The Neurobiology of Stress and Development

Megan Gunnar and Karina Quevedo

Institute of Child Development, University of Minnesota, Minneapolis, Minnesota 55455; email: Gunnar@umn.edu, queve001@umn.edu

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Key Words

HPA axis, psychopathology

Abstract

Stress is a part of every life to varying degrees, but individuals differ in their stress vulnerability. Stress is usefully viewed from a biological perspective; accordingly, it involves activation of neurobiological systems that preserve viability through change or allostasis. Although they are necessary for survival, frequent neurobiological stress responses increase the risk of physical and mental health problems, perhaps particularly when experienced during periods of rapid brain development. Recently, advances in noninvasive measurement techniques have resulted in a burgeoning of human developmental stress research. Here we review the anatomy and physiology of stress responding, discuss the relevant animal literature, and briefly outline what is currently known about the psychobiology of stress in human development, the critical role of social regulation of stress neurobiology, and the importance of individual differences as a lens through which to approach questions about stress experiences during development and child outcomes.

Contents

INTRODUCTION

Threats to well-being, whether physical or psychological, are components of life experience. Individuals differ markedly, however, in the frequency with which they experience stressful life events and their vulnerability or resilience to stressful challenges (Akil & Morano 1995). Stress, although often studied as a psychological construct, may be viewed from a biological perspective (Dantzer 1991). Accordingly, stress responses are composed of the activation of neurobiological systems that help preserve viability through change or allostasis (McEwen & Seeman 1999). Although necessary for survival, the effects of frequent physiological stress responses may increase the risk of future physical and mental health problems. The impact of physiological stress reactions on the developing brain may be of particular note, helping to explain how adverse rearing experiences heighten the risk of behavioral and emotional problems in children and adolescents (Gunnar 2000, Heim & Nemeroff 2001, Sanchez et al. 2001). In the past 20 years, advances in measurement techniques have allowed developmental researchers to assess physiological stress responses in children both in the laboratory and under naturalistic conditions (Gunnar & Talge 2006). Consequently, the field of developmental stress research has burgeoned. In the following review, we outline the anatomy and physiology of stress, discuss the animal literature relevant to the study of stress in human psychobiological research, and briefly outline what is currently known about the development of stress reactivity and regulation, the social regulation of stress in human development, the impact of maltreatment on stress neurobiology, and the importance of individual differences as a lens through which to approach questions about stress and experience during development.

NEUROANATOMY AND PHYSIOLOGY

Stress responses in mammals are effected by two distinct but interrelated systems:

the sympathetic-adrenomedullary (SAM; Frankenhaeuser 1986) system and the hypothalamic-pituitary-adrenocortical (HPA; Stratakis & Chrousos 1995) system. The SAM system is a component of the sympathetic division of the autonomic nervous system, releasing epinephrine (adrenaline) from the medulla or center of the adrenal gland. Increases in circulating epinephrine facilitate rapid mobilization of metabolic resources and orchestration of the fight/flight response (Cannon 1929). The HPA system, in contrast, produces glucocorticoids (cortisol in humans, corticosterone in rodents; hereafter GCs) which are steroid hormones. Unlike epinephrine, which does not cross the blood-brain barrier to a significant degree, the brain is a major target of GCs (Bohus et al. 1982). Also unlike epinephrine, GCs production takes some time (approximately 25 minutes to peak levels), and many of its impacts on the body and brain occur through the changes in gene expression (de Kloet 1991). Consequently, the impacts of GCs are slower to develop and continue for longer periods (de Kloet et al. 1996). As discussed more fully below, the role of the HPA system in stress is complex, and its functions are not fully captured by reference to the fight/flight response (Sapolsky et al. 2000). Regulation of both the SAM and HPA systems converges at the level of the hypothalamus, which integrates autonomic and endocrine functions with behavior (Palkovits 1987). Furthermore, inputs to the hypothalamic nuclei that orchestrate HPA and SAM responses to psychosocial stressors involve cortico-limbic pathways (Gray & Bingaman 1996). Each system is described in detail below.

The Sympathetic Adrenomedullary System

The chromaffin cells of the adrenal medulla are secretor cells developmentally and functionally related to postganglionic sympathetic neurons and are considered part of the sympathetic nervous system (see **Figure 1**) (Vollmer 1996). They are innervated by sympathetic preganglionic neurons residing in the intermediolateral gray matter of the spinal cord (Tasaptsaris & Breslin 1989). Sympathetic preganglionic neurons send axons through the ventral root of the spinal cord and form cholinergic synapses with the chromaffin cells. When these cells are stimulated, they secrete catecholamines, predominantly epinephrine (Epi) but also some norepinephrine (NE) (Vollmer 1996). Epi and NE bind to various adrenoreceptors in multiple target organs and thus play multiple roles in fight/flight reactions (Tasaptsaris & Breslin 1989). For example, they both increase heart rate and stroke volume (and hence, cardiac output) and cause vasodilatation in muscles and constriction of blood vessels in the skin and gut. These changes ensure blood supply to the brain and muscles. Critically, Epi stimulates glycogenolysis in the liver, resulting in increased serum levels of glucose and therefore energy to fuel defensive responses. Although neither Epi nor NE cross the blood-brain barrier, the peripheral actions of these catecholamines are paralleled in the brain by NE produced by the locus coeruleus (Morilak et al. 2005). Its role in response to psychosocial threats is to support vigilance, arousal, and narrowing of attention, along with participating in processes that activate the other arm of the mammalian stress system, the HPA axis.

The Limbic Hypothalamic-Pituitary-Adrenocortical Axis

The cascade of events that leads to the production of glucocorticoids by the adrenal cortex begins with the release of corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) by cells in the paraventricular nuclei of the hypothalamus (see **Figure 2**; reviewed in Gunnar & Vazquez 2006). CRH and AVP travel through small blood vesicles to the anterior pituitary, where they stimulate the release of adrenocorticotropic hormone (ACTH) (Stratakis & Chrousos 1995).

Stress: psychological condition in which the individual perceives or experiences challenges to physical or emotional well-being as overwhelming their ability and resources for coping

SAM: sympathetic adrenomedullary (system)

Hypothalamic-pituitary-adrenocortical (HPA) system: describes the complex chain of physiological events that characterizes one of the stress response systems

Glucocorticoids (GCs): a family of steroid hormones (such as or cortisol in humans and corticosterone in rodents) produced by the adrenal cortex

Cortico-limbic pathways: interconnected group of cortical and subcortical structures in the human brain that constitute the neural substrate for emotion, motivation, emotional learning, and regulation

Epi: epinephrine

NE: norepinephrine

CRH: corticotrophin-releasing hormone

ACTH: adrenocorticotropic hormone

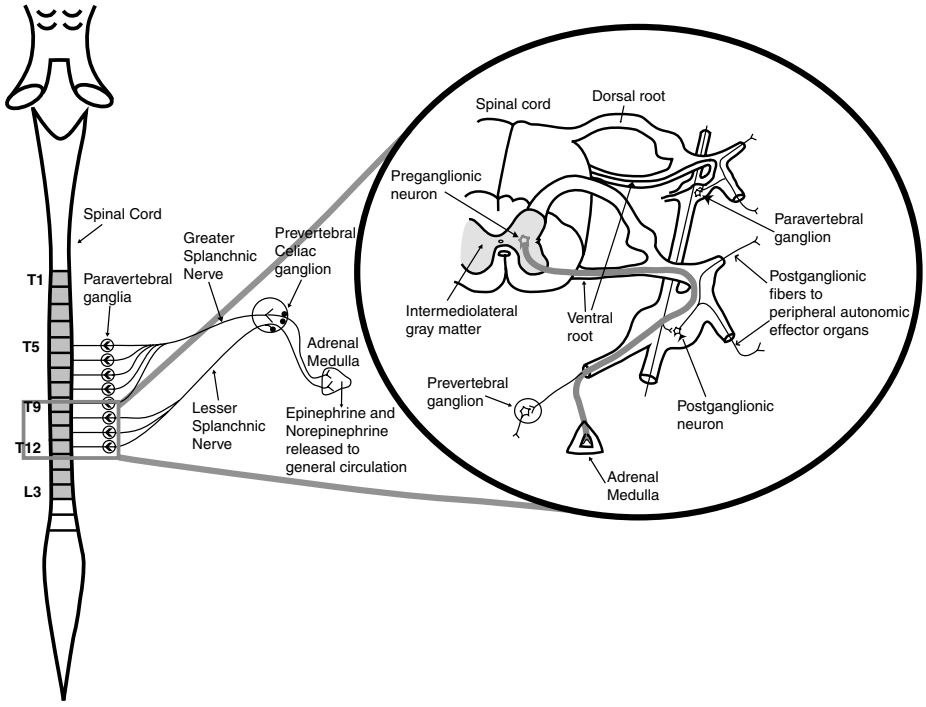

Figure 1

Anatomy of the sympathetic adrenomedullary (SAM) system. The SAM system is a component of the sympathetic nervous system. Its cell bodies (preganglionic neurons) are located in the interomediolateral (IML) cell column and exit the spinal cord via the ventral root to form cholinergic direct synapses on the chromaffin cells of the medulla of the adrenal glands. When stimulated, these chromaffin cells secrete catecholamines, epinephrine (80%), and norepinephrine (20%). The chromaffin cells of the adrenal medulla thus are equivalent to postganglionic sympathetic neurons. Secreted into general circulation, they act as hormones, affecting organs and tissues via adrenergic receptors (alpha and beta) that are activated at lower levels of epinephrine than norepinephrine. Adrenomedullary output greatly enhances sympathetic neural activity.

Sympathetic-adrenomedullary system: a primary biological system controlling stress response. Outflow of sympathetic autonomic nervous system that triggers rapid physiological and behavioral reactions to imminent danger or stressors

MRs: mineralocorticoid receptors

GRs: glucocorticoid receptors

ACTH interacts with receptors on the cortex of the adrenal gland to stimulate the production and release of GCs into general circulation. GCs enter into the cytoplasm of cells throughout the body and the brain, where they interact with their receptors (de Kloet 1991). The activated receptors then enter the nucleus of the cell, where they regulate the transcription of genes with GC-responsive regions. The action of GCs on target tissues involves changes in gene transcription, which explains why the effects of elevated GCs may take many minutes to hours to be produced and may continue to exert effects on physiology and behavior for prolonged periods (Sapolsky et al. 2000).

The effect of GCs depends upon the receptors with which they bind. There are two GC receptors: mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) (de Kloet 1991). Outside the brain, GCs operate through GRs because of the presence of an enzyme, 11-beta hydroxysteroid dehydrogenase (11β-HSD), that prevents GCs from binding to MRs. In the brain, where 11β-HSD is minimally expressed, GCs bind to both MR and GR. Indeed, GCs have higher affinity (i.e., bind more readily) to MRs than to GRs, a fact that is critical in the regulation of both basal and stress responses of the HPA system (reviewed in Gunnar & Vazquez 2006). Because of their differential affinities

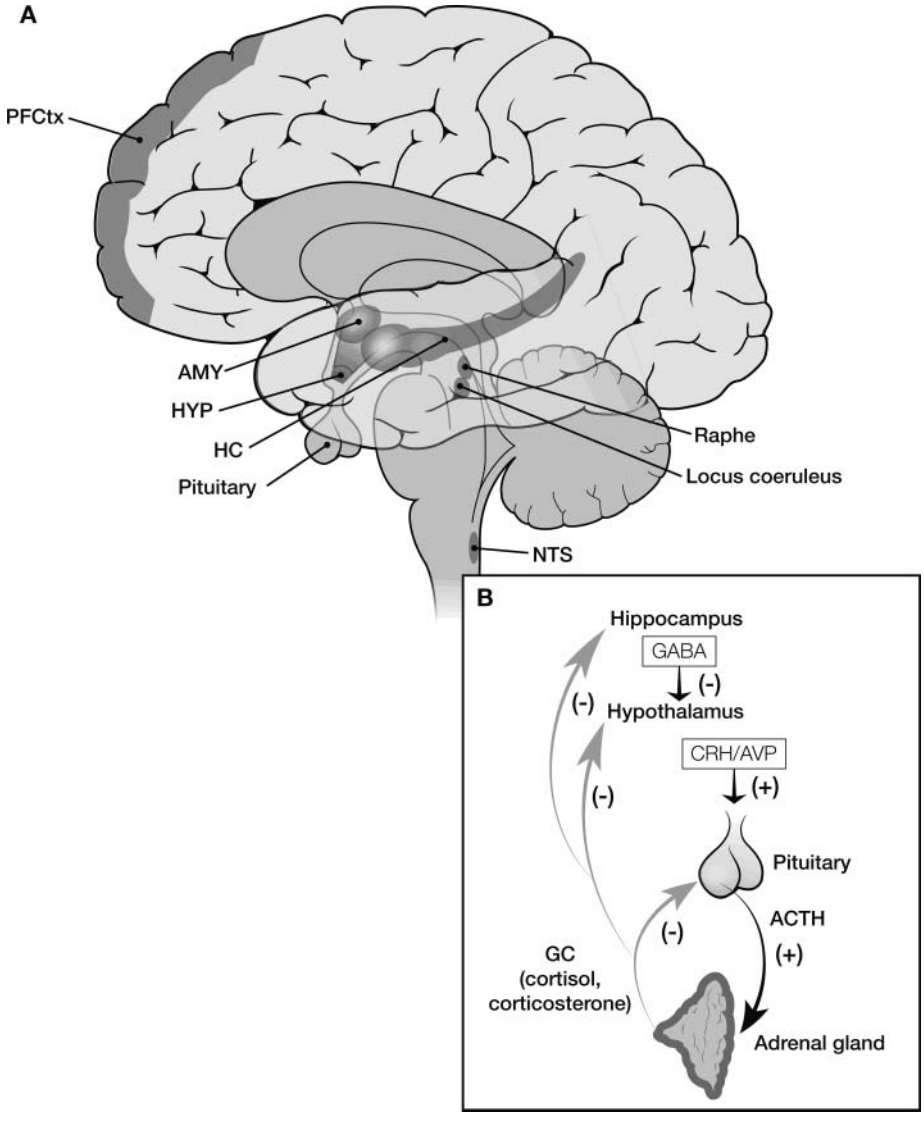

Figure 2

The anatomy of the hypothalamic-pituitary-adrenocortical (HPA) system and the structures that are important in its regulation. Also depicted is the activation (+) and negative feedback inhibition (–) pathways of the HPA system. Increases in glucocorticoids (GCs) are initiated by the release of corticotropin-releasing hormone/arginine vasopressin (CRH/AVP) from the medial parvocellular region of the paraventricular nucleus (PVN) in the hypothalamus. Negative feedback inhibition operates through GCs acting at the level of the pituitary, hypothalamus (HYP), and hippocampus (HC). ACTH, adrenocorticotropic hormone; AMY, amygdala; GABA, gamma aminobutyric acid; HC, hippocampus; HYP, hypothalamus; NTS, nucleus of the tractus solitarius; PFCtx, prefrontal cortex. Reprinted with permission from Gunnar & Vazquez 2006.

for GCs, MRs are 80%–90% occupied when GCs are in basal ranges (de Kloet 1991). By contrast, GRs are occupied only at the peak of the circadian cycle or when stressors stimulate GC elevations over basal concentrations. GRs mediate most of the stress effects of glucocorticoids, whereas MRs tend to mediate most basal effects, which include effects such as maintaining responsiveness of neurons to their neurotransmitters, maintaining the HPA circadian rhythm (highest at wakening and lowest 30 minutes after the onset of the long sleep period each day), and maintaining blood pressure (Sapolsky et al. 2000). Although these basal effects are often considered distinct from stress effects of GCs, they play a permissive role in stress. Basal levels allow effective fight/flight responses by allowing NE and Epi to have maximal impacts on their target tissues.

GR-mediated effects often oppose the ones effected through MR, leading some researchers to argue that stress resilience and vulnerability involve the ratio of MR-to-GR activation (de Kloet 1991). For example, GRs impair neural plasticity and the processes involved in learning and memory as evidenced by their impact on hippocampal neurons. By contrast, basal levels of GCs acting via MRs enhance synaptic plasticity as evidenced by a reduction of the refractory period of hippocampal neurons. MRs facilitate cerebral glucose availability, whereas GRs inhibit glucose utilization throughout the brain, thus endangering cell survival. GRs also activate pathways back to the PVN, which results in inhibition of CRH production (negative feedback) and thus a termination of the HPA stress response. It has long been a mystery why GRs, which are activated during stress responses of the HPA system, should operate to produce such deleterious effects. Why would this system have evolved to impair functioning under conditions of threat? One argument is that the suppressive effects mediated by GRs are necessary to reverse acute response to stressors and ultimately facilitate the recovery of cellular homeostasis (Sapolsky et al. 2000). Only when stress is prolonged do the costs of suppressive effects begin to outweigh their benefits.

Maintaining viability through activation of SAM and HPA reactions has been termed allostasis, or the maintenance of stability through change (McEwen & Seeman 1999). The costs imposed by frequent or prolonged stress responses are described as allostatic load. In addition, the opposing effects of MRs and GRs combined with the differential affinity of GCs for these receptors explains why the relationship between GCs and adaptive functioning frequently takes an inverted-U function (Sapolsky 1997). Both chronically low and high levels of GCs are associated with nonoptimal adaptation. In contrast, moderate (or controlled elevations) are associated with physical and behavioral health.

Psychosocial Stressors: The Role of Corticotrophin-Releasing Hormone

Both the SAM and HPA systems are centrally modulated by limbic brain circuits that involve the amygdala, hippocampus, and orbital/medial prefrontal cortex [see **Figure 3** (as reviewed in Gunnar & Vazquez 2006)]. These structures/circuits allow psychological stressors to activate stress responses. The fast, SAM-mediated, fight/flight response utilizes CRH-producing neurons located in the central nucleus of the amygdala, the noradrenergic neurons located in the locus coeruleus, and other aminergic cells in the brain stem (Morilak et al. 2005). The locus coeruleus regulates the SAM response through its projecting NE neurons. These pathways, flowing through the lateral hypothalamus, activate sites in the brain stem, which in turn directly activate the sympathetic preganglionic neurons unleashing the release of Epi from the adrenal medulla. The central nucleus of the amygdala and CRH-mediated changes are also involved in activating the HPA response to psychosocial stressors (Shekhar et al. 2005). Here, however, pathways to hypothalamic CRH-producing cells that stimulate the HPA

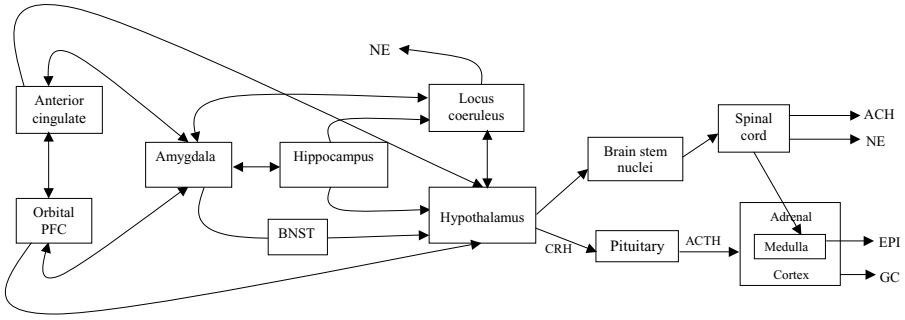

Figure 3

Three levels of neurobiological organization of the stress system responsive to psychological stressors. The cortico-limbic level of organization involves the anterior cingulate (ACC) and orbital frontal cortex (OFC), which relay information to subcortical structures involved in the stress response. The ACC and OFC are reciprocally interconnected with each other and with the amygdala, which has connections with the hippocampus and bed nucleus of the stria terminalis (BNST). The hypothalamic–brain stem level of organization involves the hippocampus and brain stem structures such as the locus coeruleus (LC), which releases norepinephrine (NE) to brain areas involved in alerting. The BNST provides pathways into the paraventricular nucleus (PVN) of the hypothalamus, which produces corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP), while the hippocampus and regions in the medial frontal cortex (e.g., ACC) maintain feedback control of the PVN. Considering the neural-to-adrenal level of analysis, nuclei in the lateral hypothalamus activate highly interconnected nuclei in the brain stem, including the parabrachial nuclei, that regulate the sympathetic (NE and epinephrine, Epi) and parasympathetic (acetylcholine, Ach) nervous systems via pathways traveling through the spinal cord to preganglionic nuclei or to target organs (e.g., the adrenal medulla). The production of CRH and AVP by the PVN regulates activity of the hypothalamic-pituitary-adrenocortical (HPA) axis and the production of glucocorticoids (GCs) as depicted more fully in **Figure 2**. Adapted with permission from Gunnar & Davis 2003.

cascade are indirect, operating through multisynaptic pathways via the bed nucleus of the stria terminalis that converge on the paraventricular nuclei in the hypothalamus (Herman & Cullinan 1997, Herman et al. 2002). These multiple, converging pathways allow modulation of the strength of the HPA responses in relation to the state of the body, time of day, and current levels of circulating hormone.

Because of the critical role of amygdalar CRH in the activating pathways for both SAM and HPA responses, there is increasing attention to the role of amygdalar CRH and its family of receptors in orchestrating stress reactions (Heinrichs et al. 1995, Nemeroff 1996, Swiergiel et al. 1993). Reacting to psychological stressors requires appraisal by higher brain structures such as the cingulate cortex and the orbital/medial prefrontal cortex (Barbas 1995, Diorio et al. 1993). Threat appraisal also involves subcortical structures such as the bed nucleus of the stria terminalis and the hippocampus, as well as the further integration by hypothalamic and brain stem structures (Davis et al. 1997). CRH receptors in all of these regions affect components of stress responding (Bale & Vale 2004). For example, CRH infused into the locus coeruleus in rodents intensifies anxiety-related behaviors, and neurons in the locus coeruleus are sensitized to CRH after being exposed to psychological stressors (Butler et al. 1990). As with GCs, there are two prominent CRH receptors (CRH-1 and CRH-2), which tend to mediate opposing actions (Bale & Vale 2004). CRH-1 appears to mediate many of the anxiety-related actions of CRH, while CRH-2 mediates more of the stress effects on vegetative functions. Consistent with this distinction, CRH-1 receptors are more abundant in cortico-limbic pathways that mediate fear and anxiety-related behaviors, whereas CRH-2

receptors are found predominantly in subcortical brain regions (Sanchez et al. 2000, Vythilingam et al. 2002). It is unfortunate for students of human development that CRH cannot be noninvasively measured. Furthermore, although CRH can be assayed in samples of cerebral spinal fluid (CSF), CSF concentrations do not allow differentiation of the brain locus of production.

Summary

The neuroanatomy and neurophysiology of the stress system involves the SAM and HPA systems. Both systems involve the adrenal gland and its secretions that are released into the bloodstream. Both also are orchestrated by activity in the central nervous system. Unlike the SAM system, however, the brain is a major target organ for the steroid hormones produced by the HPA axis. Also, unlike the SAM system, whose role in stress can be fairly simply described as "fight/flight," the role of the HPA system is more complex. Its basal activity appears to support or permit acute fight/flight responses, while its response to stressors serves to suppress the impact of fight/flight reactions. Over prolonged periods of chronic activation, the suppressive effects of the elevated GCs and the wear and tear of frequent SAM responses can have deleterious effects on physical and mental health. However, in the short term, robust, well-orchestrated activations of these systems tend to support adaptive functioning. This, plus the well-described inverted U-shaped functions relating SAM and HPA stress responses to a variety of adaptive functions, should caution researchers against thinking of increases in SAM and HPA activity as necessarily indexing risk of poor outcomes. Finally, our increasing understanding of the role of amygdalar CRH in orchestrating responses to psychosocial threats suggests that in many cases it is the activity of CRH that should be tracked by researchers studying links between emotional behavior and physiological responses to stressors. Unfortunately, CRH cannot be noninvasively measured and thus is not a part of the toolbox for researchers studying psychosocial stress and development in humans.

ANIMAL STUDIES OF EARLY EXPERIENCE AND STRESS NEUROBIOLOGY

More than a decade of research using animal models has shown that in many mammalian species, early experiences shape the neurobiological systems involved in stress reactivity and regulation, and some of these effects appear permanent. The results of these studies have shaped the formulation of questions about early experiences and stress vulnerability in human development; thus, it is useful to outline the findings of the animal models here.

The Rodent Model

The rat has been the focus of much of this research (Sanchez et al. 2001). In the rat, the period between 4 and 14 days after birth is one during which it is difficult to produce elevations in ACTH and GCs to stressors that provoke responses in older animals (Rosenfeld et al. 1992). Termed the relative stress hyporesponsive period (SHRP), it has been assumed that this period evolved to protect the developing brain from potentially deleterious effects of elevated GCs and the other neurochemicals associated with the mammalian stress response (de Kloet et al. 1988). The SHRP appears to be maintained by very specific stimuli that pups receive from the dam. If the dam is removed for 12 to 24 hours, marked activation of the HPA system and elevated brain levels of CRH are noted (Suchecki et al. 1993). However, if during this time maternal stimulation is mimicked by stroking the pup with a wet paintbrush and infusing milk into its stomach via a cannula, HPA and central (brain) CRH responses are controlled (Cirulli & Alleva 2003).

We now know that not only deprivation of maternal care but also normal variations

in rat mothering impact the developing neurobiology of stress (see review by Meaney & Szyf 2005). Dams vary in how much they lick and groom their pups. In comparison with low-licking and -grooming dams, high-licking and -grooming dams have pups that, as adults, are less fearful and better able to contain and terminate stress reactions of the HPA axis (Caldji et al. 1998). The molecular events set into motion by maternal care are increasingly understood. Particularly during the first week of the life in the rat, maternal licking and grooming regulate the extent to which GR genes in the hippocampus become methylated (Weaver et al. 2001). Methylation effectively silences genes. Licking and grooming reduce methylation of hippocampal GR genes. GR genes determine how many hippocampal glucocorticoid receptors an animal will have. Because hippocampal GRs are involved in terminating stress responses of the HPA system, high levels of hippocampal GRs mean efficient control of HPA stress response, whereas low levels mean poor or sluggish regulation, more prolonged stress reactions, and vulnerability to allostatic load over the animal's lifetime (Meaney & Szyf 2005, Weaver et al. 2001). These epigenetic effects of maternal care are potentially irreversible, except through pharmacological manipulations that induce widespread demethylation (Weaver et al. 2005). This is a powerful example of how stress neurobiology can be programmed by social experiences during sensitive periods of development.

The impact of early social stimulation becomes obvious when typical caregiving patterns are disrupted (for reviews, see Cirulli & Alleva 2003, Sanchez et al. 2001). Two closely related paradigms have been studied most: daily separations extending over the period of the SHRP that last for 3 to 15 minutes and similar daily separations that last for several (typically 3) hours. Strikingly, 15 minutes has a markedly different consequence than does 180 minutes of separation daily. In comparison with nonmanipulated dams and pups, the pups who experience 15 minutes of separation daily (termed "handling") become more stress resilient, whereas those experiencing 180 minutes of separation daily (termed "maternally separated") become more stress vulnerable. Relevant findings include evidence that separated animals, compared with control and handled animals, exhibit larger air-puff startle responses, greater freezing and anxiety behaviors to cat odor, and two- to threefold greater ACTH and glucocorticoid responses to restraint stress as adults (Cirulli & Alleva 2003). In addition, they also display evidence of anhedonia; mild cognitive impairments, especially on hippocampally mediated tasks; and greater consumption of alcohol (Sanchez et al. 2001). These behaviors correspond to increased CRH expression in the amygdala and bed nucleus of the stria terminalis, decreased GR in the hippocampus and consequently impaired negative feedback regulation of the HPA axis, increased NE in the locus coeruleus, and down-regulation of adrenergic receptors, among other changes that reflect shaping of hyperstress reactivity at multiple levels of the central nervous system (Ladd et al. 2000).

The difference between 15 minutes and 180 minutes of maternal separation appears to be conferred via differences in maternal behavior. After brief separations, dams increase their licking and grooming, whereas repeated three-hour separations appear to disorganize the dam, reducing licking and grooming of her pups. Some of the effects of maternal separation appear to be relatively permanent. However, some effects appear to be responsive to postinfancy modification by placing the juvenile animal in complex environments that stimulate exploration and expose the animal to high levels of social stimulation and novelty (Francis et al. 2002). Such enrichment experiences do not increase the previously maternally separated animal's hippocampal GR, but the experiences do appear to reduce activation of cortico-limbic fear circuits in response to novelty and threat in adulthood. Whether the continued deficit in hippocampal GR confers a risk for stress vulnerability in response to

Sensitive periods of development: periods during which an experience (or its absence) has a more marked impact on the neural organization underlying a particular skill or competence

chronic, rather than acute, stressors later in life is not yet known.

Attachment: psychosocial process resulting in strong emotional bond with a particular person and deriving security from physical and psychological contact with that attachment figure

Early Adverse Experience in Nonhuman Primates

It is generally assumed that events, whether they are positive or negative, have less of an effect on structures and circuits that are already well developed than on those that are rapidly developing (Dobbing 1981). Nonhuman primates are born more mature than are rats; thus, we would expect that postnatal experiences would have somewhat different effects in the primate (for reviews, see Gunnar & Vazquez 2006, Sanchez et al. 2001). This appears to be true, despite the fact that, as in rats, disruptions of parental care in nonhuman primates also affect the neural substrates of stress vulnerability and resilience.

Nonhuman primates form specific attachments to caregivers (Suomi 1995). Separation from the attachment figure provokes acute behavioral distress and increases activity of the HPA and SAM systems (Levine & Wiener 1988). Behavioral distress, however, does not necessarily mirror physiological stress reactions. For example, if the infant monkey can see and call to its mother, vocal distress and behavioral agitation are much greater than if it is isolated from any contact. Nonetheless, physiological stress responses, particularly of the HPA system, are much greater under conditions of isolation (Bayart et al. 1990, Smotherman et al. 1979). Studies of the impact of different pharmacological manipulations during separation also demonstrate that behavioral distress and physiological stress responses are dissociable (Kalin et al. 1988, 1989). Critically, increases in HPA activity appear to correspond more closely with activity of amygdalar CRH and activation of fear circuits (Kalin et al. 1989). Notably, infant primates can gain some reduction in both distress vocalizations and physiological stress reactions when they are provided with surrogate caregivers during separation (reviewed in Levine & Wiener 1988). Consistent with the principles of attachment theory (Bowlby 1969), access to a secure base provided by the attachment figure or attachment surrogate reduces the probability of HPA/CRH stress reactions that could have long-term consequences on brain development.

Studies of nonhuman primates also demonstrate that poor rearing conditions, including peer-only rearing, isolation rearing, repeated separations, and conditions that disrupt responsive maternal care can have long-term impacts on the neurobiology of stress and negative emotionality (reviewed in Sanchez et al. 2001). For example, variable foraging paradigms that result in neglectful maternal care also produce offspring who as adults are more fearful, low in dominance, high in brain levels of CRH, and who exhibit persistent alterations in somatostatin and metabolites of serotonin, dopamine, and NE (Coplan et al. 1996, Rosenblum & Andrews 1994, Rosenblum et al. 1994). However, the long-term effects of social deprivation on the HPA axis are unclear (Mason 2000). For example, 2.5-year-old monkeys reared in isolation for the first year of life exhibited no differences in hypothalamic-CRH expression when compared with maternally reared animals (Sanchez et al. 1999). Similarly, unlike in the rat, no one has yet to demonstrate changes in hippocampal GR. Rather, the levels of stress neurobiology that are disturbed appear to involve the cortico-limbic circuits that evaluate and regulate responses to psychosocial threat, circuits that are still rapidly developing after birth in the monkey as they are in the human child.

POSTNATAL HUMAN DEVELOPMENT AND STRESS BIOLOGY

Neurobiological systems involved in stress include genetic, organ, behavioral, and emotional components that mature and become more organized as children develop. Below is an overview of the development of the

components of the stress system, with particular emphasis on the HPA axis.

Infancy and Early Childhood

In adults, cortisol is usually bound to proteins (e.g., corticosteroid-binding globulin; CBG) (Rosner 1990). However, CBGs in newborns are initially low, although they increase over the first six months after birth (Hadjian et al. 1975). As a result, unbound levels of cortisol decrease slightly over the initial months after birth, while plasma or total cortisol increases. Only free cortisol can bind to its receptors and have biological effects; therefore, despite low plasma levels of cortisol at birth, the levels of biologically active cortisol in newborns are enough to have clear physiological effects (Gunnar 1992). Newborns can mount physiologically significant cortisol and ACTH responses to aversive medical procedures (blood draws, physical examinations, and circumcision) (reviewed in Gunnar 1992). Newborns, however, do not show the typical adult rhythm in cortisol production, characterized by higher levels in the morning at wake-up that decrease toward the afternoon and evening. They show two peaks, 12 hours apart, that do not depend upon the time of day (Klug et al. 2000). But by three months, a qualitative shift in physiological development takes place, and the single early morning cortisol peak and evening nadir (lowest level) are generally established (Matagos et al. 1998). The diurnal rhythm also continues to develop over infancy and early childhood, reflecting changes in daytime sleep patterns (Watamura et al. 2004). Specifically, until children give up their daytime naps, decreases in cortisol from mid-morning to mid-afternoon are not observed; after this, the diurnal rhythm of children is consistent with that of adults.

As in the newborn period, two-month-old babies increase cortisol significantly to medical examinations and also fuss and cry when they are examined (Larson et al. 1998). Around three months, there is a diminishing of the HPA response to stressors such as physical examinations, but this does not extend to decreased behavioral distress (Larson et al. 1998). Furthermore, across the first year of life it becomes increasing difficult to provoke cortisol increases to many mild stressors (stranger approach, strange events, 3- to 30-minute separations, and inoculations; reviewed in Gunnar & Donzella 2002). Indeed, by one year of age many infants show no evidence of increases in cortisol to stressors that typically provoke significant behavioral distress reactions. Both physiological changes in the system, such as improved negative feedback regulation of the axis, and decreased sensitivity of the adrenal cortex to ACTH may partially account for the diminution of the HPA stress response (Lashansky et al. 1991). In addition, as described below, the child's access to supportive adult care plays an increasingly salient role in buffering the activity of the HPA component of the stress system. Indeed, by the end of the first year of life, infants in supportive caregiving relationships appear to have entered the human functional equivalent of the rodent stress-hyporesponsive period (reviewed in Gunnar 2003).

As in the primate and rodent, behavioral distress is an unreliable index of HPA activation in young children. In the first weeks of life, this is demonstrated strikingly through studying infants with colic (White et al. 2000). Infants with colic, who by definition exhibit markedly high levels of crying, tend to exhibit low basal levels of cortisol and produce changes similar to those of noncolic babies in cortisol and heart rate in response to distressing events. By the time infants have formed attachment relationships to one or a few caregivers, the presence and history of responsiveness of the attachment figure both influences whether infants exhibit cortisol increases to stressors and whether behavioral distress correlates with these increases (reviewed in Gunnar & Donzella 2002). In secure attachment relationships (Nachmias et al. 1996) and with responsive surrogate caregivers (Gunnar et al. 1992), infants exhibit crying directed at soliciting care but do not exhibit elevations in

Cortisol: arguably the most powerful human glucocorticoid. Essential for regulation and support of vital functions including metabolism, immune response, vascular tone, and general homeostasis

Sensitive and responsive care: qualities of parenting characterized by timely and adequate responsiveness to the child's needs

Temperament: individual differences in reactivity and self-regulation assumed to have a constitutional basis. Develops and is influenced over time by heredity, maturation, and experience

cortisol. Conversely, in insecure relationships or with unsupportive caregivers, stressors continue to be capable of producing elevations in cortisol and distress, and heart rate increases tend to more closely approximate activations of the HPA system (Spangler & Schieche 1998). This generalization tends to hold for acutely stressful experiences, but may not be accurate for more prolonged periods of stress such as those experienced when toddlers enter full-time child care. Here it has been noted that the security of the child's attachment relationship does not determine the magnitude of the cortisol increase as the child adjusts to repeated daily separations, and over time it is the securely attached children whose behavioral distress corresponds to their increases in cortisol during these prolonged periods of separation (Ahnert et al. 2004).

Changes in other stress-sensitive systems are also observed over the early months of life. Notably, corresponding to the diminution of HPA responses to stressors, there is an increase in vagal tone (parasympathetic input to the heart) that may allow more nuanced cardiac and behavioral responses to psychosocial threat (Porges 1992, Porges et al. 1994). Whether changes in vagal tone are related to the emergence of secure-base attachment relationships has not been clearly demonstrated (although see Izard et al. 1991). However, there is evidence that emotion-related patterns of brain electrical activity measured over the frontal cortex are related to the infant's history of sensitive and responsive care. Specifically, infants of mothers who are highly sensitive and responsive exhibit greater left frontal brain electrical (electroencephalogram, or EEG) activity patterns associated with positive emotionality and approach, whereas those with low-responsive mothers exhibit greater right frontal EEG patterns associated with negative emotionality and fearful, inhibited temperament (Hane & Fox 2006). In nonhuman primates, greater left frontal EEG asymmetry has been shown to correlate with lower cortisol reactivity to stressors (Kalin et al. 1998). Higher vagal tone, lower cortisol reactivity to stressors, and greater left frontal EEG patterns suggest that, at least under conditions of supportive care, the human child enters a period of relative stress hyporesponsivity by the latter part of the first year that may buffer or protect the developing brain and result in a more stress-resilient child.

Later Childhood and Adolescence

There is increasing evidence that the period of relative stress hyporesponsivity or buffering does not end with infancy but extends over most of the childhood years. As is the case with toddlers, it is difficult to find laboratory situations that provoke large increases in cortisol throughout childhood (reviewed in Gunnar & Fisher 2006). Although many children may be largely buffered from stress during infancy and childhood, there is also increasing evidence that this period of relative stress buffering draws to a close as children transition into adolescence. In addition to the psychosocial changes associated with the adolescent transition, biological processes associated with puberty may shift the child's stress neurobiology to adult-responsive patterns (Spear 2000). It is now clear that the increasing level of basal cortisol shown in children between the ages of 6 and 17 years is remarkably similar to that of the rodent, which exhibits increases in basal GC levels at the close of the stress-hyporesponsive period (Kiess et al. 1995, Legro et al. 2003, Netherton et al. 2004, Shirtcliff 2003). Some studies suggest that the increases in basal GCs peak between 10 and 14 years or at around Tanner stage three (Elmlinger et al. 2002, Netherton et al. 2004), whereas others show a more gradual increase with age (Jonetz-Mentzel & Wiedenmann 1993). In addition to increases in basal cortisol levels, there also is increasing evidence that cortisol responses to laboratory stressors may increase with age and pubertal status over the adolescent transition (Klimes-Dougan et al. 2001, Walker et al. 2001, Wewerka et al. 2005). Not all studies

have demonstrated such increases in stress responsivity over the transition into adolescence (for review, see Gunnar & Vazquez 2006), but the weight of the evidence is beginning to suggest that an adolescent emergence out of a period of relative stress hyporesponsivity or buffering is real and may have implications for the heightened risk of psychopathology noted among adolescent-aged children (Spear 2000).

SOCIAL REGULATION OF STRESS NEUROBIOLOGY IN HUMANS

The Role of Caregivers

Children's development takes place within the close social relationships with adult caregivers. One of the functions of the caregiving system is to modulate and enable control of physiological and behavioral responses to stressors. In humans, social modulation of physiological stress responses may lay the foundation for the development of emotion regulation competencies (Stansbury & Gunnar 1994). Patterns of social relatedness in infancy can be characterized, in part, by the security of the infant-caregiver attachment relationship (Ainsworth et al. 1978), and physiological stress responses have been found to be mediated by attachment security (Gunnar et al. 1996, Spangler & Schieche 1998, Sroufe & Waters 1979). In the presence of the attachment figure, toddlers who are in secure attachment relationships do not show elevations in cortisol to distress-eliciting events, whereas toddlers in insecure attachment relationships do (reviewed in Gunnar & Donzella 2002). The power of secure attachment relationships to buffer or prevent elevations in cortisol to otherwise mildly stressful events has been demonstrated in both laboratory and naturalistic situations. In comparison to organized but insecure attachment relationships, disorganized/disordered attachment may signal even greater stress vulnerability. Disorganized attachment relationships are believed to arise, in part, from the infant's experience of frightening behavior and episodes of dissociation in the caregiver (Lyons-Ruth et al. 1995). Children in disorganized/disoriented attachment relationships are characterized by their inability to organize or regulate affect and behavior toward their caregiver in stressful situations (van Ijzendoorn et al. 1999). These children are also most likely to exhibit disturbances in HPA axis activity (Hertsgaard et al. 1995, Spangler & Grossmann 1997) and are most at risk for behavioral and emotional problems (van Ijzendoorn et al. 1999).

There is also evidence that family dynamics, beyond attachment security/insecurity, influence cortisol reactivity in developing children. Naturalistic observations from households of typically developing children (ages 2 month to 17 years) yield evidence that traumatic family events (conflict, punishment, shaming, serious quarrelling, and fighting) are strongly associated with periods of elevated cortisol levels when the child's response to acutely traumatic events is compared with their own levels on less traumatic days in the family (Flinn & England 1995). There is also evidence that early disruptions in the parent-child relationship may produce increased levels of cortisol by the preschool years and that these heightened levels predict increased behavioral and emotional problems in the school-aged child (Essex et al. 2002). Likewise, social adversity that results in high maternal expression of depressive symptoms, including disrupted patterns of parenting, has been shown to be related to higher and less-regulated cortisol activity in school-aged children and adolescents (Halligan et al. 2004, Lupien et al. 2000). Additionally, in clinical populations of children with behavior problems, cortisol increases during a parent-child conflict-discussion task have been found to be associated with dysfunctional parenting attitudes and symptoms of anxiety and depression in the child (Granger et al. 1996). In summary, adult caregivers and family influences are powerful regulators of the HPA system.

Caregivers can prevent elevations in cortisol for infants and children even during threatening external events. Responsive caregiving allows children to elicit help by expressing negative emotions, without triggering the endocrine component of the stress response. Conversely, when the parenting is inadequate and/or is the source of threat, relationships can be a major source of physiological stress for children (Repetti et al. 2002).

Peers and Early Socialization Experiences

As children mature, their social circle expands to include other children and adults, particularly in the context of school and daycare centers. This entails the entrance into a complex and challenging environment that demands the emergence of social skills including control of inappropriate behaviors, adapting communication to the listener point of view, interpreting emotional cues, and maintaining play themes over transitions (Rubin et al. 1998). The social challenges posited by peer groups may explain reported cortisol increases over the day in full-day child-care settings (Dettling et al. 1999, 2000; Tout et al. 1998; Watamura et al. 2002a, 2002b, 2003). In such child-care settings, the majority of 2- to 4-year-old children showed increases in cortisol production over the day, whereas this is not observed for the same children at home on days they do not go to child care. As a group, children 5 to 8 years of age do not show increases in cortisol in group-care settings, although individually some children do. It has been suggested that increases in cortisol at child care emerges at the age when peer relations become salient. The challenge of managing interactions with others for children whose social skills are just emerging may tax the young child's coping abilities and, combined with long hours of care, may tax the child's capacity to maintain basal cortisol levels (also reviewed in Gunnar & Donzella 2002). This hypothesis is strengthened by evidence that children with the largest increases in cortisol over the child-care day have been rated by multiple adult observers as less socially competent and less capable of regulating negative emotions and aggression (Dettling et al. 1999, 2000). However, consistent with the argument that support from adults is critical to psychosocial regulation of stress in early childhood, elevations in cortisol in child-care settings are not observed when the child receives individualized, supportive care from care providers (Dettling et al. 2000).

Aside from normative developmental trends and variations associated with social competence, cortisol levels measured when children are in peer group settings also reflect peer acceptance or rejection (Gunnar et al. 1997, 2003). As early as the preschool years, peer-rejected children produce higher levels of cortisol in the preschool classroom in comparison to average or popular children. Peer rejection is associated with poor social skills and poor emotion regulation (Coie et al. 1990). This is often expressed as poorly contained aggression and inability to regulate negative emotions, all of which is associated with poorer peer relations and higher cortisol levels (Gunnar et al. 2003). Interestingly, in studies of preschool-aged children, there is little evidence that children who few others nominate as either liked or disliked (i.e., peer-neglected children) exhibit elevated levels of cortisol (Gunnar et al. 2003). By contrast, at least by early as adolescence, children who are socially neglected and who consequently spend hours alone even when they are with peers (i.e., at school) do exhibit higher levels of cortisol production (Adam 2006). The psychosocial pathways through which peer-rejected and peer-neglected children experience stress related to their social status are not yet understood, although it seems likely that social threats, disappointments, and other aversive interactions are likely involved. In addition, pathways from poor family relationships to poor peer and friendship relations need to be considered.

STRESS NEUROBIOLOGY AND ADVERSE EXPERIENCE: PARENTAL NEGLECT AND ABUSE

Maltreatment during development has been repeatedly linked to maladaptive outcomes (Cicchetti 1996). Adult survivors of childhood maltreatment reveal greater prevalence of psychiatric disorders, including affective disorders, eating disorders, somatic complaints, sexual dysfunction, and substance abuse. Alterations in stress-sensitive neurobiological systems, including regulation of GCs and CRH, have been posited as mechanisms through which adverse experience increases the likelihood of psychopathology (see reviews by Bremner & Vermetten 2001, De Bellis 2001, Heim & Nemeroff 2001, Teicher et al. 2002).

The Stress Neurobiology of Adult Survivors

Researchers studying the impact of maltreatment during childhood are dealing with a still-developing neural system in which developmental change and effects of maltreatment can be difficult to disentangle (Cicchetti & Tucker 1994). It is helpful, therefore, to consider first what is known about the stress neurobiology of adult survivors of childhood maltreatment. Much of the adult survivor research has focused on adults with depression and/or posttraumatic stress disorder (PTSD) pursuant to their maltreatment histories (Glaser 2000, Heim & Nemeroff 2001, Heim et al. 2004). Many of these studies lack appropriate controls. For example, adult survivors of childhood maltreatment who have PTSD may be compared to healthy controls so that differences associated with PTSD and impacts of childhood abuse cannot be disentangled. Nonetheless, the general pattern of findings suggest that severe, early maltreatment may have neurobiological consequences that last into adulthood and that increase the risk of psychopathology. To understand the findings, it is important to briefly describe alterations in stress neurobiology noted for adults with these disorders who do not have childhood maltreatment histories.

PTSD and depression appear to share hyperactivity of CRH at hypothalamic and extrahypothalamic levels (Bremner et al. 1997, Heim et al. 2004). Chronic CRH drive on the pituitary in both disorders appears to result in counter-regulatory down-regulation at the level of the pituitary, leading to blunted ACTH in response to pharmacological CRH challenge tests (Heim et al. 2004). However, these disorders differ in the sensitivity of feedback regulation of the HPA axis. Depression among adults is often associated with reduced negative feedback regulation (e.g., Young et al. 1991), whereas PTSD appears to be associated with increased negative feedback (e.g., Yehuda 2000). As a result, adults with depression often hypersecrete cortisol and exhibit prolonged cortisol elevations, whereas adults with PTSD often hyposecrete cortisol and rapidly return to baseline concentrations following perturbation. The question is whether childhood maltreatment alters these patterns.

Studies using pharmacological challenge tests provide evidence that pituitary down-regulation of ACTH is comparable in adults with depression and PTSD regardless of their childhood maltreatment histories (for a review, see Heim et al. 2004). At the level of the adrenal and with regard to negative feedback regulation, the picture is more complex. There is some suggestion that depression plus early childhood maltreatment may be associated with an exaggerated negative feedback in comparison with what is observed in depression without childhood abuse (Newport et al. 2004). However, this may reflect unmeasured PTSD in the adult maltreatment survivors (Rinne et al. 2002). The picture changes when psychological stressor tests are used. Here hyper-responsiveness of ACTH and in some instances cortisol has been noted, particularly among adult survivors with depression compared with depressed adults without childhood abuse histories (Heim et al.

2000, 2002). Unlike pharmacological challenges, psychological stressors depend on recruitment of cortico-limbic activation pathways. Thus, hyperactivation for psychological as opposed to pharmacological challenge suggests that adult survivors of maltreatment who have PTSD and/or depression may have even more hyper-responsive threat/stress systems at the cortico-limbic level than do nonmaltreated adults with these disorders.

Critically, however, a very different picture emerges when one studies adult survivors of childhood maltreatment who are free from psychopathology (Gunnar & Fisher 2006). By definition, such individuals are resilient. Given their resilience, perhaps it is not surprising to find that across various studies these adults show evidence of reduced activity of stress neurobiology. For example, the CRH challenge test, which produces blunted ACTH responses in individuals with PTSD and/or depression, produces larger-than-average responses in resilient adult survivors of childhood maltreatment (Heim et al. 2001). Because the magnitude of the ACTH response is inversely proportional to the pituitary's chronic or trait-like exposure to CRH (Newport et al. 2003), these results suggest chronic low CRH production in resilient adult survivors. Similar ACTH results have been obtained in response to psychosocial stressors combined with normal to low cortisol and cardiac responses among resilient adult survivors (Girdler et al. 2003). Finally, the adrenals of resilient adult survivors also show lower-than-expected production of cortisol to ACTH challenge tests (Heim et al. 2001). What is not clear is whether this pattern of low stress responding is a risk factor for subsequent physical and mental disorders or is a reflection of individual differences in stress reactivity that may have protected the developing brain from adverse impacts of maltreatment. Both possibilities exist, and the latter should alert developmental researchers to the importance of considering individual differences and their genetic substrate in pursuing questions about the impact of childhood experiences on stress and emotion reactivity and regulation.

Child Maltreatment and Stress Neurobiology

It has been hypothesized that traumatized children initially exhibit complex environmentally induced developmental disorders that later branch toward more specific and adult-like pathologies such as depression and anxiety (Cicchetti 1996). This complexity is evidenced in the data on the stress physiology of abused children, which are often challenging to interpret. For example, sexually abused girls evidence blunted ACTH response in reaction to CRH injections, similar to adult survivors of childhood abuse with depression or PTSD (De Bellis et al. 1994). However, enhanced ACTH responses and normal cortisol levels to CRH challenges have also been reported for depressed, abused children if they are still experiencing adverse home lives (Kaufman et al. 1997). As it does in adults, concurrent psychopathology contributes to the heterogeneous presentation of stress functioning in maltreated children. For example, in one study, maltreated externalizing boys at a summer camp had higher cortisol levels relative to nonmaltreated boys with externalizing problems; however, they did not have elevated cortisol levels relative to nondisordered nonmaltreated boys (Cicchetti & Rogosch 2001b). Indeed, hyporesponsiveness of both the SAM and HPA systems has been related to externalizing symptomatology (McBurnett & Lahey 1994, McBurnett et al. 2000, van Goozen et al. 2000). In a study of maltreated preschool-aged children compared with SES controls, maltreated children exhibited less cortisol reactivity and produced even lower cortisol levels on days when there were high levels of conflict and aggression in their classrooms (Hart et al. 1995). Furthermore, although adults with PTSD and adult survivors of child maltreatment may exhibit low levels of basal cortisol activity, in several studies, children with PTSD pursuant to severe

childhood maltreatment exhibited elevated cortisol levels relative to controls (Carrion et al. 2002, De Bellis et al. 1999) and higher urinary excretion of Epi relative to nonmaltreated clinically anxious and nonanxious children (De Bellis et al. 1999). Researchers have argued that the adult PTSD-cortisol pattern may emerge with development and/or time since the trauma exposure (e.g., De Bellis 2001). In addition to the HPA and SAM systems, there is also evidence that cortico-limbic structures involved in emotions and stress are affected by early childhood maltreatment. Prepubertal children with PTSD secondary to maltreatment evidence smaller cerebral volumes, smaller corpus callosa relative to brain volume, and less asymmetry of the prefrontal cortex than do matched controls (reviewed in De Bellis 2001).

Not only physical and sexual maltreatment have an impact on the developing neurobiology of stress. There is increasing evidence that severe neglect also alters the stress neuraxis (De Bellis 2005). Children living in orphanages serve as an example. Cortisol levels in orphanage-reared infants and toddlers tend to be low in the early morning and lack the normal diurnal rhythm (Carlson & Earls 1997 and Kroupina et al. 1997, as reviewed in Gunnar 2000). Similar low early-morning levels have also been noted for domestically neglected children soon after placement in foster care (Dozier et al. 2006, Gunnar & Fisher 2006). There is increasing evidence that severe early neglect affects the development of cortico-limbic circuits involved in emotion and stress responding (Glaser 2000). For example, postinstitutionalized children have been found to have larger amygdala volumes, and amygdala size and function (fMRI findings) correspond to duration of institutional care (Tottenham et al. 2006). It is not clear whether neglect and abuse have different effects on the neurobiological systems that regulate stress and emotional function or whether these effects are comparable. One challenge in answering this question is that many abused children also suffer from neglect (Cicchetti & Toth 1995). Indeed, there is some evidence that neglect and various types of abuse, along with exposure to violence, have cumulative effects; the most profound effects on stress reactivity and regulation are noted for children with the largest cumulative exposures (Cicchetti & Rogosch 2001a).

INDIVIDUAL DIFFERENCES: CONTRIBUTIONS FROM TEMPERAMENT AND GENETICS

As discussed above, adverse early experiences produce different patterns of stress responding in different individuals; hyperreactivity in some and seemingly hyporeactivity in others. Although the nature and timing of adverse or maltreating experience may partly explain these differences, it is likely that to some extent they also reflect individual differences that have a genetic contribution. Studies of both temperament as a reflection of genetic dispositions and, more recently, candidate genes have begun to flesh out this hypothesis. Most of the temperament work has focused on behavioral dispositions, particularly extreme shyness or behavioral inhibition, that may increase the risk of anxiety and depressive disorders (Kagan et al. 1987). Kagan has argued that the extreme 5% to 10% of behaviorally inhibited children are at risk for developing anxiety disorders, and recent studies have demonstrated that as adults, these individuals do show evidence of exaggerated amygdala responses to social stimuli (i.e., unfamiliar faces; Schwartz et al. 2003). In comparison with extremely noninhibited children, these extremely inhibited children also exhibit heightened vigilance, higher heart rates, lower heart-rate variability or vagal tone, and greater right-frontal EEG activity (Fox et al. 2001, Kagan et al. 1988).

Several researchers have suggested that the transition from extreme temperamental shyness or inhibition to pathological anxiety may involve hyperactivity of the HPA axis and its capacity to increase amygdalar CRH activity,

thus orchestrating larger fear and stress reactions with less provocation (Rosen & Schulkin 1998). This would seem to require evidence of greater HPA reactivity to stressors among temperamentally inhibited children, something that has not been reliably found. Researchers have reported higher early-morning basal cortisol levels among more extremely inhibited children (Kagan et al. 1987, Schmidt et al. 1997). But few studies have found higher cortisol increases to psychological stressors such as entering a new play group, starting a new school year, or being exposed to laboratory stressors (for review, see Gunnar 2001). One problem may be that researchers have been searching for main effects of inhibited temperament, while temperament may more often moderate effects of stressors or operate in relation to the social support available to the child. Thus, as noted above, children with more negative emotional temperaments are at risk for larger increases in cortisol when they are in child-care settings, but this is only observed when the care provider is low in supportive and responsive care (Dettling et al. 2000).

The need to consider temperament in relation to the supportiveness of the care children receive is mirrored by recent findings regarding genes that may increase the risk of emotional disorders. Thus, a common regulatory variant (5-HTTLPR) in the serotonin transporter gene (SLC6A4) has received attention because it may increase the risk for anxiety and depression (Lesch 2001). However, several studies have now shown that individuals carrying alleles that result in altered transcription and transporter availability are not at increased risk for depression unless they have experienced more stressful life events, including childhood maltreatment (Caspi et al. 2003, Kaufman et al. 2004). Similarly, among temperamentally inhibited children there is now evidence that this gene variant is not associated with increasing levels of behavioral inhibition with development unless the child also experiences less social support and supportive care during early childhood (Fox et al. 2005). These findings are of note because there is evidence that a functionally equivalent gene variant in rhesus monkeys is associated with larger HPA responses to stressors, but only among animals that grow up in less-supportive care conditions (Barr et al. 2004). This is not the only genetic variation that likely makes important contributions to individual differences in stress reactivity and regulation; however, as with the work on shy, inhibited temperament and on the serotonin transporter allele, it is very possible that their consequences need to be considered in the context of the supportiveness of the child's social relationships.

CONCLUSIONS AND FUTURE DIRECTIONS

In the past 20 years, a tremendous amount has been learned about the development of stress reactivity and regulation during human development. Stress reactivity is better understood as the result of intertwined biological and psychological processes that ultimately ensure an organism's survival. Adjusting to external challenges through adaptive internal changes is a universal mechanism through which live organisms interface with their environment. However there is a cost to frequent physiological adjustments (allostatic load). Frequent activation of neurobiological stress responses increases the risk of physical and mental disorders, perhaps particularly while organisms are developing. As such, one of the most interesting findings emerging from the research on the psychobiology of stress is that in the absence of supportive care, stressors experienced during sensitive periods of development can in fact leave permanent imprints in the neural substrate of emotional and cognitive processes. Stress that is chronic, severe, and delivered during vulnerable periods of neural development will ripple through all levels of an organism's vital activity—be it a rat's inability to find its way through a maze or a maltreated child's hypersensitive response to angry faces. It would not be an overstatement to say that

the nervous system of mammals carries their singular epigenetic history and expresses it in unique but lawful (i.e. predictable) ways. This is manifested both in the way organisms react to environmental challenges and in the way their neural structures are organized. The negative effects of stress, however, are not always irreversible. The psychobiology of stress reflects both epigenesis and current life circumstances. Improved living conditions and enriched environments have the potential of correcting the impact of early adverse stressors. For example, exposing juvenile rats to complex environments can reverse the neurobiological effects of rearing by a low-licking and -grooming mother. Similarly, maltreated preschool children placed in an early intervention foster care program (which promoted positive parenting strategies) showed both improved behavioral adjustment and more normative regulation of the HPA axis in comparison with children in typical foster care settings (Fisher et al. 2000). Intervention at other levels of the organism's functioning may also correct the long-term effects of early stressors. Antidepressants and CRH antagonists, for example, eliminate many of the behavioral disturbances that animals suffer due to early adverse experience; other pharmacologic agents also may be found to improve stress resilience among at-risk children.

A common theme in stress research is that, consistent with other mammals, during human development social relationships play critical roles in regulating physiological stress reactions and protecting the developing brain from potentially deleterious effects of the hormones and neurochemicals associated with stress reactions. Disturbances in supportive care and care environments that are themselves threatening appear to rob children of an effective stress buffer and expose them to the consequences of biological stress responses that can have deleterious effects for later development. Caregivers and close relatives in a child's life are both potentially the strongest sources of stress and the most powerful defense against harmful stressors. Complex patterns of social stimulation may be part of the critical experiential input that (in interaction with genetic predispositions) shapes children's emotional and biological reactivity. Children's stress responses are also sensitive to social experiences beyond the context of the family. Negotiating peer interactions in school settings is a potent challenge to the stress system, particularly at the stage in development when social skills are just emerging. Above and beyond these normative challenges, children who are less socially competent and/or rejected might be at risk for more frequent and prolonged activation of the stress response. One of the areas that need integration into models of developmental health and psychopathology is how stress activation that is related to social status may affect children's later adaptation and health.

Despite tremendous advances in our understanding of stress neurobiology and development, there is still a great deal that is not understood. Principle among our lacunae is an adequate understanding of the genetic variations among children that moderate the reactivity, regulation, and impact of stress responses. However, numerous candidate genes are being identified whose impacts are now available for study. Integrating genetic studies into work on temperament, social experiences, stress responses, and behavioral outcomes will likely be an increasing focus of future research. Likewise, the emerging field of developmental affective neuroscience has a great deal to offer researchers concerned with understanding how the activity of stress-sensitive systems affects the development of brain systems involved in learning, memory, and emotion (Pollak 2005). Together, these foci of future research on stress should provide developmental researchers with a richer understanding of both normal and pathological development along with increased targets for interventions that will improve outcomes for children at risk for behavioral and emotional problems.

SUMMARY POINTS

1. Stressors trigger the activation of physiological systems designed to ensure the survival of the organism to the temporal detriment of systems controlling growth, reproduction, and replenishment. Although these adaptations through internal changes are desirable, under conditions of chronic stress they are deleterious. Chronic stress can cause inhibition of neurogenesis, disruption of neuronal plasticity, and neurotoxicity. Frequent activation of the stress response tilts the organism toward consuming resources without sufficient recovery and increases the risk for physical and behavioral problems. This has been termed "allostatic load."
2. Glucocorticoids regulate gene expression in multiple brain structures, thus simultaneously affecting central regulation of organic processes. The physiological and molecular events cascading from the activation of the stress systems have a powerful impact on neural tissues and the functions they support at any stage of development. However, these effects may be profound during periods of development, when the brain is undergoing rapid change. Sensitive periods and stages of enhanced brain plasticity are particularly vulnerable to the long-term effects of stress hormones. Chronic elevations of stress hormones can affect synaptic connectivity and neurogenesis and can increase cellular death, effectively altering the typical pathways and organization of the young brain.
3. Stress neurobiology can be shaped by the social environment experienced by young organisms, and adult patterns of stress reactivity can be permanently imprinted by key social influences (whether positive or negative) early in development. Of the various social influences that mammals experience, caregivers are by far the most powerful source of stress and the most effective defenseagainst harmful stressors. Disruption of the mother-infant relationship or failure of the caregiver to provide adequate care contributes to individual differences in physiological and behavioral responses to environmental challenges.
4. Maternal behavior can effectively change gene-controlled patterns of stress responsivity. Genetic information linked to neuroendocrine reactivity can be programmed by early maternal stimulation. In rodent models, highly responsive maternal behavior actually promotes a stress neurobiology that is less reactive and more resilient to challenges. The mechanisms are highly specific and involve relatively permanent modification of DNA controlling the expression of glucocorticoid receptors. However, these effects can be temporarily reversed by pharmacological intervention and in some cases by interventions that dramatically alter the care received by young mammals. The fact that DNA structure can be environmentally programmed posits both a mechanism for the impact of social stimulations and the molecular basis for intervention and healing.
5. The neurobiology of stress changes with development. Normative changes in the neurobiology of stress provide windows of opportunity and risks that are specific to that developmental stage. Reorganization of the stress response is species specific and seems to be tied to maturational changes in nervous system activity. For example, it is likely that with the onset of puberty, the relative low-stress responsivity of childhood ends and is marked by an increase in basal cortisol levels and heightened

neurobiological responses to stressors. If the onset of puberty indeed is characterized by enhanced stress reactivity, this would place adolescents at a heightened risk for psychopathology and could partly explain why there is an increase in the incidence of emotional disorders during adolescence.

6. Stress neurobiology is highly responsive to changes in the environment. Stress neurobiology, although very sensitive to early social contexts, is not a fixed or inflexible system. It reflects both the organism's epigenetic history and its new circumstances. Improved living conditions, enriched environments, and corrective emotional experiences can reverse the adverse consequences of early adversity.
7. Genes and environment interact in stress neurobiology. Constitutional predispositions intertwine with environmental influences to steer the developing stress neurobiology. Certain alleles of genes involved in neurotransmitter activity, neuronal connectivity, and differentiations seem to place children and adults at risk for a wide array of mental and physical disorders, especially when paired with adverse environments and multiple stressors such as those experienced in neglectful and abusive homes. Similarly, temperamentally inhibited children seem to be at risk for higher stress reactivity and behavioral inhibition in the context of lack of supportive care during childhood.

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