caregiver to serve as a powerful stress buffer.

However, during these early months, different components of caregiving likely regulate different stress-mediating systems. Thus, facets of caregiving that reduce crying (e.g., feeding, nonnutritive sucking) are less capable of buffering heart-rate responses to painful stimulation, and have no apparent effects on CORT responses to stress (Hostinar & Gunnar, 2012).

The emergence of social relationships as powerful stress buffers is one of the most remarkable phenomena during the first year of life (Hostinar, Sullivan, & Gunnar, 2013). This appears to occur around the onset of independent locomotion, which corresponds roughly to when the child begins to actively organize security-seeking behavior around attachment figures. At this point it is not just what the attachment figure does but who the person is and his or her relationship with the child that is important. We can see this clearly in studies that have used childhood inoculations as the stressors. Children show marked increases in CORT despite the parent's presence at 2, 4, and 6 months. Then from as early as 12 to at least as late as 18 months, these elevations are no longer seen and CORT responses remain low in the parent's presence.

The attachment figure needs to be present to provide buffering during infancy and early childhood. This has been demonstrated in studies of children in childcare. When the parent is present, securely attached children do not show elevations in CORT whereas insecurely attached children do; but in the first days when the parent leaves the child, CORT levels are equally elevated for securely and insecurely attached children. For children who have adapted to their daycares, a secure relationship with their parent may make the HPA axis more sensitive to variations in childcare quality. Thus, securely attached children both produce the largest increases in CORT in poorer quality daycares and the smallest elevations in higher quality ones (Badanes, Dmitrieva, & Watamura, 2012).

We still do not know how the attachment figure's presence works to provide such a potent stress buffer, although oxytocin and other antistress hormones that are fostered by his or her presence may play a role (Hostinar et al., 2013). In addition, the presence of the attachment figure may activate brain regions associated with safety signals, thus reducing fear and anxiety even to noxious stimuli. This has been demonstrated in adults for whom viewing an image of the romantic partner while experiencing a pain stimulus activated a safety signal–related neural region in the ventromedial PFC (vmPFC) and reduced the experience of pain (Eisenberger et al., 2011). We do not know how long in development the parent is able to play this stress-buffering role. It may be that parental stress-buffering potency declines in adolescence.

Preschool and Middle Childhood

According to current knowledge, the HPA axis is quite mature by the preschool period. Two psychosocial changes, however, begin to affect its activation and regulation during this period and become increasingly important during

middle childhood: the development of emotion regulatory competencies and the increasing focus on peers and peer relationships.

There are marked increases in the child's ability to regulate behavior and emotions during early childhood. Neurodevelopment of regions in the prefrontal cortex involved in the effortful regulation of behavior (dlPFC) and emotions (vmPFC) may play a role (Belsky & de Haan, 2011). The development of self-regulatory competence should allow the child to modulate activity of the HPA axis more independently. However, there is a complex relation between stress and the PFC and the relations between measures of effortful control and activity of the HPA axis are positive under some circumstances and negative under others (Shansky & Lipps, 2013). CORT is necessary for PFC functions because it supports the central production of DA and NE (Mizoguchi, Ishige, Takeda, Aburada, & Tabira, 2004). Thus higher levels of CORT within basal ranges might support functioning on effortful control tasks if the higher levels occur in anticipation of the task and prepare the child for task demands. This has been demonstrated in several studies. Stress levels of CORT, however, impair prefrontal functioning, in part through the overenhancement of DA production (Shansky & Lipps, 2013). Thus among children experiencing high lifetime stress, the opposite pattern of associations may be found, as was noted among preschoolers in a homeless shelter (Cutuli, Wiik, Herbers, Gunnar, & Masten, 2010). If we measure effortful control in relation to basal or ambulatory CORT levels, negative associations would be expected because children with better self-regulatory abilities should be better able to regulate their emotions and avoid stressful conflicts with others. This has generally been found (Turner-Cobb, Rixon, & Jessop, 2008).

Effortful control also mediates relations between children's emotional dispositions and the quality of their relations with peers. Children who tend to be easily angered when frustrated and those who are exceedingly exuberant have problems with aggression unless they also have good self-regulatory competences. Although simply inhibiting expressions of anger when provoked might increase adrenocortical and sympathetic activity (Spinrad et al., 2009), because unregulated anger and aggression increase the risk of rejection and ostracism, children with better self-regulatory abilities should, overall, experience fewer stressful social interactions, (e.g., Gunnar, Sebanc, Tout, Donzella, & van Dulmen, 2003).

As noted, threats to the social self are powerful stressors. Rejection and ostracism are powerful social threats that activate neural pain circuits (Cacioppo & Cacioppo, 2012). Social isolation increases attention to threatening aspects of the environment and in animal studies activates the HPA axis. Peer-rejected preschoolers and older children exhibit elevated CORT at school, although having even one friend reduces this effect (e.g., Peters, Riksen-Walraven, Cillessen, & de Weerth, 2011). It may not so much be peer rejection but loneliness that is stressful for children and youth, particularly if loneliness is chronic (Doane & Adam, 2010).

While some rejected children are simply ignored, others are targets of bullying. Bullying can be highly stressful for children and is associated with significant psychopathology. Only a few studies have examined the relation between peer victimization and CORT and the results have been mixed. There are two reasons for this. First, some victims are also bullies. Bully-victims may be comorbid for conduct disorder and have low CORT levels (van Goozen, Fairchild, Snoek, & Harold, 2007). Second, the duration and intensity of victimization may be critical. When victimizing begins or if it is only occasional it should increase CORT, but after a long period of intense bullying the HPA axis is likely to downregulate (G. E. Miller, Chen, & Zhou, 2007). Intermittent victimization has been associated with elevated CORT, while chronic victimization has been correlated with low CORT in boys (Vaillancourt et al., 2008). Likewise, children experiencing more cumulative stress may exhibit blunted CORT in response to peer victimization (Ouellet-Morin et al., 2011). As children move into preschool and middle childhood, peer relations become increasingly important and problems in relations with peers are important stressors affecting activity of the HPA axis.

PUBERTY AND ADOLESCENCE

Adolescence, a period of rapid development and marked changes in social relationships, is also a period when emotion systems and their neural substrates mature and become more sexually differentiated (Dahl, 2004). Sex steroids have regulatory effects on the amygdala and mPFC in adults and although less studied, there is evidence that puberty and increasing levels of gonadal steroids affect the developing brain in a sexually dimorphic fashion (Neufang et al., 2009). Consistent with these findings, activity of the HPA axis becomes sexually differentiated with advancing sexual maturity. For example, in a large sample of youth aged 16 years, CORT levels were higher and ACTH levels

were lower in fasting morning plasma samples for girls than boys (Reynolds et al., 2013). Sex differences in response to social stressor tasks are observed among adults with men responding more strongly than women (Kudielka & Kirschbaum, 2005). Sex differences in responses are not reliably seen in childhood, but emerge around the pubertal transition and are clearly present by mid-adolescence (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009). CORT levels also increase with puberty. The increase is clearly seen in basal levels; whether it is present for reactivity is less clear. CORT reactivity has been reported to increase with pubertal stage/age in some studies (e.g., Gunnar et al., 2009).

It has been argued that the pubertal increase in HPA activity, along with the increased sexual dimorphism, contributes to girls' vulnerability to depression and to increases in psychopathology for both sexes during adolescence (Dahl & Gunnar, 2009). In animal studies there is evidence that the peripubertal period is a second sensitive period of vulnerability for the HPA system (Eiland & Romeo, 2012). However, at least one study indicates greater invulnerability during this period; specifically, the researchers found that chronic unpredictable stress in the adolescent period in the rat enhanced avoidance learning, whereas it impaired it among adults (Ricon, Toth, Leshem, Braun, & Richter-Levin, 2012). However, as noted by Eiland and Romeo (2012), when similar studies are conducted with adolescent female rats, impairments are noted. Thus sex may influence whether stress increases vulnerability or resilience during puberty.

If stress vulnerability increases during adolescence, it could partly be due to a decrease in the power of parental buffering of the stress system. Just prior to puberty, even being able to phone the mother blocked increases in CORT and increased oxytocin (Seltzer et al., 2010). In children of roughly the same age, allowing the mother to be present and supportive during the speech preparation period of the TSST also blocked elevations in CORT, while providing the child with a supportive but unfamiliar adult did not (Hostinar, Johnson, & Gunnar, 2014). In the same study, parental presence among 15-year-olds had no buffering effect on CORT. Whether this developmental shift is mediated by puberty or psychological changes in the parent–child relationship remains to be determined. In addition, it seems likely that when parent-as-buffer decreases in potency, other social relationships may take over the stress-buffering role. The role of friends and romantic partners as stress buffers in adolescence remains to be explored. Finally, it seems unlikely that parents completely lose their stress-buffering potency for adolescents. It might depend on the type of stressor facing the youth. This too remains to be examined.

Summary and Future Directions

As the HPA axis develops, both reactivity and regulation shift from infancy to adolescence. From the emergence of attachment figures as stress buffers in infancy to the potential role of romantic partners as regulatory forces in adulthood, social relationships play a crucial role in stress regulation across the life span. Further, as peer structures become more complex during middle childhood and adolescence, social standing may play a critical role in HPA functioning. As research accumulates on the development of self-regulatory skills that emerge in early childhood, care should be taken to examine its relation to stress reactivity and regulation in the context of both children's lifetime stress as well as task demands. At the pubertal transition, future research is needed to understand the potentially differential effects of sex hormones on vulnerability to stress during adolescence. Exploring shifts in stress-buffering social systems during this period is a promising avenue for better understanding these processes.

THEORETICAL PERSPECTIVES

Child development research on the psychobiology of stress has largely been conducted from a developmental systems perspective. Adult work on the psychology of coping has been guided by Lazarus and Folkman's (1984) transactional model, emphasizing individual differences in appraisal and response to events. Both of these perspectives have influenced current thinking. Evolutionary perspectives have also challenged our dominant models.

Allostasis and Allostatic Load

The allostatic load model (ALM) is the most influential psychobiological stress theory (McEwen & Wingfield, 2010). In developing ALM, the starting point was the concept of allostasis, which describes the body's ability to up- and downregulate vital functions to achieve new steady states in reaction to challenge. As a shorthand, allostasis is often defined as "achieving stability through change." There are a number of allostasis-mediating systems; however, CRH and the HPA system, the immune system, and the central and peripheral catecholamine systems have received the greatest attention.

As Selye noted decades ago, activation of these allostasis- or stress-mediating systems allows us to cope (Selye, 1946). In the face of chronic adversity, the mobilization of these systems can allow us to look like we are coping exceptionally well for prolonged periods, and then somehow, we are overcome by disease. Selye thought the disease states were due to exhaustion of these systems. He was wrong. In place of exhaustion, ALM inserts allostatic load (McEwen & Wingfield, 2010). Allostatic adjustments, if frequent or chronic, can take a toll on the body. Allostatic load or overload refers to the wear and tear produced by either too much stress or from inefficient regulation of stress mediators. Inefficient regulation can mean a failure to turn off or return to baseline once the threat has passed and/or a failure to appropriately activate the response. Both under- and overactivation of allostasis-mediating systems can develop through prolonged overuse. The cumulative wear and tear of allostasis and/or dysregulation of allostasis-mediating systems defines allostatic load, which leads to many diseases of aging as well as undergirds cognitive deficits and stress-related mental disorders in some individuals.

Allostasis-mediating systems influence one another, but their relations are expected to be nonlinear and stressor specific (Joëls & Baram, 2009). Different patterns of responses are provoked by different classes of stressors (e.g., infectious agents, social threat) and the time courses differ across systems in their activation and the time it takes for them to affect function. Catecholamines produce their effects quickly and dissipate rapidly, which is why epinephrine and norepinephrine undergird the fight-or-flight system whereas CORT takes 25 minutes to reach peak reactions and its gene-mediated effects can play out over hours and days.

Hypothalamic-Pituitary-Adrenal and Autonomic Nervous System Asymmetry

No one attempts to measure all stress-mediating systems; however, there are increased calls to measure more than one system at a time, especially combining HPA and SAM measurement (Bauer, Quas, & Boyce, 2002). Bauer and colleagues argue that the HPA and SAM systems evolved to work together and moderate levels of co-activation should be related to healthier functioning, while SAM and HPA asymmetries may reflect allostatic load. Because chronic stress tends to downregulate the production of CORT (G. E. Miller et al., 2007) and increase catecholamine production, high sympathetic and low HPA activity may be the product of chronic stress. Some studies (Gordis, Granger, Susman, & Trickett, 2006) have supported this argument, whereas others have found the opposite results (El-Sheikh, Erath, Buckhalt, Granger, & Mize, 2008).

One challenge in testing the asymmetry hypothesis is that the HPA system habituates to repetition of the same stressor after as little as one trial, whereas the type of chronic stress that downregulates the axis requires presentations of changing and unpredictable stressors. The HPA axis often habituates whereas the sympathetic system keeps responding, particularly if the stressor demands an effortful response (Ursin, Baade, & Levine, 1978). Thus, it is unlikely that symmetry or asymmetry between the HPA and SAM systems will consistently be associated with health or disorder. Rather, the meaning of these patterns will be context and stressor specific, reflecting situational demands, stressor appraisal, and prior experience.

Allostatic Load Model Indices in Children and Adolescents

Allostatic load is measured through systems affected by chronic activation of allostasis-mediating systems. Its indices include high systolic and diastolic blood pressure; high waist–hip ratio; elevated cholesterol (HDL and total); high glycosylated hemoglobin; and high overnight urinary CORT, norepinephrine, and epinephrine. Typically one counts up the number of these indicators. These measures of allostatic load were developed for work with adults and it is an open question whether they are predictive in children whose systems are still developing. Other indices may be sensitive in childhood. We have proposed that a slowing of linear growth may be an index of allostatic load in children (A. E. Johnson, Bruce, Tarullo, & Gunnar, 2011). Evidence is accumulating that the standard allostatic load indicators are useful by later childhood or early adolescence (Evans & Kim, 2012). There is also evidence that individuals who are highly resilient psychologically and behaviorally may exhibit higher indices of allostatic load by late adolescence (Brody et al., 2013). Although this might seem surprising, resilience in the face of heavy odds should require frequent activation of allostasis-mediating systems, producing an accumulating allostatic load.

Although ALM may help explain the development of children exposed to harsh conditions, it is not a developmental model. Because there is increasing evidence that there are sensitive periods in the organization of stress reactivity and regulation, a developmental framework is needed. Similarly, although ALM acknowledges individual differences related to temperament and sex/gender, it does not provide an explanation for these differences or

build predictions based on them. We now turn to a model that does.

Adaptive Calibration Model

The adaptive calibration model (ACM; Del Giudice, Ellis, & Shirtcliff, 2011) is an evolutionary-developmental model based in life-history theory (Coall, Callan, Dickins, & Chisholm, Chapter 3, this *Handbook*, this volume). Its proponents argue that it is an extension of ALM, specifically addressing what they see as its shortcomings. According to ACM, both positive and threatening environments have been part of our evolutionary heritage, and we have evolved to maintain reproductive fitness across a range of environmental harshness. What might be thought of as dysfunction, if reliably produced by harsh experiences, should better be thought of as choice of a different life-history strategy. For example, when early harsh conditions result in earlier-onset puberty, earlier and more frequent reproduction, and greater risk-taking, this is viewed as a fast life-history strategy (Belsky, Steinberg, Houts, & Halpern-Felsher, 2010). ACM argues that the stress response system, in interaction with brain neurochemistry, acts as a filter and amplifier of life-history relevant experiences to mediate their effects on life-history traits: growth/learning, maturation/fertility, competition/risk-taking, and pair-bonding/caregiving. Beginning before birth, experiences are sampled by the stress response system, which leads to the selection of different life-history strategies that get modified during each developmental period. In some instances, response patterns may adversely affect the health and happiness of the individual and those around him or her, but they have been selected because they increase reproductive fitness, or did so in the environment in which we evolved.

Perhaps because this model was developed precisely to apply to human development, when measures of the stress response system are discussed, they only include those that can be noninvasively measured in children (i.e., CORT, ANS measures, and perhaps immune). The many other systems discussed in ALM are not a focus, though presumably are not excluded.

There are two aspects of ACM that are of particular note with regards to developmental stress research. First, the model has incorporated the biological sensitivity to context hypothesis (Boyce & Ellis, 2005; see also differential susceptibility hypothesis, Pluess & Belsky, 2010). Accordingly, some individuals are shaped more by their developmental history than are others and, consistent with adaptive calibration, it is reactivity of the stress systems that determines sensitivity to context. Individuals with relatively nonreactive stress systems tend to have similar life-history strategies across a wide range of life-history relevant environmental inputs. In contrast, those with more responsive stress systems will be more sensitive to context. These individuals will exhibit the socially positive characteristics of a slow life-history strategy (low aggression, high agreeableness, focus on long-term goals, low reproductive rate, high investment in each offspring) if reared in supportive environments, but the socially negative characteristics of the fast strategy (high aggression, early puberty, risky behavior, early pregnancy, low rate of investment in individual offspring) if reared in harsh environments.

On a behavioral level, there is clear evidence that some phenotypes are more sensitive to context, perhaps based on their genetic endowment. What is unclear is whether stress reactivity determines this sensitivity, and whether the relationship is stressor specific or general. As noted by Obradović (2012), reactivity of the PNS has been shown to increase sensitivity to context, but in studies of marital conflict and domestic violence, PNS reactivity reduces sensitivity to context (i.e., tends to buffer children). Thus, simple models that are not context, stressor, and system specific may fail to capture the complexity of the stress-development landscape.

As another outgrowth of the biological sensitivity to context theory, ACM also argues that the stress response system is toned or tuned by the harshness or supportiveness of the early environment. From an evolutionary perspective, this is a form of conditional or predictive adaptation that has evolved to help preadapt the child. ACM argues for a U-shaped function between early care conditions and stress reactivity. Specifically, both highly supportive and very harsh conditions will produce a highly responsive stress response system, which supports sensitivity to the environment, better learning, and good outcomes in supportive contexts, but high vigilance and anxiety in harsh contexts. Moderately supportive, slightly harsh developmental contexts result in a buffered stress response system. ACM also describes a fourth grouping that results in traumatic rearing contexts that is differentiated by sex, with girls remaining vigilant and highly stress reactive and boys becoming unemotional with blunted stress reactivity. These four patterns are expected to be accompanied by differential activity of the ANS and HPA systems as follows: (1) Sensitive (high PNS basal and response activity; high to moderate SNS reactivity and moderate basal SNS activity; high HPA reactivity and moderate basal HPA levels), (2) Buffered (moderate PNS and HPA basal and response

activity, low to moderate SNS basal and response activity), (3) Vigilant (low to moderate PNS reactivity, low basal PNS activity; high SNS basal and response activity, high HPA reactivity, and high to moderate basal HPA levels) and (4) Unemotional (low basal and response activity of PNS, SNS, and HPA systems).

This is a complex theory with many moving parts. Currently, there are only a few studies testing parts of the theory. Critical to the theory is the existence of the four phenotypes and their correspondence to the patterns of stress responding. There is some support for these four groupings. Using finite mixed modeling, these theorists have recovered four patterns that roughly fit the predicted ones, although they only used measures of PNS and SNS activity (Del Giudice, Hinnant, Ellis, & El-Sheikh, 2012). Examination of the results showed that the four groups differed most in baseline skin conductance (a measure of SNS activity), with the Buffered being low and the Vigilant high as predicted; but the Unemotional were moderate rather than low in skin conductance baseline. Counter to expectations, males were not overrepresented in the Unemotional Group, but girls were overrepresented, as predicted, in the Vigilant group.

It is critical in the model that the relation between childhood adversity and the stress response system is *not* linear. There is more evidence of nonlinearity, but not always in the predicted direction. For example, in a study of kindergarteners (4–6 years old), measures of socioeconomic class and measures of adverse family events bore different relations with CORT when assessed at two different times of the school year. In the fall, the expected U-shaped function was found; while in the spring, the relationship was an inverted-U. Measures of adversity were linearly, not curvilinearly related to CORT and many of the associations were moderated by race (Bush, Obradović, Adler, & Boyce, 2011). In a study of 9–16-year-olds, another inverted-U rather than U-shaped function was found, with moderate levels of recent adversity associated with the highest CAR, whereas both the lowest and highest levels of accumulated adversity were associated with smaller CARs (Gustafsson, Anckarsäter, Lichtenstein, Nelson, & Gustafsson, 2010). As in HPA and SNS asymmetry, relations between experience and physiology seem to be contextualized and nuanced, challenging attempts to contain them in simple phenotypes.

The four patterns (Sensitive, Buffered, Vigilant, and Unemotional) are conditional or predictive adaptations, which presumably increase reproductive fitness. This is a difficult concept to prove in human research, but also not a concept peculiar to ACM. A number of researchers have discussed the possibility that early programming of the HPA axis is a form of predictive adaptation. Predictive adaptation provides a framework in which to understand the "developmental origin of adult health and disease" model (DOAHaD; Gluckman, Hanson, & Beedle, 2007). The idea is that harsh fetal or early postnatal conditions shape an organism with a thrifty phenotype (i.e., a smaller body, lower metabolic rate, reduced behavioral activity, avoidance of novelty and exploration), which reduces the need for food and promotes survival under harsh conditions. If conditions continue to be harsh, a thrifty phenotype fosters longevity and reproductive fitness. However, if there is a mismatch in conditions, poor health ensues. This idea can readily be combined with the ALM to produce predictions of heightened reactivity of allostasis-mediating systems as a function of early adversity leading to obesity and even more rapid acceleration of allostatic load in an overly rich environment (McEwen & Wingfield, 2010).

The ACM, however, does not require a mismatch between programming cues and the encountered environment to result in behavioral and health disorders. In this regard, it should also be noted that Pluess and Belsky (2011) suggested that the heightened stress reactivity and timidity that is reported among offspring of stressed pregnancies (see "Prenatal Stress") are a different form of programming—specifically, prenatal programming of postnatal plasticity or sensitivity to context.

Finally, predictive adaptation models, although assuming an increase in reproductive fitness, do allow for trade-offs, particularly with regards to longevity. In one example, the type of maternal separation in rats shown to increase reactivity of the HPA axis has also been shown to enhance hippocampal-dependent learning in the juvenile and young adult period followed by rapid cognitive decline in aging rats (Suri et al., 2013). In long-lived animals, such as humans, there may be life-history stages when the stress system is reprogrammed. The ACM describes multiple recalibrating periods from infancy to adulthood. Other models describe fewer. Among these periods, in addition to the fetal/early postnatal period, puberty stands out as potentially important for recalibration prior to the onset of reproductive maturity (Romeo, 2010).

OTHER THEORETICAL PERSPECTIVES OF POTENTIAL RELEVANCE TO DEVELOPMENTAL RESEARCH

While the ALM and ACM are the two most prominent theories guiding studies of stress and development in children,

there are several theories applied only to adults and/or in animal studies that may be useful to include in our developmental models.

Tend and Befriend

As we will note later, there is little evidence of sex differences in HPA-axis activity until puberty. However, that does not mean that boys and girls perceive the world similarly with regards to threats to their physical and/or social selves or that the sexes have evolved and/or have been socialized to cope in the same way. The ACM begins to address this problem, but a much more elaborate theory was proposed for adults. Over a decade ago, Taylor and colleagues (2000) proposed that there are marked sex differences in the organization of stress responses and in the consequences of exposure to stressors. Because the roles of males and females differ with regards to the bearing and rearing of the young, especially in species like ours where males have not been the primary caregivers until recently, the female stress system evolved to manage protection of both the female and her offspring. Thus, unlike males who "fight or flee" under threat, threat activates "tend and befriend" tendencies in women that foster seeking and banding together with others in the protection of the young. With regards to the neurobiology of these stress responses, they argue that the attachment system, supported by oxytocin and endogenous opioid peptide mechanisms, works to keep HPA and sympathetic responses in check during periods of stress. To be effective, nurturing relationships need to be present. Lack of nurturing relationships should be a particularly acute source of stress for women. Female reproductive hormones should play a role in modifying patterns of stress responding or producing patterns that differ from men, and these tendencies should increase with puberty, pregnancy, and childbirth.

There are clear differences in the types of stressors that activate the HPA axis in adulthood, with men being more responsive to stressors involving threats to how others perceive their intelligence and performance and women to situations involving threats of social rejection and exclusion (e.g., Stroud, Salovey, & Epel, 2002). However, some studies show that both men and women increase the type of prosocial behavior that supports social networks in reaction to stress (von Dawans, Fischbacher, Kirschbaum, Fehr, & Heinrichs, 2012). In addition, women do not differ from men in HPA responses to performance stressors at certain points in their menstrual cycle (Kudielka & Kirschbaum, 2005). Thus, as is typical of sex differences, there are more overlaps in behavior than prototype models would suggest. In addition, as discussed in "Normative Development of the HPA System," it is not clear when these differences develop; however, this could be an important avenue for developmental research.

Hawks and Doves

As discussed in the section called "Temperament and Stress Vulnerability and Resilience," shy/inhibited children appear to be particularly sensitive to social stress, yet we do not have stress theories that really address temperamental differences. The one that comes closest is the Hawk and Dove theory (Korte, Koolhaas, WingWeld, & McEwen, 2005). This is an evolutionary theory based on the expectation that populations should include individuals who vary in their typical responses to threats and challenges. The theory describes two phenotypes: Hawks and Doves. Those with Hawk phenotypes are aggressive and bold. They fight or flee when threat is encountered. They are proactive rather than reactive, and take risks. They are at a fitness advantage when energy resources are high but at a disadvantage when energy resources are low because their phenotype requires a good deal of energy to sustain. They are also at an advantage when population density is high because their aggressiveness allows them to compete successfully. Doves, in contrast, prefer to freeze or blend into the background when conditions become threatening. They are risk averse, inhibited, and cautious. They are at a survival advantage when energy resources are low because their strategies tend to conserve energy. They do better when population density is low because they are poorer competitors. These phenotypes are theorized to differ in their underlying stress physiology. Hawks are expected to have low-responsive HPA systems and low basal HPA tone, whereas Doves are predicted to have highly reactive HPA systems and higher basal HPA tone. Hawks are supposed to be more SNS reactive than Doves, whereas Doves are supposed to be more PNS reactive than Hawks. Theoretically, the effects of chronic stress differ for these phenotypes, being associated with problems of impulse control, violence, hypertension, and autoimmune disorders for Hawks and metabolic syndrome, internalizing disorders, and infections for Doves. There has only been one child study to apply the Hawk/Dove model explicitly. In this study, researchers used the Hawk and Dove prototypes to effectively identify factors moderating the effects of harsh parental discipline (Sturge-Apple, Davies, Martin, Cicchetti, & Hentges, 2012). Among the Hawks, harsh

discipline did not affect levels of basal cortisol or vagal tone, but did increase sympathetic tone over time, and this mediated a rise in externalizing problems. Among the Doves, harsh discipline increased vagal tone and basal cortisol levels, while lowering sympathetic tone, and this mediated a rise in internalizing problems. Although it is unclear whether the Hawk/Dove prototypes are the best to use in developmental research, these results suggest that temperamental differences among children will be important to incorporate into our theories.

Summary and Future Directions

None of our models of stress and development are completely satisfactory. The ALM is biologically based and consistent with the complexity of the systems involved in stress responding, but it was never intended to be a developmental theory. The ACM is explicitly developmental, which is a benefit for developmental researchers. However, it elaborates ultimate arguments and does not adequately deal with proximal processes. The patterns it proposes are likely elusive as they suppose much less stressor and context specificity than has been richly demonstrated in the literature. While neither theory is completely adequate, both theories have, in the case of ALM and likely will in the case of ACM, stimulated research. Furthermore, the many concepts derived from or that have been absorbed into these theories and brought into the human developmental literature (e.g., sensitivity to context, differential susceptibility, predictive adaptation) are enriching the study of stress and development. Finally, neither of the main theoretical models deals adequately with sex/gender differences or temperamental differences; thus we might be wise to consider "tend and befriend" and "hawk/dove" models or other similar theoretical arguments as we enrich our models of stress and human development.

CHILDHOOD ADVERSITY: STRESS AND BIOLOGICAL EMBEDDING

Increasingly, we are called to attend to early adversity in order to improve lifelong health. Several research areas converge to fuel this focus. First, there is evidence that the socioeconomic gradient in health may have its roots in childhood social class (Ziol-Guest, Duncan, Kalil, & Boyce, 2012). Second, the evidence that birth weight, as a reflection of prenatal adversity, predicts cardiovascular disease in adulthood established a field termed the fetal origins of adult disease (Gluckman et al., 2007). Finally, over a half century of research on early adversity in animals provides invaluable insights into the processes through which adversity gets under the skin to affect health and disease (Zhang et al., 2013). Less than a decade prior to the time of this writing, the concept of biological embedding was introduced to provide an umbrella term for a variety of processes through which experience becomes part of our biological makeup during development. The concept of biological embedding has since entered the mainstream of scientific discourse (Shonkoff, Boyce, & McEwen, 2009). Because animal models have been critical to providing hypotheses about biologically plausible pathways through which embedding can occur, key points from this work are highlighted before reviewing the human literature.

Animal Models and Early Life Stress

Nearly all early adversity paradigms manipulate the mother–offspring relationship in some way, either through deprivation, separations, or other manipulations that disturb maternal behavior. Those that do not manipulate the mother–offspring relationship use naturally occurring variations in maternal care to index early adversity (Schmidt, Wang, & Meijer, 2011). Thus, one of the earliest and most productive hypotheses about how adversity gets transmitted is that it alters maternal behavior, which in turn affects the offspring (Smotherman & Bell, 1980). Animal studies, however, have shown that although many early adversity effects are transmitted through maternal care, some are not (Tang, Akers, Reeb, Romeo, & McEwen, 2006). The question of which effects do and do not depend on caregiving has not been addressed in human studies.

The HPA axis has been a prime focus of rodent early experience research. The axis is immature in the rat pup at birth and matures during the first two weeks postnatal when early experiences program GR via regulating methylation of the GR gene (Zhang et al., 2013).

However, it is now apparent that the programming effects of early maternal care extend far beyond epigenetic modification of the GR gene to include (a) the estrogen receptor alpha gene, which influences maternal behavior into the next generation (Champagne, 2012), (b) neurotrophic genes (e.g., BDNF; Roth & Sweatt, 2011), and (c) genes involved in inflammation (G. E. Miller, Chen, & Parker, 2011). Studies are now documenting similar programming effects in other species, as well as our own (reviewed in Champagne, 2012, and G. E. Miller et al., 2011).

What is often missed when this literature is translated to the human case is that there is little evidence that these effects in the rodent depend on elevated CORT. Rather, with regards to the GR gene, its epigenetic modification involves stimulation of thyroid hormone, increases in serotonin turnover and greater expression of nerve-growth factor-inducible factor-A transcription factor in the hippocampus (Zhang et al., 2013). Many of the destructive effects on the hippocampus in the rodent are due to CRH, not CORT (Faturi et al., 2010). Thus, we need to be aware that there may be pathways from early adversity to later effects on the HPA system and other stress-mediating systems that are not produced by activity of the axis during the period of early adversity. Because the HPA axis is more mature in humans than in rodents at birth, early adversity effects in humans may involve CORT even when this is not the case in some rodent models.

Finally, the animal literature makes it clear that exposure to stressors early in life is not always associated with poor outcomes. First, the changes produced by early life adversity may actually support survival in harsh and unpredictable environments. Second, in some instances it is the animals that were exposed to stressors who score higher on tests of cognitive performance, exhibit more robust neurodevelopment, and produce lower levels of stress hormone in response to provocation in adulthood (Lyons & Parker, 2007). In these latter instances, it appears that early life stress has served a stress-inoculation function. We are far from understanding what makes some experiences *stress inoculations* whereas others increase the risk of disease and disorder. The possibility that inoculation effects were obtained because the stressor was *challenging but not overwhelming* has been suggested (Lyons & Parker, 2007). However, so far, this is a post hoc explanation. Nonetheless, if we understood what differentiates stressors that inoculate versus those that increase vulnerability, we would have a much better understanding of resilience.

Other Pathways to Early Adversity Effects

In this chapter we focus on the role of early experiences in programming the neurobiology of stress with an emphasis on the HPA axis and the genes regulating it. However, there are other pathways to early adversity effects that should be acknowledged and that may overlap with those examined here. First, early adversity may affect the development of neural circuits through experience-expectant and experience-dependent processes that influence cell death and synapse pruning (Fox, Levitt, & Nelson, 2010). When these experiences affect the development of neural systems that process threat and orchestrate coping, they may contribute to individual differences in allostatic load across development. Indeed, there is increasing evidence that the amygdala is particularly sensitive to early adversity (Pechtel & Pizzagalli, 2011). There is also increasing evidence that oxidative stress in response to extreme stressors results in damage to DNA, RNA, and lipids (Schiavone, Jaquet, Trabace, & Krause, 2013).

CORT bears a complex, U-shaped relationship with oxidative stress. At low to moderate levels, CORT helps reverse oxidative stress and thus is neuroprotective, whereas at high levels CORT decreases mitochondrial functioning and increases cell death (Aschbacher et al., 2013). These processes may explain why children exposed to longer periods of early deprivation in Romanian orphanages have greater evidence of cellular aging (i.e., shorter telomeres) by middle childhood (Drury et al., 2012). Indeed, in typically developing kindergarten children it has been shown that those who show larger CORT and sympathetic reactions to a stressor protocol have shorter telomere lengths in buccal cells by the end of kindergarten (Kroenke et al., 2011).

Finally, there is increasing evidence that the immune system is programmed by early adversity (G. E. Miller et. al., 2011). Early adversity is believed to program heightened reactivity in inflammatory pathways and down-regulate the GR gene that mediates anti-inflammatory effects of CORT. Programmed thus, the immune system interacts with ongoing life stress and the hormonal signals generated by reaction to these stressors in ways that contribute to the onset of cardiovascular disease, tumors, and bone and muscle loss leading to frailty. The programming mechanisms may involve CORT and CRH.

With this as background, we now turn to a review of the major types of early adversity studied in humans: poverty, parental loss, prenatal stress, risky families, and maltreatment. The categories overlap, but each literature has its unique aspects, justifying their separate treatment.

Childhood Poverty and Lower Socioeconomic Position

Socioeconomic position is a contextual factor associated with a host of adverse early conditions. There is increasing evidence that socioeconomic position during childhood predicts health outcomes in childhood and later in life (Shonkoff et al., 2009). A number of studies have found that a lower economic position in childhood is associated with higher CORT levels. Some of these studies have used

income-to-needs ratios in generally low income samples (Blair, Raver, Granger, Mills-Koonce, & Hibel, 2011), others have used parental reports of financial strain (Essex, Klein, Cho, & Kalin, 2002), and still others have used cumulative risk indices composed of adversities common in low income families (Evans & Kim, 2012). Basal CORT has typically been the focus, either as measured in saliva, overnight urine, or in hair (Vaghri et al., 2013). The ages studied have ranged from infancy to adolescence. Not all studies, however, have found evidence of higher CORT with low socioeconomic position. Some have found the opposite (Badanes, Watamura, & Hankin, 2011). It has been argued that one reason sometimes high and sometimes low CORT is found is that the relationship is actually U-shaped (Boyce & Ellis, 2005; Bush et al., 2011; Marsmana et al., 2012). This might be an attractive solution, except that both U-shaped and inverted U-shaped functions have been found, sometimes in the same study at different time points, (e.g., Bush et al., 2011).

Whereas the above studies are all correlational, one study has manipulated family economic circumstances and then assessed the HPA axis (Fernald & Gunnar, 2009). This study used a quasi-randomized design to examine the effects of a conditional cash transfer program on children living in extremely poor communities in rural Mexico. The children were 2 to 6 years old when assessed after the family had been in the intervention for at least 3 years. The sample was large (over 500 intervention and 700 comparison children). The intervention lowered CORT levels but not reactivity and the effect was larger for children of depressed mothers. Low income and financial strain increases maternal depression. Later we will cover the role of maternal depression in the development of stress reactivity and regulation, but here we note that consistent with the Fernald and Gunnar (2009) study, maternal depression appears to mediate the effect of financial strain on children's HPA axis functioning (Hostinar & Gunnar, 2012).

None of the studies cited above provide evidence that early socioeconomic position programs the HPA axis. Evidence of programming has been examined in adult studies that have contrasted current with childhood socioeconomic status. There are very few studies of this sort and the results are mixed. Using a subsample of the 1958 British Birth Cohort, home basal CORT levels assessed at middle age were found to be associated with lifetime socioeconomic position. Low childhood economic position added to the effect but was not sufficient to program a higher basal set point in the HPA axis in adults who improved in socioeconomic status after childhood (Li, Chiou, & Shen, 2007). On the other hand, using a sample of adults in their 30s who were specifically selected to represent low or high socioeconomic status prior to the age of 5, higher CORT levels were found across the day as evidence that the immune system had been programmed for larger inflammatory responses and poorer containment by CORT (G. E. Miller et al., 2009). These findings were not dependent on current income or position. Of course, even if childhood economic and social circumstances predict adult CORT levels, this would not prove that early socioeconomic adversity programmed the HPA axis. Childhood socioeconomic position may have affected other aspects of the individual's functioning that helped carry its effects forward. This appears to be the case in a study of middle-aged adults for whom childhood disadvantage predicted higher diurnal CORT at middle age (Franz et al., 2013). This effect was mediated by intellectual functioning in early adulthood, which in turn influenced adult socioeconomic position, which then predicted adult CORT. Such findings strongly argue for the need to develop and test cascade models to understand how early adversity ultimately affects stress reactivity and regulation in adulthood. Also, given the variability in results, it is likely that it is not poverty but factors associated with poverty, such as maternal depression leading to lower quality care, that affect the development of stress reactivity and regulation.

Parental Separation and Loss

Loss of a parent in childhood is a risk factor for poorer mental and physical health throughout development (Wilcox et al., 2010). A number of studies have examined CORT in adults who lost or were separated from their parents during childhood. The strongest evidence that such experiences produce long-term effects on the HPA axis comes from studies conducted on adults who were children during World War II and who, for their protection, were sent away from their families. Studying the responses of elderly men and women, one research group (Pesonen et al., 2010) found larger CORT responses to the TSST for those who were separated from their mothers or both parents, but not for those separated only from their fathers.

Interestingly, adults who were separated as preschoolers differed more from the control group than those separated as infants or school-aged children. There are more studies examining adults with childhood bereavement or separation, but none of them differentiated early from later loss. One study of middle-aged men found higher early morning and late afternoon but not bedtime home CORT (Nicolson,

2004). Another study of young adults probed the HPA axis using the DEX/CRH test and found that adults who had experienced loss of a parent or close friend prior to age 19 exhibited larger CORT responses. The largest responses were from those who reported a warmer and more supportive relationship with the parent prior to the parent's death (Tyrka et al., 2008). In sum, studies examining CORT years after childhood bereavement find HPA hyperactivity.

At least two studies have examined HPA-axis activity closer in time to bereavement. For example, children 7 to 13 years old were studied every 6 months for 2 years beginning an average of 19 months after losing a parent in the terrorist attacks on the United States on September 11, 2001. A number developed anxiety, depression, and attention-deficit/hyperactivity disorder (ADHD). Compared with children from the same communities who did not have family members who were killed that day, the bereaved children had higher diurnal CORT levels early in the morning and at 4 p.m. but not at bedtime and they also showed less suppression of CORT to dexamethasone (Pfeffer, Altemus, Heo, & Jiang, 2007).

In sum, there appears to be growing evidence that losing a parent during childhood is associated with anxiety, depression, and a more hyperactive HPA axis. Increased activity of the axis appears to emerge with bereavement and to remain for years, well into adult life. As is discussed in the sections that follow, this contrasts with the effects of maltreatment and trauma, which appear to shift from a hyper- to a hypoactive pattern with time, unless the person develops depressive illness. Parental loss increases the risk of depression, but depression was not necessary to observe increases in HPA-axis set points in the above studies. Clearly the HPA axis can be reset to a higher baseline and response level and stay there for years without becoming downregulated. There must, then, be something different about the neurobiological response to separation and bereavement from the response to other kinds of chronic threats and stressors. Understanding this difference would seem critical in understanding the sequelae of early adversity. One possibility that has not been explored is that the emotions accompanying the initial elevations in CORT (i.e., sorrow versus fear) may set different neuroendocrine and epigenetic processes into motion.

Although studies of childhood loss and bereavement are taken as evidence that early experiences may program the HPA axis, caution is warranted. First, the wide ages over which long-term effects take place raise questions about whether a programming or sensitive period interpretation really is appropriate. If it is a sensitive period effect, it would appear that the HPA axis is sensitive to programming by loss of an attachment figure from birth until at least Age 19, the oldest age used in these studies. Second, no adult comparison group is included. It is not known whether loss of an attachment figure as a child has a greater long-term effects on the HPA axis than loss that produces grief at any other point. Third, while many of these studies also measured psychopathology, none examined whether the HPA axis mediated associations between bereavement and symptoms of emotional problems. Future studies must address these questions.

Prenatal Stress

Some of the strongest evidence that stress has developmental programming effects comes from research on the prenatal period. We have reviewed the work on prenatal stress and rely heavily on that review here (Gunnar & Davis, 2013). The concept of fetal programming arose with evidence that birth weight and/or preterm delivery predicts adult disorders, including heart disease, diabetes, and obesity. Two major hypotheses have been proposed to explain the processes of fetal programming: malnutrition and chronic exposure to CORT. These may be two related hypotheses because the effect of maternal malnutrition on the fetus has been shown in animal studies to depend on elevated CORT (Monk, Georgieff, & Osterholm, 2013).

Although poor maternal nutrition, exposure to toxins, and infections are all stressors reflecting a harsh environment, researchers have focused more narrowly on the role of maternal psychosocial stress. There is evidence that above nutrition and other risk factors, the mother's mental and emotional state has effects on her fetus. Minority status and discrimination may also conspire to produce prenatal stress and poor birth outcomes. Among immigrants, acculturation, rather than reducing poor pregnancy outcomes, increases low birth weight and premature birth (Callister & Birkhead, 2002). Greater acculturation among immigrant Hispanic women has been associated with a flatter diurnal CORT rhythm during pregnancy, which mediated the association between acculturation and birth weight (D'Anna-Hernandez et al., 2012). In another study of Hispanic women, acculturation predicted higher maternal stress, higher plasma CRH levels at 22 to 25 weeks gestation, and earlier delivery (Ruiz, Dolbier, & Fleschler, 2006).

Individual differences in maternal anxiety and perceived stress predict birth outcomes and child psychological functioning, even after controlling for other confounding factors. These studies, however, could simply mean that

women who are anxious and who report high perceived stress transmit these proclivities to their offspring genetically. This cannot be the case for babies conceived through in vitro fertilizations (IVF) in which the birth mother is not genetically related to the fetus. Studying a large number of twins representing both IVF pregnancies of related and unrelated mothers and fetuses, birth weight, duration of gestation, and conduct problems were all shown to be associated with the birthing mother's stress during pregnancy, regardless of genetic relatedness (Rice et al., 2010). Although more studies of this sort are needed, when combined with the animal studies and the work on natural disasters, it seems that there is clearly a phenomenon to understand. The following questions are relevant to this chapter: (a) are the HPA axis or its hormones and peptides involved in mediating these effects, and (b) do programming effects of prenatal stress include programming of the HPA axis? The answers to these questions are still uncertain, but considerable progress has been made since 2005.

Before discussing these issues, it is necessary to describe the physiology of stress during fetal development more completely (Gunnar & Davis, 2013; Sandman & Davis, 2012). During pregnancy there is an integration of the maternal HPA axis, the placenta, and the fetus's HPA axis (see Figure 4.3). During pregnancy, elevations in maternal CORT stimulate increases in CRH gene activity in the placenta, resulting in increases in CRH and ACTH. CRH produced by the placenta stimulates increases in both fetal and maternal CORT production.

As the total production of CORT by the mother increases across her pregnancy, so do her levels of binding globulin. Therefore, for part of pregnancy, levels of unbound CORT are within or close to the levels of nonpregnant women. Also, during this time 11β-HSD2 in the placenta increases and serves the function of converting CORT to an inert substance, thus reducing and regulating the ability of maternal CORT to affect the fetus. All of these effects change as the baby approaches term. In the last trimester, levels of unbound, biologically active CORT in the mother increase precipitously as her cortisol binding globulin levels drop. Further opening the fetus to maternal CORT efflux, levels of 11β-HSD2 in the placenta decrease and there is a marked reduction in the fetus of co-localized 11β-HSD 2 in GR-expressing cells. Thus under low-stress conditions, the fetus is protected from normal pregnancy levels of maternal CORT during roughly the first two-thirds of gestation, and then open to maternal CORT levels after that. Why? It seems likely that this reflects the dual roles of CORT during gestation; specifically, as a stress hormone and as a maturational hormone. During the last trimester

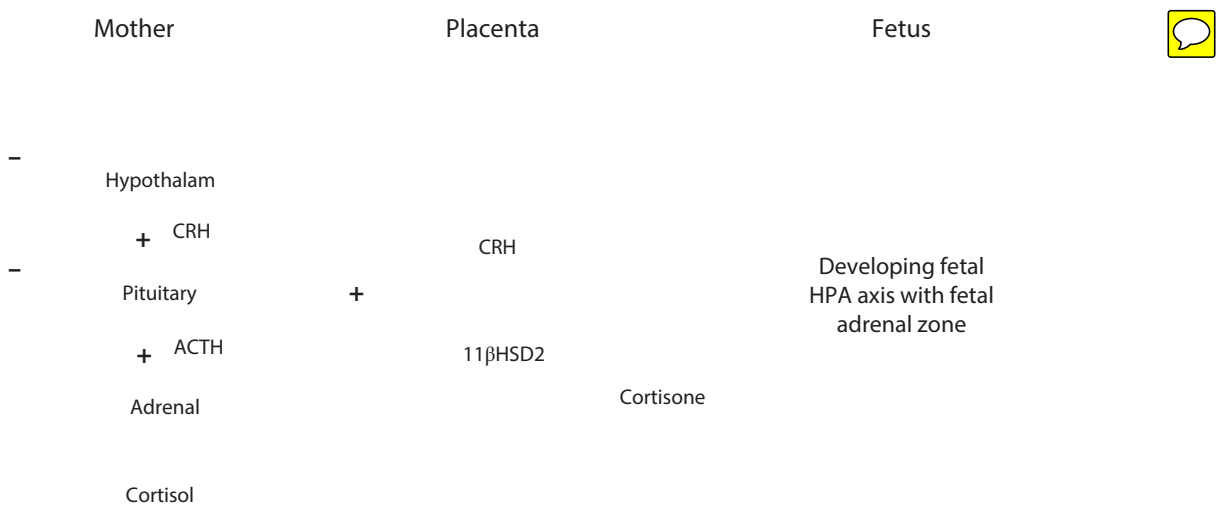

Figure 4.3 Schematic of the maternal, placental, and fetal HPA axis during gestation. During pregnancy, CRH is released from the placenta into both the maternal and fetal compartments. Cortisol *increases* the production of CRH from the placenta. Placental CRH (pCRH) concentrations rise exponentially over the course of gestation; however, the effects of maternal cortisol on the fetus are modulated by the presence of a placental enzyme, 11β-HSD2, which oxidizes cortisol into an inactive form, cortisone. Activity of this enzyme increases as pregnancy advances and then drops precipitously near term, allowing cortisol to promote maturation of the fetal lungs, central nervous system, as well as other organ systems. The fetal HPA axis begins its development early in gestation and becomes increasingly functional with the progression toward term. See text for description.

Reprinted with permission from Gunnar and Davis (2013).

of pregnancy, CORT serves to mature the infant, preparing it for delivery. For example, CORT stimulates the lungs to produce surfactant, which is necessary to allow the baby to breath air.

Because the baby needs to experience elevated CORT levels for its tissues to mature, it would seem reasonable to assume that nature has equipped the fetus with the ability to cope with higher CORT levels during the last trimester, although not perhaps the supraphysiologic levels used therapeutically to rapidly mature the infant's lungs when there is the risk of premature labor. In contrast, given the multiple mechanisms present during early pregnancy to protect the fetus from maternal CORT, we might expect that elevated levels in the mother that are high enough to overwhelm these mechanisms will have significant long-term effects. Indeed, when the mother is chronically stressed and producing elevated CORT levels, this serves to downregulate 11β-HSD2. This has been observed as a function of maternal anxiety and depression during pregnancy (Gunnar & Davis, 2013).

In animal studies, there is strong evidence that the effects of maternal stress on the fetus are mediated by the mother's production of CORT (Meaney, Szyf, & Seckl, 2007). What evidence exists of HPA-axis mediation of prenatal stress effects in humans? The answer to this question is a bit complex. Although there is evidence that maternal CORT affects fetal CORT (as measured in amniotic fluid), associations between maternal reports of stress, anxiety, and/or depressive symptoms do not always correspond to either maternal or fetal CORT levels, (Baibazarova et al., 2013). Furthermore, maternal psychological state in pregnancy and maternal CORT levels independently predict child outcomes (Sandman & Davis, 2012). Thus, it is not clear that the HPA axis is the primary pathway through which maternal emotions produce effects on the fetus. What does seem fairly clear, however, is that activity of the mother's HPA axis affects fetal development. Furthermore, there is evidence that the timing of elevated maternal CORT levels matter in determining the nature of the effects.

Given the changes in mother–infant HPA physiology over the course of pregnancy, it has been argued that elevated CORT earlier in pregnancy, before the third trimester, will have more negative effects on fetal development than elevated CORT later in pregnancy (Sandman & Davis, 2012). A number of the results point in this direction. For example, placental CRH (pCRH) levels at 25 weeks gestation predicted increased risk of preterm delivery and increased fearfulness at 2 months postnatal, while pCRH levels at 31 weeks did not. Likewise, high levels of maternal CORT in the second trimester predicted lower mental development scores at one year, whereas higher levels of maternal CORT in the third trimester predicted the opposite (for review, see Sandman & Davis, 2012). Finally, higher maternal CORT earlier but not later in gestation has also been associated with larger amygdala volume and more emotional problems in 7-year-olds, mediated in part by amygdala size (C. Buss et al., 2012).

In a few of the above studies, effects were observed only in girls (Gunnar & Davis, 2013). There is also evidence in animal studies that prenatal stress differentially affects male and female fetuses with more emotional effects seen in girls and more learning problems observed in boys (Sandman & Davis, 2012). The question of sex differences in the effects of prenatal stress in humans has not been sufficiently examined to allow for conclusions at this point.

There are an increasing number of studies examining whether prenatal stress has programming effects on the HPA axis, although the issue is far from settled. Thus, both pregnancy-specific anxiety and maternal CORT levels during the first trimester have been shown to independently predict higher CORT levels in the child at 4 years during an inoculation stressor and at 5 years in response to starting school (Sandman & Davis, 2012). High levels of CORT in amniotic fluid at 17 weeks gestation, but notably not in maternal saliva, predicted atypical patterns of CORT response to the Strange Situation, compared with moderate to low amniotic fluid levels (O'Connor, Bergman, Sarkar, & Glover, 2013). Controlling for prenatal and postnatal factors, maternal but not paternal prenatal anxiety predicted a blunted CAR and flatter diurnal rhythm in 14-year-old boys and girls (O'Donnell et al., 2013). Finally, in a study of women and their fetuses exposed to anxiety about radiation from Chernobyl, higher CORT levels at 14 years of age were noted for both boys and girls relative to levels for adolescents close in age who were not in utero during this anxious period (Huizink et al., 2008).

The strongest evidence that CORT affects fetal development comes from studies in which the fetus has been exposed to high levels of CORT for therapeutic reasons (Reynolds, 2013). In women at risk for preterm labor, CORT in some form (e.g, betamethasone) is administered. If preterm delivery does not follow, children carried to term provide a model of prenatal CORT effects. The results show reduced birth length, weight, and head circumference, and increases in CORT responses in the neonatal period. Effects are larger when CORT is administered earlier in gestation (i.e., closer to 24 weeks than to 34 weeks, the age range

when the drug is given). Finally, CORT exposure is associated with bilateral cortical thinning, most clearly in the rostral anterior cingulate cortex (Sandman & Davis, 2012).

There is growing evidence that even if prenatal stress affects fetal development, many outcomes are moderated by the care the infant receives after delivery. In the study of prenatal stress, similar findings have been reported for emotional and cognitive outcomes (Bergman, Sarkar, Glover, & O'Connor, 2010). However, there have been few studies examining whether prenatal stress interacts with postnatal caregiving to predict activity of the HPA axis. In one of the few studies available, prenatal maternal anxiety and postnatal caregiving had independent effects on infant CORT responses to the still-face procedure (Grant et al., 2009); however, in another study, postnatal CORT levels were moderated by maternal sensitivity, but only for infants whose mothers had a mental health diagnosis (Kaplan, Evans, & Monk, 2008). Studies are needed to determine whether prenatal stress effects can be eliminated by postnatal caregiving.

To summarize, there is a growing body of evidence indicating that prenatal stress has long-term or programming effects on the fetus, that CORT is involved in at least some of the effects, and that the programming effects may include the HPA axis, increasing basal levels and stress reactivity. There are arguments, however, over how to interpret these effects. Are they impairments or shifts in developmental strategies? There are also arguments over whether the effects are comparable across all levels of prenatal stress or at all points in development. Taking the second issue first, some have argued that the effects of prenatal stress are overstated and that in some populations they enhance development (Dipietro, 2012) or that if mild, they may have positive effects (Sandman and Davis, 2012). The question of whether the effects of prenatal stress should be viewed as impairments or as a reflection of adaptive developmental plasticity are more complex. The programming argument typically has been framed from an evolutionary perspective; specifically, the effects of stress prenatally serve to increase survival of the fetus and the reproductive success of the genes the mother and fetus share. However, the models differ in the importance of the match between pre- and postnatal environment in predicting whether healthy or unhealthy outcomes are predicted. Typically health is predicted in these models when there is a mismatch between the harshness of pre- and postnatal environments (Gluckman et al., 2007). Pluess and Belsky (2011), in contrast, argue that prenatal stress increases fear and stress reactivity but that the effect is to make the child more sensitive to context; thus the prenatally stressed offspring will do poorly in harsh contexts (environments that match prenatal conditions) but extremely well in supportive ones (environments that mismatch prenatal conditions). There is support for both types of predictions. For example, in a study of maternal depressive symptoms, infants did better in terms of health and IQ in their first year of life if the mother's symptoms were stable from the pre- to the postnatal period and worse if she either developed symptoms postnatally that were not there earlier or the reverse (Sandman & Davis, 2012). In contrast, postnatal experiences may moderate associations between prenatal CORT levels and postnatal outcomes, with some evidence that more reactive infants were more sensitive to postnatal experiences (Bergman et al., 2010). Thus far, there are too few studies that have examined, rather than statistically controlled for, postnatal experiences to differentiate between these perspectives.

Parenting and Risky Family Environments

Repetti, Taylor, and Seeman (2002) coined the term *risky families* to refer to family environments that were chronically stressful and/or deficient in warmth and support. While such families can be found at all income levels, they tend to concentrate more among those lower in income, and thus may mediate some of the effects of socioeconomic position on the HPA axis and lifelong health (Repetti et al., 2002). As already described "Normative Development of the HPA System," the presence and availability of a supportive adult with whom the child has a secure attachment relationship provides a powerful buffer that reduces activation of the HPA axis to a range of potentially threatening events. In the following section we examine evidence that variations in care shape children's stress responses and their ability to regulate those responses. We examine this question first in relation to parental warmth and support and then with regards to harsh discipline and interparental conflict and violence. Finally, we examine the few parenting intervention studies that have examined effects on the HPA axis.

Regarding warmth and support, or rather the lack thereof, despite the ranges of ages studied and the different types of measures used, most studies provide evidence that less supportive care is associated with higher CORT levels and greater CORT reactivity. The largest study was conducted in the Netherlands (Marsmana et al., 2012) and included over 1,500 11-year-olds. Children who described less parental support and more parental rejection had

higher basal levels of CORT and higher CARs. Results were obtained controlling for family income. In another large sample of younger children, direct observations of mother–infant interaction at 7 months showed that lower maternal support was associated with less CORT responsiveness at 7 months but overall higher CORT levels by the time the babies were toddlers (Blair et al., 2008). The 7-month measures were obtained in response to a combination of one fear and two frustration tasks. Distress responses to frustration are greater for infants with higher expectations of agency, which might explain the direction of effects at their 7-month age point (Lewis, Hitchcock, & Sullivan, 2004). In another study of 7-month-olds (Grant et al., 2009), using the still-face paradigm that mimics maternal withdrawal of affection, lower maternal sensitivity predicted larger CORT responses. More negative interaction with fathers has also been related to CORT activity in infants at 7 months and in a longitudinal study with toddlers at 24 months (Mills-Koonce et al., 2011). In several studies, mothers who were more withdrawn had children who either showed larger CORT responses to the Strange Situation or exhibited initially elevated and then declining levels of CORT in response to this task (Sturge-Apple et al., 2012).

Nonetheless, higher CORT activity has not always been associated with lower warmth and support. In one of several examples, preschoolers whose mothers were more negative and lower in warmth exhibited a flatter diurnal slope in CORT (Zalewski, Lengua, Kiff, & Fisher, 2012). In this study maternal negativity and low warmth mediated the relations between family income and children's CORT. Notably, in this and another study that also found lower cortisol with lower maternal warmth, the children were drawn from populations for whom low warmth was compounded by poverty and, thus, other adversities. Thus, cumulative stress may have resulted in a downregulation of the HPA axis in these studies.

Hostile, threatening forms of discipline such as yelling and spanking can be frightening to children. While there tends to be a negative association between discipline and parental warmth and support, these dimensions can be disentangled. A small study revealed that mothers who used physical punishment had infants who showed larger CORT responses to maternal separation and interaction with a stranger at 12 months (Bugental, Martorell, & Barraza, 2003).

In a larger study, children on a Caribbean island were sampled for CORT in the morning and evening daily for months. Using each participant as his or her own control, CORT levels were significantly elevated following bouts of harsh discipline and these elevations were larger than responses to other common stressors (Flinn & England, 1995). Finally, combining three samples of 2- to 6-year-olds that used similar methods, mothers who reported using more shouting with their children had children who exhibited higher CORT levels 20 and 65 minutes after strangers arrived at the homes to assess both mothers and children (Hastings et al., 2011). Other studies have also found positive associations between CORT and harsh discipline, but for only some of their participants. Thus, for example, this association was found among children whose mothers were high on depressive symptoms, but not for the other children who experienced harsh discipline (Essex et al., 2011).

Finally, there is at least one publication reporting an association between blunted CORT and greater conflict. This was a study of preschoolers in which the child wore a voice-activated recorder for one weekend day and CORT was assessed across the day on both weekend days (Slatcher & Robles, 2012). Children who were involved in more conflicts had a lower CORT at wakeup and a flatter diurnal slope. It is unclear whether the conflicts were with parents and there was no measure of parental harsh discipline. These findings might reflect associations with conduct problems rather than with parenting (see "Developmental Psychopathology" later in this chapter).

Poor marital quality and aggressive conflict tactics among parents are important contributors to risky family environments (Repetti et al., 2002). Violent arguments between parents should be a significant stressor for children, but not all children show adverse effects. Indeed, there is evidence that emotional insecurity in response to parental fighting determines long-term effects (Davies, Sturge-Apple, & Cicchetti, 2011). Few studies have examined whether CORT responses in children reflect their insecurity in response to parental conflict. In one that did (Koss et al., 2013), children who were more distressed, more dysregulated, and more involved in parental fights were more likely to show a rising pattern of CORT in response to a simulated parental argument. The other studies by this research group all showed that greater exposure to parental fighting was associated with a smaller CORT response to the simulated fight paradigm (Sturge-Apple et al., 2012). This might be because children accustomed to their parents fighting judged the simulated fight to be of low intensity relative to fights they experienced at home. Indeed, overall, CORT levels decreased from pre- to post-testing in this paradigm. In contrast to children's

responses to a simulated fight, infants exposed to more violence in the home showed larger CORT responses to fear- and frustration-eliciting tasks (Towe-Goodman, Stifter, Mills-Koonce, & Granger, 2012). Likewise, in both kindergarteners (5–7 years) and adolescents, poor marital quality has been associated with higher morning and evening CORT levels (Pendry & Adam, 2007). Although more studies are needed to clarify the effects of marital conflict on children's stress responding, it seems likely that the effects may be twofold: increasing HPA reactivity among children who become emotionally insecure as a result of exposure, and habituating the system to mild examples of parental conflict.

Interventions provide the best proof that parenting affects children's CORT activity. To date, there have been seven randomized clinical trials of parenting interventions in which basal and/or diurnal CORT has been measured. All of these studies have been with infants or preschoolers (e.g., Bakermans-Kranenburg, Van Ijzendoorn, Mesman, Alink, & Juffer, 2008; Cicchetti, Rogosch, Toth, & Sturge-Apple, 2011; Fisher, Stoolmiller, Gunnar, & Burraston, 2007). This work has shown that interventions that improve parenting lower CORT or, in studies of maltreated children, bring patterns of CORT production in line with those of children in the nonmaltreated comparison group. In one study, the intervention effects were observed only for the children with the 7-repeat DRD4 polymorphism; however, they were the ones expected to be in greater need of the intervention (Bakermans-Kranenburg et al., 2008).

Finally, so far we know of only one study that has examined the effect of a parenting intervention on CORT reactivity. This study was done with the preschool siblings of adjudicated youth who were themselves at high risk of developing conduct problems and antisocial behavior. As discussed earlier, low arousal and the failure to mount physiological reactions to interpersonal threats is believed to play a role in antisocial behavior problems (van Goozen et al., 2007). Thus this intervention was designed to improve parenting, children's social competence, and to *increase* CORT levels in anticipation of entering a new peer group (O'Neal et al., 2010). The results revealed that, over time, the preschoolers in the intervention group showed increasing levels of CORT just prior to entering new peer groups and the increase in CORT predicted reductions in aggressive behavior during peer entry. There was evidence that this anticipatory CORT was correlated with improvements in parenting, but a mediational analysis was not reported. It would be useful to have more studies examining CORT reactivity.

Overall, studies of the relations between parenting and activity of the HPA system provide good support for the hypothesis that the parent–child relationship is important in regulating activity of the system. Furthermore, intervention studies clearly show that parenting plays a causal and not just correlative role in stress hormone activity during childhood. Most studies indicate that adverse parenting is associated with greater activity of the HPA axis. What is unclear in these studies is whether set points have been programmed. The fact that interventions can alter HPA-axis activity in children suggests that results do not reflect stable epigenetic changes in the axis. More long-term studies that include interventions at different ages are needed to determine whether there are sensitive periods for parenting effects on the axis.

Of course, even if the axis is not programmed by normative variations in parental care, brain systems that are developing during periods of poorer parental regulation of the axis might be affected. Thus the importance of parenting effects on the HPA activity does not solely lie in whether long-term effects on CORT are observed. Studies are needed to analyze whether parenting effects on other outcomes, including brain structure and function, are mediated in part through effects on activity of the HPA axis. In addition, there is the possibility that individual differences among children may influence the openness of the axis to programming by parent–child relationship. Finally, it also may be that when poor parenting becomes abusive and traumatic there will be longer-term effects on the HPA axis and on other neurobiological systems involved in defensive responding. We now turn to that area of research.

Maltreatment

Neglect and abuse are potentially traumatic experiences that threaten a child's viability. Experiences of physical and sexual abuse can co-occur with adequate or even good parenting, while neglect is typically more chronic and may even threaten healthy development more severely (De Bellis, 2005). Maltreated children typically experience multiple forms of maltreatment along with other types of adversity during childhood (see also Cicchetti & Toth, Chapter 13, this *Handbook*, this volume). These experiences increase the risk of a range of pathological conditions, although many and perhaps even most maltreated children display remarkable resilience (Cicchetti & Rogosch, 2007).

Much of the neurobiological work in this area has been guided either by adult research on posttraumatic stress disorder (PTSD) or by work on depression. In adults,

these disorders display markedly different neuroendocrine signatures. PTSD is associated with upregulation of the sympathetic nervous systems in conjunction with a downregulation of the HPA axis and increased negative feedback regulation (Yehuda, 2009), while depression is associated with hyperactivity of the axis and reduced negative feedback regulation (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). One of the major challenges is determining how different signatures could emerge and what effect childhood maltreatment has for those who are resilient and do not develop disorders. We cover issues of depression, maltreatment, and the HPA axis later in the section called "Developmental Psychopathology." In this section we first focus on adult survivors of childhood maltreatment with and without PTSD. After dealing with the adult literature, we examine the effects of childhood maltreatment on the HPA axis in childhood.

Studies of adult maltreatment survivors provide a fairly consistent picture of the long-term consequences of childhood maltreatment. Across abuse subtypes, adults who were maltreated as children exhibit lower basal levels of CORT later in the day and stronger suppression to dexamethasone (Morris, Compas, & Garber, 2012), as well as blunted responses to psychosocial challenges such as the TSST (Heim & Binder, 2012). Notably, meta-analyses have shown that suppressed afternoon and evening basal levels and enhanced response to DEX do not differ for adult survivors of maltreatment as a function of whether they have developed PTSD or not (Morris, Compas, et al., 2012). In addition, trauma in childhood appears to reduce methylation of the ~~FBKP5~~ gene in regions of the gene that are responsive to CORT (Klengel et al., 2013). Recall that FKBP5 is the co-chaperone that reduces the ability of CORT to bind to GR. CORT regulates this gene, with increases in CORT increasing gene transcription as one mechanism that protects the organism from being overly affected by stress-stimulated increases in CORT. Thus, demethylation of the FKBP5 gene amplifies the protective mechanism, but protection from some insults can increase risk of others. There is evidence that in conjunction with childhood trauma, individuals who already carry the version of the FKBP5 gene that is hyperresponsive are at risk for developing PTSD, perhaps because stimulation by elevated CORT ~~posttrauma~~ is actually important for normal processing of the traumatic event (Heim & Binder, 2012). Another factor that might increase the risk of PTSD given childhood maltreatment is upregulation of the sympathetic system. Hyperresponsiveness of the sympathoadrenal system is noted among adults with PTSD and adolescents who will show increasing emotional problems following trauma, but not among trauma-exposed but psychiatrically healthy adults (Lovallo, Farag, Sorocco, Cohoon, & Vincent, 2012).

One reason that the adult work is informative is that pharmacological probes can be used to determine whether changes in CORT production are due to physical changes in the axis as opposed to changes in psychological processing of negative events in higher brain regions. Here the evidence strongly suggests that epigenetic changes within the axis are responsible for the blunting of the CORT response. Indeed, in addition to evidence of upregulation of the GR gene as suggested by enhanced suppression to DEX, blunted ACTH and CORT responses to stimulation by the DEX/CRH test have also been observed in psychiatrically normal adult survivors (Klaassens et al., 2009).

Thus, setting aside adult depression, exposure to maltreatment in childhood appears to downregulate the HPA axis. The processes are complex and interactive, with evidence of upregulated GR but also upregulation of mechanisms that prevent CORT from binding to GR. The complexity within the HPA system should alert us to the general systems nature of adaptation to maltreatment. There are likely many adaptive systems that show this type of reaction and counterregulatory responses. The complexity is nearly overwhelming, so it should not be surprising to find that when the dynamics of development are added, the picture will be unclear, at least until much more is understood about these neurobiological processes.

Indeed, studying children exposed to abuse and neglect has yielded elevated, suppressed, and nonaltered patterns of CORT activity, and there have been a number of good reviews (e.g., Carrion & Wong, 2012; De Bellis, 2005). There are likely a number of reasons for this inconsistency, but the most salient is that this is not only a developing system, but one that may be changing over time in relation to time-since-trauma. This is notable in studies of children with PTSD. Unlike adults with PTSD, children with PTSD tend to exhibit higher than normal levels of CORT (Morris, Compas, et al., 2012). One of the major questions has been whether there is a shift from elevated to suppressed activity as these children mature and, if so, is this shift a function of age or time since the trauma?

At this point the answer is still unclear. Adolescents who were in a relocation camp 2 months after Hurricane Katrina exhibited lower basal CORT levels but not salivary alpha-amylase levels than did age, sex, race, and economically matched comparison teens (Vigil, Geary, Granger, & Flinn, 2010). Thus CORT appeared to already

be downregulated 2 months after a trauma in these youth. In another sample of adolescents, exposure to violence over the previous year was associated with blunted CORT responses to the TSST (Peckins, Dockray, Eckenrode, Heaton, & Susman, 2012). In contrast, in children, those experiencing more traumatic events in the previous year were found to have higher diurnal CORT (Bevans, Cerbone, & Overstreet, 2008). In none of these studies were children with PTSD examined separately from other children and many of the children did not carry any psychiatric diagnosis. When children with varying degrees of PTSD were followed from childhood through adolescence and into early adulthood, a shift in basal CORT levels from elevated to blunted occurred approximately 6–8 years posttrauma (Trickett, Noll, Susman, Shenk, & Putnam, 2010). Trickett and colleagues (2010) reported that this shift was more closely associated with time since identification of the trauma than child age; however, this was only one study and the information it contains pertained only to girls who were sexually abused. Notably, however, a similar conclusion was obtained in the meta-analysis described earlier that included adult-onset trauma exposure as well (Morris, Compas, et al., 2012). More longitudinal studies are needed examining different types of trauma exposure for children at different ages to distinguish between time-related and development-related effects.

A second very critical issue is whether the child is experiencing ongoing adversity. Even if the child is no longer being maltreated, his or her ongoing family situation may be difficult and parenting might still be poor. Often, ongoing family stress is not reported or examined. However, as demonstrated by Kaufman and colleagues (1997), maltreated and depressed children show larger responses to a CRH challenge test, but only if they are experiencing ongoing adversity at home. Likewise, for children in foster care, morning CORT concentrations become more dysregulated with each major care transition (Fisher, Van Ryzin, & Gunnar, 2011). Thus current stressors and protective processes may introduce tremendous heterogeneity making it difficult to discern how maltreatment has affected children's stress reactivity and regulation. Another potential problem in the child literature is that there are very few studies of stress responses to challenging tasks. Nearly all of the data pertain to ambulatory levels. This adds additional complications when researchers have taken samples at different times of the day and in different contexts (i.e., coming to the laboratory, in the home, at a summer camp).

Because of the heterogeneity of findings, much of the attention in the child literature has been focused on trying to understand how individual differences in children might help to explicate inconsistent findings. Thus, Cicchetti, Rogosch, Gunnar, and Toth (2010) examined whether internalizing problems in maltreated school-age children moderated effects on CORT levels assessed during a summer camp. Only children with high internalizing symptoms exhibited altered CORT levels and then only if they had been abused (not just neglected) before Age 5. In a subset of this sample, the same effect was noted for children with the TAT haplotype of the CRHR2 gene, but for this subset it did not matter whether abuse began before or after Age 5 (Cicchetti, Rogosch, & Oshri, 2011). Finally, children with PTSD exhibit higher CORT levels over the day; elevated late afternoon and evening levels in these children predicted decreasing volume of the hippocampus and left ventral PFC (Carrion & Wong, 2012).

We and others have examined children adopted from conditions of deprivation and institutional neglect as a way of examining neglect relatively independently from abuse in children who are not suffering ongoing maltreatment. The results of these studies have also been mixed (Hostinar & Gunnar, 2012). One factor that appears to be significant is whether the child suffered a pattern of growth delay consistent with psychosocially induced short stature (D. E. Johnson & Gunnar, 2011). Children who are stunted at adoption but then exhibit catch-up growth and are no longer stunted at assessment tend to display a flatter pattern of CORT production over the day due to slightly lower morning and higher evening levels (A. E. Johnson et al., 2011).

Importantly, among postinstitutionalized children, late afternoon and evening levels correlate positively with the frequency and severity of the types of problems, specifically indiscriminate friendliness, attention problems, and emotion regulatory problems, that characterize these children (A. E. Johnson et al., 2011; Kroupina et al., 2012).

In all of this work on maltreated children, it is not clear whether the lowered morning levels are characteristic of the children or responses to events on the previous day and evening. There is evidence in animal models that it is critical to bring CORT levels down to near zero in order to reset the diurnal cycle (Akana et al., 1992). In foster care children, CORT levels are suppressed at wake-up on days after the foster parents reported that they were stressed by the child's problem behavior, but not if the foster parents reported child behavior problems that did not create much parenting stress (Fisher & Stoolmiller, 2008). Because, in this intervention study, the intervention lowered parent reports of stress in response to child problem behaviors, one interpretation of the CORT findings is

that stressed parents communicate their irritation with the children, which produces elevated child CORT into the evening hours, which in turn suppresses morning levels. The possibility that morning levels are being driven down by higher levels into the evening is consistent with data on overnight urinary CORT collected from preschoolers adopted from Russian and Eastern European orphanages who were at least 3 years postadoption (Wismer Fries, Shirtcliff, & Pollak, 2008). Although these children's first void CORT concentrations did not differ from those of comparison children, concentrations were higher for those who had suffered severe neglect. Because urinary concentrations reflect activity of the axis many hours earlier, these data suggest increased activity in the late evening and early period after sleep onset. Similar studies combined with salivary measures over the day would be helpful. CORT and sleep are intimately related and thus including sleep measures would be informative (Tininenko, Fisher, Bruce, & Pears, 2010).

Finally, as noted above, there are very few studies examining CORT reactivity among maltreated children, even though most theories involve effects on reactivity rather than basal levels. Here again the results are mixed. Studying 12-year-olds who had been abused by parents, peers, or both, one study reported blunted responses to the TSST with lower CORT responses being associated with more behavioral and emotional problems for the abused children (Ouellet-Morin et al., 2011). Studying postinstitutionalized children of about the same age, we found no difference in response as a function of early institutional care (Gunnar, Frenn, Wewerka, & Van Ryzin, 2009). We did find, however, that the postinstitutionalized children exhibited higher sympathetic tone (Gunnar, Frenn, et al., 2009). Both types of social engagement raised CORT levels in postinstitutionalized preschoolers interacting with strangers (rather than mothers), whereas among children in the nonadopted comparison group, interacting with mothers lowered CORT (Wismer Fries et al., 2008). Despite the ethical challenge of conducting stress tests on emotionally vulnerable children, a much better understanding of how neglect and abuse affect stress reactivity is still needed.

In summary, there is increasing evidence that childhood maltreatment affects the developing HPA axis. The evidence is clearest in studies of adults where there has been enough work to determine that trauma exposure alone is sufficient over time to result in a downregulated HPA system. It is unclear whether age at exposure matters; although, the passage of time does appear to be relevant. Numerous factors moderate these findings, the most critical of which appears to be the development of affective pathology. PTSD is associated with asymmetrical effects on the HPA (blunted) and autonomic (heightened) systems, whereas depression produces the signature of heightened adrenal production of CORT and often a reduced capacity for negative feedback (e.g., Heim et al., 2008). Longitudinal studies are needed to focus on understanding the relations among maltreatment, stress biology (both HPA and autonomic), and the development of neural systems involved in stress and emotion regulation. These studies, however, will have to examine ongoing as well as prior adversity along with the quality of children's relationships and their ability to use relationships to regulate stress.

General Summary of Research on Early Adversity

As this section has shown, studies of early adversity have burgeoned in the decade prior to the time of this writing, from work on poverty to bereavement, prenatal stress to maltreatment. A wealth of evidence shows that adversity in childhood affects the HPA axis and CRH and a small but growing body of evidence that this serves as a pathway through which early adversity affects neurobehavioral development and health. There is still a good deal that is not understood. Poverty, in and of itself, seems to be unreliably related to stress reactivity and regulation. Other types of adversity discussed here are likely mediators. Prenatal stress, but not necessarily maternal emotional state, seems to upregulate the HPA axis, decrease birth weight and increase fearfulness. Parental loss and risky family environments also seem to upregulate the system, but in contrast, maltreatment, perhaps particularly physical and sexual abuse, downregulate the HPA axis, except possibly in those individuals who develop depression (see Depression section). Why different types of stressors have different effects, whether it is type or severity, whether there are sensitive periods and, if so, whether they are the same for different facets of the stress system are questions that must be answered to move the field forward.

TEMPERAMENT AND STRESS VULNERABILITY AND RESILIENCE

Temperamentally shy, behaviorally inhibited children are at risk for developing social anxiety disorders by adolescence, and thus much of the research on stress vulnerability and resilience has focused on this temperament dimension (see review, Fox et al., 2010; Hostinar & Gunnar,

2012). We argue that temperamental shyness increases vulnerability to both adverse childhood experiences and the normative challenges of childhood. It is associated with the affective neurobiology of fear and social phobia that, when activated, stimulates increased HPA axis activity. Furthermore, elevations in CORT can act on these systems to enhance fear memories, increase vigilance to threat, and lower thresholds for subsequent anxious reactions to socially challenging situations (Rosen & Schulkin, 1998). However, low shyness and high extroversion are not necessarily protective. The protective value of a socially outgoing temperament depends on whether extroverted children have sufficient self-regulation to manage their exuberance in appropriate ways. If not, these children are vulnerable to the stress of peer conflict and rejection, and this vulnerability may foster the development of externalizing problems (Oldehinkel, Hartman, De Winter, Veenstra, & Ormel, 2004).

As we discuss in this section, shy/inhibited children do not always activate the HPA axis in response to social challenge. Whether or not they do depends, in part, on whether they embrace or avoid the challenge. If they successfully avoid, the very behavior (i.e., inhibition of approach) that defines behavioral inhibition reduces HPA axis reactivity. If they cannot avoid or choose to approach situations they find threatening, increased HPA axis activity may be observed (Tarullo, Mliner, & Gunnar, 2011). Because of these dynamics, it is helpful to have a cumulative measure of HPA-axis activity that reveals responding over time to multiple instances of challenge, some of which can be avoided and some cannot. In monkeys, behaviorally inhibited temperament is associated with higher CORT levels assessed using hair CORT (Laudenslager, Jorgensen, Grzywa, & Fairbanks, 2011). No studies with children have examined hair CORT in relation to shyness/inhibition, but such work would be helpful. Instead, there are studies examining children's reactions to different social situations.

Shy/inhibited children tend to exhibit relatively low levels of CORT in anticipation of entering a new social group, but higher late afternoon and evening CORT levels following the social challenge (for review, see Hostinar & Gunnar, 2012; Russ et al., 2012). Thus, unlike exuberant children who mount a preparatory response and then return to baseline levels, many shy/inhibited children do not prepare physiologically for the challenge of being with peers and then fail to bring levels to baseline for hours after the encounters are over. Once in the peer group, whether or how fast CORT increases depends on the shy/inhibited child's coping strategies. Shy/inhibited children who spend more time in solitary play show lower CORT responses to group entry (Davis & Buss, 2012). Similarly, over the course of a preschool year, shy/inhibited children who avoid social contact show stable or declining CORT levels (Tarullo et al., 2011). Of course, avoiding social contact, while it may reduce acute experiences of stress, sets children up for developing poorer social skills and experiencing continuing problems in negotiating the social landscape of childhood. This may be why mothering that is overprotective and controlling is associated with sustained inhibition throughout childhood and increased likelihood of developing anxiety disorders (Lewis-Morrarty et al., 2012).

Approaching what frightens you should activate the stress system. There is now evidence that this is what happens when shy children attempt social engagement. For example, in one study shy children who spent more time hovering and attempting to enter into peer interaction produced a more prolonged CORT response to group entry than did shy children who spent more time playing alone (Davis & Buss, 2012). Studying shy/inhibited children across a year of preschool, those who showed increases in CORT levels as the year progressed surprisingly were more socially competent, had more friends, and were better integrated socially into the classroom (Tarullo et al., 2011).

The fact that social approach and peer engagement are both stressful for shy children and essential for developing social competence points to the possibility that activation of the HPA system may, at times, be a component of resilience. What is not known is whether social competence developed at this cost will result in increases in allostatic load for these children. The allostatic load associated with social engagement for shy/inhibited children may depend on whether or not the social competence gained is sufficient to result, over time, in a reduction of anxiety about social interaction.

In addition to these data about peer interaction, stress, and shyness, there is increasing evidence that shy/inhibited children are especially vulnerable to increases in HPA-axis activity in response to adverse childhood experiences. This has been shown for interparental violence, harsh and/or less sensitive maternal care, and poorer quality childcare (Hostinar & Gunnar, 2012).

There is also increasing evidence that for shy/inhibited children, higher allostatic load and/or higher levels of CORT late in the day predicts the development of anxiety disorders and internalizing problems, perhaps most predictably for girls (K. A. Buss, Davis, & Kiel, 2011). Thus, in studying children in full-day childcare, the combination of shy/inhibited behavior and rising levels of

CORT over the childcare day predicted increasing levels of inhibition at childcare and higher internalizing problems (Gunnar, Kryzer, Van Ryzin, & Phillips, 2011). Notably, when CORT followed the normal diurnal decrease over the day in childcare, shy/inhibited children became less fearful over time and showed fewer internalizing problems relative to non-shy children. This last finding is reminiscent of the differential susceptibility and sensitivity to context hypotheses. Indeed, regarding internalizing problem scores, children lower in inhibited behavior were unaffected by whether they experienced increasing or decreasing CORT levels over the childcare day.

In work by Rothbart (Derryberry & Rothbart, 1997), shyness loads negatively on a higher-order temperament factor labeled surgency or extraversion. Children who score high on this factor seek stimulation, are impulsive, enjoy novelty, are not shy, and are high in activity. As noted earlier, such children are at risk for developing externalizing problems (Oldenhinkel et al., 2004). Although they tend to be the opposite of shy/inhibited children, highly surgent children are not necessarily stress resilient. Surgent children do tend to show habituation of the CORT response to parental fighting over time (Sturge-Apple et al., 2012). They are also less sensitive to whether they are in a childcare that produces increases or decreases in CORT over the day (Gunnar et al., 2011). However, while they do not tend to develop altered patterns of CORT or vagal tone reactions in response to harsher maternal care, they do show changes in sympathetic activity that, in turn, mediates externalizing behavior problems (Sturge-Apple et al., 2012).

Indeed, whether the surgent child experiences chronic or frequent elevations in CORT depends on whether they have the self-regulatory competencies to manage their exuberance in ways that do not create conflicts with others. For example, in a study of preschool children, surgency plus poor effortful control was associated with aggressive peer interactions that then resulted in more peer rejection and elevated CORT (Gunnar et al., 2003). For children who are social and outgoing, being isolated or ignored is emotionally distressing. Indeed, there is now evidence that social rejection activates the same circuits that process physical pain (Eisenberger, 2012). Although most surgent children show decreases in CORT over the school year, highly surgent preschoolers who were not well integrated into the social network and who had no close friendships did not show these declining CORT values (Tarullo et al., 2011).

These findings suggest that the relations between emotional temperament and stress vulnerability and resilience depend to large measure on self-regulation. This has been shown in a large sample of 10- to 12-year-olds in the Netherlands. Among these youth, poor self-regulation increased the risk of behavior disorders later in adolescence, with temperament mediating the type of disorder: surgent temperament with externalizing, shy/inhibited temperament with internalizing (Oldehinkel et al., 2004). In that study, self-regulation was assessed as effortful control, a construct that reflects regulation of reactive emotional dimensions of temperament (i.e., approach/impulsivity and fear/withdrawal) by corticolimbic attentional circuits (Derryberry & Rothbart, 1997). In work with Posner, Rothbart identified executive attention involving the anterior cingulate cortex (ACC) and the dlPFC, as fundamental to effortful control (Posner, Rothbart, Sheese, & Tang, 2007). Executive attention and other executive functions influence circuits in the vmPFC that can put the brake on the amygdala and hypothalamic autonomic and neuroendocrine systems. Under resting conditions, one would expect that children scoring higher on measures of effortful control would have lower basal HPA activity (Watamura, Donzella, Kertes, & Gunnar, 2004). Under conditions of cognitive challenge that require recruitment of effort, modest increases in HPA and autonomic activity should support better performance (Blair, Granger, & Razza, 2006). Finally, under conditions of emotional threat that require modulation of amygdala reactivity, higher levels of effortful control should result in reduced HPA reactivity (Slattery, Grieve, Ames, Armstrong, & Essex, 2013). Interestingly, in response to the TSST, better executive functions (in the form of working memory) predicted a smaller CORT response in nondisordered adolescents, but the opposite was found in adolescents with internalizing disorders (Slattery et al., 2013). It is not only cognitive skills but likely the uses to which they are put (adaptive coping versus ruminating) that influences stress responding. Also, as discussed earlier, elevations in CORT can impair executive functions and effortful control. Thus, there is a dynamic relationship between the cognitive abilities that support self-regulation and the activity of stress-sensitive systems.

Inputs from the vmPFC to the amygdala appear to be critical in extinction of fear responses, and perhaps as these inputs develop they may be critical in regulating the responses of temperamentally shy/inhibited children. Experience also affects the development and functioning of the vmPFC and the strength of its control over amygdalar threat processing.

In studies of adult humans and animals, those with prior experiences of control over potent stressors cope better

with subsequent threats, responding with less activation of the HPA axis and with stronger apparent expectations of being able to protect themselves from harm. There is increasing evidence that this facet of resilience reflects control-induced activation of the vmPFC (Maier & Watkins, 2010). These data add to an understanding of why overprotective parenting sustains shy/inhibited temperament as such parenting may neither allow nor promote children's experiences with manageable threat (Lewis-Morrarty et al., 2012). In addition to experiences of controllable threat, there is evidence that children's ability to regulate emotions and reduce stress is promoted by parental scaffolding, which reflects responsiveness to the child's needs and respect for the child's autonomy (Eisenberg et al., 2010).

Summary and Future Directions

Children's emotional dispositions and their ability to regulate those dispositions contribute to their stress vulnerability and resilience. Experiences affect how temperamental differences among children influence development and how self-regulatory capacities develop and modify stress vulnerability and resilience. The two reactive dimensions of temperament that were discussed, shyness/inhibition and surgency, affect the odds that children will develop internalizing and externalizing disorders. We now turn to what is known about relations between stress and psychopathology in childhood and adolescence.

DEVELOPMENTAL PSYCHOPATHOLOGY

Activity of the HPA axis has been implicated in several mental disorders. We already discussed its potential role in PTSD in the section on maltreatment. Here we focus on two disorders that emerge in childhood and adolescence: major depressive disorder and disruptive behavior disorders (DBDs). Two major questions guide our discussion of this work: (1) What is the evidence that dysregulation of the HPA axis is involved and (2) is stress experienced during development critical to the role that CORT and/or CRH play in these disorders?

Depression

Dysregulation of the HPA axis in depression is one of the most robust findings in biological psychiatry. Depression is often accompanied by a flat diurnal rhythm due to failure to bring CORT down to low levels in the late afternoon and evening (Heim & Binder, 2012).

Depressed individuals exhibit a larger CORT elevation in response to stressors and they remain elevated for a longer period of time before returning to baseline post-stressor. In addition, they often show failure to suppress to the dexamethasone challenge test, indicating poor negative feedback regulation of the HPA axis. Both the remitted and current major depression groups exhibit a higher CAR than never-depressed individuals (Vreeburg et al., 2009). Adults with depression consistently show a blunted ACTH response to CRH challenge, possibly due to a chronic CRH drive and subsequent downregulation of pituitary responsiveness to CRH (Heim & Binder, 2012). This adult literature on depression and the HPA axis has been challenged by work on adults with depression who do and do not have histories of child abuse (Heim & Binder, 2012). Many of the findings described above appear to be characteristics of depressed adult survivors of child abuse rather than depressed adults without maltreatment histories.

Consistent with this argument, suicide victims with a history of child abuse compared with those without were found to exhibit increased methylation of the same gene in the hippocampus (i.e., NR3C1 promoter region of the GR gene) shown to be methylated in rodent studies of poor maternal care (McGowan et al., 2009). Because of the frequent comorbidity of PTSD and major depression, the association of major depression with hyperactivity of the HPA axis and PTSD with hypoactivity has long been very puzzling. If, however, trauma is associated with hyperactivity of the axis followed by downregulation in most individuals but not in those who develop major depression, then this provides a way of focusing the research question.

Specifically, why, in adult survivors with major depression, has the HPA axis up- rather than downregulated in response to frequent or chronic elevations in CORT experienced in response to maltreatment?

Treatment studies provide the most compelling evidence that the HPA system and CRH play causal roles in the induction and maintenance of major depression. For example, antidepressants reduce CRH in the cerebral spinal fluid (CSF) of healthy controls as well as in patients with major depression, indicating that antidepressants directly manipulate CRH levels rather than the reduction of CRH being a side effect of improved depressive symptoms (Wilkinson & Goodyer, 2011). Treating depression with SSRIs reduces CORT levels of depressed adults to those of nondepressed adults, and this decline is correlated with lower levels of depressive symptoms. Rodent studies

support the causal role of the axis by showing that depressive behaviors and HPA hyperactivity induced by low maternal care can be reversed in adulthood by pharmacological and dietary interventions that reverse methylation of hippocampal GR (Heim & Binder, 2012). Individuals with high CRH have the greatest risk of relapse following antidepressant treatment (Wilkinson & Goodyer, 2011). In addition, greater CORT reactivity predicts increases in depressive symptoms (Morris, Rao, & Garber, 2012) and a smaller CAR, or blunted HPA axis activity and low morning CORT predict an unfavorable psychiatric course and/or greater risk of relapse (Morris, Rao, et al., 2012; Vreeburg et al., 2009).

The role of the HPA axis in child and adolescent depression is less clear (Wilkinson & Goodyer, 2011). Although high CORT levels are often reported for depressed youth studied in outpatient settings, it has been more difficult to identify endogenous dysregulation assessed by acclimatizing children and adolescents to a sleep laboratory for several days, providing them with warm and supportive adult attention, and then testing them for both sleep and HPA-axis impairments (Dahl et al., 1991). It is hypothesized that children may be more resilient than adults to endogenous dysregulation and that the period of late adolescence or more chronic depression may shift individuals to greater endogenous vulnerability. The experience of depression may also have different effects on children and adults. For example, in adolescents, those studied soon after symptom onset showed elevated CORT levels, whereas those studied following more chronic symptoms showed blunted activity of the HPA axis. By contrast, adults with more chronic symptoms are, if anything, hypercortisolimic. In depressed youth, the system may still be resilient enough to downregulate following periods of prolonged activation.

HPA measures have also shown predictive power in adolescents. A higher CAR in adolescence predicted the onset of a major depressive episode 2.5 years later although it was not predictive beyond that time point (Vrshek-Schallhorn et al., 2013). In another study, higher basal CORT in the morning and afternoon predicted an increase in depressive symptoms over 2 years in boys tested initially between 10 and 14 years (Heim & Binder, 2012). Although HPA dysregulation is less common in children and adolescents with depression, these findings indicate that regulation of the HPA axis likely contributes to the onset and maintenance of depression prior to adulthood.

Some of the most persuasive evidence that abnormalities in the HPA axis precede the onset of depression come from the study of not-yet-depressed children who are at high risk because of a family history of depression. When the depressed family member is the mother, as is often the case in these studies, alterations in the axis before the children develop depression likely reflects the interaction of both shared genetics and shared environment along with the effects of parents and children on one another. That said, offspring of postnatally depressed mothers had higher and more variable morning CORT levels over 10 days when they were 13 years old, and these levels predicted the development of depressive symptoms over the next few years (Halligan, Herbert, Goodyer, & Murray, 2007). At the transition to adolescence, girls but not boys with depressed parents showed blunted CORT responses to a psychosocial challenge (Bouma, Riese, Ormel, Verhulst, & Oldehinkel, 2011). Children with depressed mothers may also be more likely to develop dysregulated patterns of HPA axis activity when exposed to other family risk factors such as harsh parenting (Dougherty, Klein, Rose, & Laptook, 2011), high expressions of anger in the family (Essex et al., 2011), or insecure attachment (Heim & Binder, 2012). The timing of maternal depression may also matter, which suggests that more than shared genetics are involved (Dawson & Ashman, 2000).

Of course, it is not just the HPA axis that may be altered prior to symptom onset in the offspring of depressed mothers. There is at least one report that low levels of vagal tone and poor vagal regulation are observed in children of depressed mothers (Gentzler, Rottenberg, Kovacs, George, & Morey, 2012), which is consistent with evidence that low vagal tone and blunted CORT responses may co-occur with higher levels of internalizing symptoms in children (El-Sheikh, Arsiwalla, Hinnant, & Erath, 2011). Thus, interactions of HPA axis anomalies with anomalies in other developing stress-mediating systems need to be examined. In addition, given the increase in depressive symptoms and the emergence of the gender bias in depression with puberty, special consideration must be given to interactions between the HPA and hypothalamic-pituitary-gonadal axes.

Researchers are actively pursuing whether genes involved in regulating the HPA system (e.g., CRHR1, GR and MR polymorphisms, FKBP5) affect the risk for depression. We have already discussed FKBP5, which seems to moderate the effect of childhood abuse on adult PTSD (Klengel et al., 2013). For depression, it may be the CRHR1 gene that moderates the effects of child maltreatment (Heim & Binder, 2012). This pattern would suggest that genes that increase the potency with which

threats can affect the pituitary-adrenal system and other fear-stress orchestrating targets of CRH increase the risk of depression, while genes that downregulate CORT effects may increase the risk of PTSD. This is highly speculative, but it does suggest the relevance of a systems neuroscience approach to understanding genes, stress, and developmental psychopathology.

Disruptive Behavior Disorders

Disruptive behavior disorders (DBDs), including conduct disorder and oppositional defiant disorder, have been associated with low basal and reactivity measures of both the HPA and ANS systems. There have been a number of reviews on this topic, which we draw on in this section (Hawes, Brennan, & Dadds, 2009; Shirtcliff et al., 2009; van Goozen et al., 2007). One study by van Goozen and colleagues (2007) proposed a neurobiological model of childhood antisocial behavior according to which genetic factors interact with childhood adversity to produce neurobiological and self-regulatory deficits, which then enhance the development of antisocial behavior. Diminished activity of the HPA axis plays an important role in this model based on evidence that, in animals, CORT interacts with serotonin receptors in the amygdala to support typical aggressive responses to threat provocations and insufficient CORT then fails to provide this input. This then leads to abnormal, hyperaggressive behavior. Studies supporting the association between CORT and DBD in children include evidence that (a) when exposed to a stressor that involves taunting and disparaging remarks made by another child, typical children respond with elevations in CORT and autonomic activity, whereas DBD children do not but do engage in more hostile retributive actions, (b) youth with lower CORT levels and reactivity respond less to interventions designed to reduce antisocial behavior, and (c) even subclinical levels of externalizing problems have been associated with lower baseline levels of CORT. Despite these arguments, a meta-analysis revealed that the association between CORT and externalizing behavior is less strong than once thought. This led Hawes and colleagues (2009) to posit two pathways to adult antisocial behavior distinguishable by whether the children display callous-unemotional traits. These traits are viewed as developmental precursors of psychopathy. One pathway to adult antisocial behavior runs through this disposition, which is associated with blunted activity of the HPA axis, whereas another runs through adverse childhood experiences, poor emotion and behavior regulation, and more reactive stress responding. The Hawes et al (2009) analysis is complemented by another (Shirtcliff et al., 2009) that reviewed the neuroscience research on psychopathy, callousness, and empathy and provided a rationale for why low levels of CORT and reduced HPA axis reactivity should be associated with the observed patterns of brain impairments in callous-unemotional antisocial individuals. Despite this, the empirical evidence for a relation between callous-unemotional traits and low levels of CORT activity is weak. Among boys with ADHD and DBD, blunted CORT reactivity to the TSST has been associated with callous-unemotional traits (Stadler et al., 2011). However, two other studies failed to find any association with basal CORT levels, although aggression was negatively associated with basal levels in these studies (e.g., Poustka et al., 2010). Because the relation between antisocial behavior and low sympathetic tone and reactivity is better established, it may be that a combination of low CORT and low sympathetic activity will be more consistently associated with DBDs (van Goozen et al., 2007).

Treatment studies are particularly telling. Thus, boys with DBD were found to have lower CORT levels than healthy controls before treatment and a larger increase in CORT over time, suggesting that interventions may reduce disruptive behaviors through normalization of basal CORT levels (Dorn, Kolko, Shenk, Susman, & Bukstein, 2011). Studies have also shown that ~~that~~ DBD interventions increase HPA axis responses to a frustration stressor (van Goozen et al., 2007) and CORT levels in anticipation of peer entry in boys at risk for DBD, as discussed earlier (O'Neal et al., 2010).

Comorbidity is a problem for researchers studying DBD, as anxiety and attention disorders are often present simultaneously with DBD. Furthermore, there is evidence that, when comorbid with an anxiety disorder, the relations of DBD with CORT may invert. That is, in the absence of an anxiety disorder, children with DBD may have lower than normal levels of CORT or CORT reactivity, but when combined with an anxiety disorder, CORT levels and reactivity may be higher than in nondisordered children (van Goozen et al., 2007). Thus, variability in findings may have to do with other comorbid problems present in children with DBD.

It may also be that activity of the HPA axis is associated with an endophenotype that contributes to the development DBD but may do so to different degrees for different children or for different subtypes of DBD. As we have discussed, callous-unemotional traits might be one such endophenotype. Another may be low sensitivity to

punishment. Low punishment sensitivity has been associated with amygdala hyporeactivity to negative events, lower CORT reactivity, altered fear conditioning, and changes in serotonin and noradrenaline regulation (Matthys, Vanderschuren, & Schutter, 2012). There is evidence that disrupted serotonergic regulation is related to low CORT levels or CORT downregulation following chronic stress, but more research is needed to understand the nature of this association. Impaired sensitivity to punishment and its accompanying physiological characteristics may disrupt children's and adolescents' abilities to pair inappropriate actions and negative consequences. Disruptions have been related to hyposensitivity to reward, which encourages adolescents to engage in sensation seeking as a compensatory behavior, and to problems with executive functioning, which impair the ability to overcome emotion-driven behaviors (Matthys et al., 2012).

Sex differences are essential to consider in research on DBD. There is evidence that boys with DBD and healthy control girls have lower basal CORT than girls with DBD and healthy control boys (Dorn et al., 2009). The timing of puberty and activity of specific systems are also important moderators of disruptive behaviors. In boys, high CORT responses to stress were related to antisocial behavior in adolescents with later onset puberty. However, in boys with earlier puberty, lower salivary alpha-amylase activity—an index of autonomic activity—was related to more antisocial behavior (Susman et al., 2010). Future research needs to consider the effects of testosterone, SNS mediators, and hormones with antiglucocorticoid properties (e.g., DHEA) in order to understand the complexities of DBD in relation to the HPA axis.

Summary and Future Directions

One of the most perplexing questions confronting neuroendocrine researchers is whether HPA-axis dysregulation precedes psychopathology or if the onset of psychopathology produces alterations in HPA functioning. Although there is growing evidence of HPA abnormalities preceding the onset of psychiatric disorders, future research must track children before any sign of disorder to determine how early alterations can be detected and whether this information can be used in preventative interventions. The role of genes in mediating HPA-axis contributions to the development of psychopathology, as well as the effects of stress in epigenetic changes contributing to psychopathology are critically important and growing areas of research.

Future models of HPA axis development must explain how the system acts to mediate the effects of experience on physical, cognitive, and socioemotional domains across time and in concert with other stress-mediating systems. These models must also describe how individual characteristics affect HPA regulation and predict who goes on to develop psychopathology. As knowledge of HPA correlates of psychological functioning accumulates, translational efforts should be made to aid the treatment of disorders. For example, should practitioners manipulate CORT levels or GR levels and sensitivity in order to prevent or treat depression? Can altering stress hormone levels affect individuals' ability to cope following a major stressor to prevent PTSD? Any such efforts should be made with the understanding that the HPA axis does not operate in isolation and that manipulation of the system may also affect susceptibility to other disorders closely related to stress system activity.

GENERAL CONCLUSIONS AND FUTURE DIRECTIONS

There is little doubt that stress plays a critical role in development and that activity of the HPA axis and CRH, in interaction with other stress mediators, is involved in many of the effects of childhood adversity on physical and mental development. Despite the broad evidence for this conclusion organized in this review, there are a number of issues that remain to be resolved.

First, are there sensitive periods for the development of stress reactivity and regulation, and if so, when are they and how are they characterized? Although there are clear sensitive periods in the rodent models that spawned this field, rodents are born with less mature neuroendocrine systems than humans are and translating the timing of sensitive periods from rats to humans is problematic. Yet there is increasing evidence that the homologous GR gene is methylated by postnatal experiences in rats and humans (McGowan et al., 2009). Nature appears to be able to accomplish similar outcomes in the infant rat and young human, though it is unknown whether they occur through the same molecular processes. Still, the issue of sensitive periods for shaping the stress system persists and is one of the more critical ones in the field.

Second, how can we move beyond analyzing each stress-mediating system separately? The dynamics of the HPA axis defy many of our attempts to do so. For example, while elevated sympathetic and suppressed HPA activity

might reflect the effects of chronic stress, it depends on the type of stressor, the context, the individual's prior history with similar stressors, and likely, the stage of development. To be useful, theoretical models of multisystem patterning need to be as nuanced and contextualized as the neurobiology and neuroendocrinology of stress.

Third, theories and research plans in the study of development have paid relatively little attention to temperament, sex differences, or gender socialization. Nonetheless, temperament has been shown repeatedly to moderate stress responses and the effects of stress on development. With regards to sex and gender, although we see few sex differences in physiological reactivity until puberty, it seems quite possible that gendered worlds of childhood will begin to affect how children weigh the threats they encounter and influence their best strategies for managing threat. No theories of stress adequately address sex differences, although the Tend-and-Befriend hypothesis (Taylor et al., 2000) might provide inspiration for how to begin examining and thinking about how gendered stress and coping emerges during development.

Fourth, we need to understand how development, and particularly puberty, affects stress physiology for children exposed to early life stressors and trauma. Time-since-trauma may explain changes in the direction and activity of stress-mediating system during adolescence, but it seems highly unlikely that this is the whole story. Puberty may open windows for reorganizing the neurobiology of stress and emotion shaped in particular ways by earlier experiences, and pubertal hormones and processes may have differential effects on this neurobiology depending on the way earlier experiences have shaped the system. Given the importance of adolescence in psychopathology, this is a critical avenue for future research.

Finally, we need to figure out how best to incorporate work on genes and epigenetics into our theories and research on stress and development. We now know of a number of polymorphisms for stress-relevant genes. Studies are beginning which, generally, ask the same question: Does this genetic polymorphism moderate the stress response? These studies are likely to yield conflicting findings. Until the field of developmental science can move beyond the simple directional hypothesis (increase or decrease the stress response), it will not reap the benefits of molecular genes. What is needed are hypotheses that take into account the nature of the stressor, the level of the system the gene should affect, the potential counterregulatory activity that may have developed to negate the effects of the "faulty" gene and the time during the stress response that effects should be most apparent. In all of this, the developmental stage is also likely to be relevant. The same applies to epigenetics. It is necessary to move beyond asking whether the epigenome is affected by childhood experiences, although this was an important first issue, and move on to asking about specific epigenetic effects. Again, it may also be necessary to adjust predictions to the specific tissue under analysis. And again, are there sensitive periods for epigenetic programming of stress-relevant genes, and the same sensitive periods for brain, buccal, and white blood cells? These are challenging questions, but ones that will be at the forefront of research on stress and development in the coming years.

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