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Stress physiology and developmental psychopathology: Past, present, and future

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Abstract

Research on the hypothalamic–pituitary–adrenocortical (HPA) axis has emerged as a vital area within the field of developmental psychopathology in the past 25 years. Extensive animal research has provided knowledge of the substrates and physiological mechanisms that guide development of stress reactivity and regulation using methods that are not feasible in humans. Recent advances in understanding the anatomy and physiology of the HPA axis in humans and its interactions with other stress-mediating systems, including accurate assessment of salivary cortisol, more sophisticated neuroimaging methods, and a variety of genetic analyses, have led to greater knowledge of how psychological and biological processes impact functioning. A growing body of research on HPA axis regulation and reactivity in relation to psychopathology has drawn increased focus on the prenatal period, infancy, and the pubertal transition as potentially sensitive periods of stress system development in children. Theories such as the allostatic load model have guided research by integrating multiple physiological systems and mechanisms by which stress can affect mental and physical health. However, almost none of the prominent theoretical models in stress physiology are truly developmental, and future work must incorporate how systems interact with the environment across the life span in normal and atypical development. Our theoretical advancement will depend on our ability to integrate biological and psychological models. Researchers are increasingly realizing the importance of communication across disciplinary boundaries in order to understand how experiences influence neurobehavioral development. It is important that knowledge gained over the past 25 years has been translated to prevention and treatment interventions, and we look forward to the dissemination of interventions that promote recovery from adversity.

Twenty-five years goes by in the blink of an eye, so it is remarkable to look back over those years and realize how much has happened in the study of stress physiology and developmental psychopathology. Today, research on the hypothalamic–pituitary–adrenocortical (HPA) axis has a central place in the study of developmental psychopathology, but in 1989 it was just beginning to be examined. The dexamethasone suppression test was being studied for its diagnostic relevance in work on depressed prepubertal children (e.g., Fristad, Weller, Weller, Teare, & Preskorn, 1988). The Puig-Antich group was beginning its sleep laboratory studies of child and adolescent depression at Western Psychiatric Clinics and Hospitals, which included a focus on the HPA axis (Puig-Antich et al., 1989). There were some initial attempts to study the role of hypocortisolism in disruptive behavior disorders using urinary cortisol measures (Kruesi, Schmidt, Donnelly, Hibbs, & Hamburger, 1989). However, beyond that there were few studies of the HPA axis in either low- or high-risk children and adolescents.

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Even in the dark ages of 1989, we knew from animal studies that early experiences (i.e., handling) shaped the reactivity of the HPA axis, and we had known that for decades (Levine, 1957), but in 1989, Paul Plotsky was just beginning his rodent studies showing that prolonged, repeated separations early in life produced patterns of HPA axis activity in adulthood that mimicked those seen in depression (Plotsky & Meaney, 1993). This work, and the epigenetic studies that followed from Michael Meaney's laboratory (discussed below), opened the door to the possibility that early neglect and maltreatment might be preparing children's stress systems to be at risk for affective pathology by making them vulnerable to stressors later in development. However, attempts at studying these processes in children were yet to come.

The lag in psychoendocrine studies of children existed largely because, until about 1985, one had to take samples of either blood or urine to measure cortisol, the end product of the HPA axis. The first was too invasive for ready use in studies of children who were not already being sampled for other reasons, and the latter was complicated and messy. In 1985, arguably the first peer-reviewed developmental psychopathology paper was published on *salivary* cortisol measurement in children. It was an attempt to determine whether plasma and saliva measures of cortisol were correlated in depressed and nondepressed children (Burke et al., 1985). At that same time, Megan R. Gunnar, the second author of this anniversary article, was beginning her salivary cortisol studies

of children, which began to be published in 1989 (Gunnar, Mangelsdorf, Larson, & Hertsgaard, 1989). Soon after, Gunnar began to collaborate with Dante Cicchetti on the first studies of HPA axis regulation in maltreated children (Hart, Gunnar, & Cicchetti, 1995, 1996). In the years that followed, we have seen the study of the HPA axis and other physiological systems that are responsive to stress become central to research on developmental psychopathology. What follows in this article is not a review of this field. There are other recent articles that fulfill that role (Cicchetti & Toth, 2009; Gunnar & Quevedo, 2007). What we will do instead is examine how our approaches to the study of the neurobiology and neuroendocrinology of stress have changed over the last 25 years: where we are now, and where we need to go in order to use our understanding of psychoendocrine processes to more effectively intervene to improve outcomes for children and youth at risk for affective and behavioral disorders. We will cover the following areas: (a) anatomy and physiology; (b) methods, including statistics; (c) development and sensitive periods; (d) theory/conceptualization; and (e) translational research.

Anatomy and Physiology

It is remarkable that it was not until 1981 that we knew the structure of corticotropin-releasing hormone (CRH; Vale, Spiess, Rivier, & Rivier, 1981). This critical accomplishment allowed the development of ligands, which in turn, permitted researchers to map the location of CRH receptors. By 1987, we were beginning to realize that CRH was being produced outside of the HPA axis and that its receptors were judiciously located to orchestrate the mammalian stress response, including its HPA and sympathetic–adrenomedullary (SAM) arms (Aguilera, Millan, Hauger, & Catt, 1987). By 1989, Ned Kalin was showing that CRH potentiated freezing and other fear behaviors in infant monkeys during maternal separation, and we were seeing a rapid accumulation of knowledge about the role of CRH in triggering the stress system and orchestrating fear behavior and its potential involvement, when dysregulated, in depression and other affective disorders (Nemeroff, 1996). Not long after Vale identified the structure of CRH, researchers found that a ligand developed because of its antiprogestin and abortifacient properties, RU-486 or Mifepristone, was also a powerful glucocorticoid antagonist (Jung-Testas & Baulieu, 1983). This opened the door for studies in animals of the impact of blocking glucocorticoid actions, and it led to our understanding of the role of the mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) in the regulation of the HPA axis, the translation of glucocorticoids into action in the central nervous system (Reul & de Kloet, 1985), and the importance of MR and GR balance in health and disease (de Kloet, Vreugdenhil, Oitzl, & Joëls, 1998).

In the late 1980s, researchers were beginning to understand that brain structure and function could be impacted by chronic elevations in cortisol. In a rodent model, elevated cortisol levels were related to a reduction in hippocampal neurons, indicating that cortisol could be a mechanism by which age-related neural degeneration is accelerated (Sapolsky, Krey, & McEwen, 1985). The protective and harmful effects of glucocorticioids were further explored, with McEwen and colleagues (1992) emphasizing the role of glucocorticoids in facilitating adaptation to the environment and stress as well as returning physiological systems to baseline following acute stress. Excitatory and inhibitory effects of cortisol and corticosterone were well recognized, and the knowledge that these hormones could operate through genomic mechanisms and the possibility, only recently proven, that they also had membrane-mediated effects (Groeneweg, Karst, de Kloet, & Joëls, 2011) prompted many research questions. However, one of the biggest challenges to stress researchers was to make sense of how the stress system impacted the brain, both facilitating actions that promote the stress response and operating mechanisms to reestablish homeostasis.

Research on the anatomy and physiology of stress-mediating systems has increased exponentially in the past 25 years. We have accumulated a great deal of knowledge about HPA feedback mechanisms, interrelations of physiological systems, cortical regulation of the stress system, epigenetic processes, and the impact of stress on the brain, to name a few burgeoning topics. An example of groundbreaking work on HPA axis regulation is the research of James Herman and his colleagues. Their work illuminated the pathways regulating CRH-producing neurons in the paraventricular nucleus (PVN) of the hypothalamus and the hierarchical organization of limbic and cortical networks with multisynaptic inputs to the PVN (Herman et al., 2003). Negative feedback regulation and rapid glucocorticoid action occurs at multiple levels, including the hippocampus, amygdala, hypothalamus, and the anterior pituitary (Tasker & Herman, 2011). For example, systemic stressors stimulate neural systems in the periphery that directly project to the PVN for immediate action, whereas psychological stressors activate the HPA axis through multisynaptic limbic pathways to the PVN following stressor interpretation (Herman, Prewitt, & Cullinan, 1996). Future work examining rapid regulatory mechanisms of the HPA axis will need to integrate knowledge of feedback and feed-forward processes originating from various locations into a model that demonstrates how these mechanisms interact to produce homeostasis after challenge (Tasker & Herman, 2011).

The interaction between the HPA axis and other stress-mediating and regulatory systems has been heavily researched, and the extensive coordination between these systems in response to challenge has been aptly described as a "neurosymphony of stress" (Joëls & Baram, 2009). As such, it is inadequate to conceptualize stress through only one system. Emerging evidence indicates that each stressful event elicits multiple mediators to exert their effects in a pattern that is dependent on the type, duration, and context of the stressor; the organism's developmental stage; and individual characteristics (e.g., genetic background; for a review, see Joëls & Baram, 2009). Stress mediators include a number of monoamines, neuropeptides, and steroid hormones that occupy their own spatial and temporal niches, thus performing different,

necessary functions for the individual. However, overlap in spatial and temporal niches allow for significant interactions between mediating systems, and there is growing evidence for direct interactions between individual mediators (Joëls & Baram, 2009). Understanding the coordination of stress-mediating systems across multiple levels of organization will allow for a fuller understanding of individual differences in responses to stressors.

Although researchers had already recognized the hippocampus as being a modulator of stress-system activity, the role of the medial prefrontal cortex (mPFC) in regulating the HPA axis and other stress systems has been of particular interest in the last few decades. The mPFC has been linked to emotion regulation, and it utilizes numerous connections to other regulatory brain regions, including the amygdala, hypothalamus, and the nucleus accumbens (Arnsten, 2009). It appears to mediate glucocorticoid signals and negative feedback in response to psychological rather than systemic stressors, thus providing top-down control of the HPA axis (Ulrich-Lai & Herman, 2009). Because GRs are highly expressed in the mPFC whereas MRs are minimally expressed there, at least in rodents, it is thought that the mPFC supports basal HPA tone and downregulation in response to high GC levels (Ulrich-Lai & Herman, 2009).

Whereas physiological responses to stress are moderated by numerous top-down neural circuits, chronic stress has consistently been shown to have significant bottom-up effects on hippocampal, prefrontal cortical, and amygdalar development. Although there is evidence that mildly stressful experiences enhance cognitive skills controlled by the prefrontal cortex (Lyons & Parker, 2007), chronic or severe stress has the opposite effect, often impairing higher order cognitive processes (Arnsten, 2009). The mPFC and hippocampus experience dendritic atrophy and decreased GR expression, whereas the basolateral amygdala shows increased dendritic branching and the central nucleus of the amygdala exhibits increased CRH expression (Ulrich-Lai & Herman, 2009). In addition, the neural circuitry controlling stress responses often show alterations in typical response patterns following chronic stress by over- or underrecruiting certain brain regions responsible for reacting to stress (Ulrich-Lai & Herman, 2009). It is likely that corticolimbic circuits are reorganized at least partially through the involvement of GCs and the CRH system (Korosi & Baram, 2008).

Currently, one of the most exciting research domains involves the study of epigenetics, which are alterations to the genome that affect how genes are expressed while preserving the original nucleotide sequence. DNA methylation and histone modification are examples of epigenetic modifications that change the rate at which DNA is transcribed and thus alter protein production to affect physiology and behavior. Modification of neural circuits and stress-mediating systems in response to the environment is partially accomplished by alterations in epigenetic regulation of the GR receptor. Meaney and Moshe Szyf pioneered research on epigenetic modifications of the stress system as a result of variations in maternal care early in life (Szyf, McGowan, & Meaney, 2008). Their experiments showed that low maternal licking behavior leads to DNA methylation of the GR gene promoter and less GR in the hippocampus, which are associated with poorer HPA axis regulation (for a review, see Kaffman & Meaney, 2007). In contrast, neonatal rats experiencing high levels of licking and grooming demonstrated greater hippocampal GR, greater sensitivity to GCs, and enhanced feedback efficiency compared to nonhandled rats (Meaney, Aitken, van Berkel, Bhatnagar, & Sapolsky, 1988). Evidence of epigenetic modifications in the hippocampus has also been reported in humans. Suicide victims who experienced childhood abuse were more likely to have decreased GR mRNA and increased cytosine methylation of a neuron-specific GR (nuclear receptor subfamily 3, group C, member 1 gene [*NR3C1*]) promoter in the hippocampus (McGowan et al., 2009). In addition, increased methylation in *NR3C1* in cord blood was observed in mothers who experienced greater third trimester depressed/anxious mood, and the infants of the more depressed/anxious mothers had a higher cortisol response to stress at 3 months (Oberlander et al., 2008).

These studies have greatly influenced the field and promoted further research on epigenetic modifications in response to early stress. At this point, epigenetic modifications have primarily been studied through cheek swabs or serum samples. An unfortunate caveat for researchers is that epigenetic changes are tissue specific so that epigenetic alterations in serum or buccal cells may not translate to similar changes in the brain. As a result, it would seem wise for researchers to have a biologically plausible model of how epigenetic alterations in the target tissue(s) they are examining might impact health and behavior. When approached in this way, epigenetic modifications can be studied together with functional physiological changes (e.g., altered cortisol response to stress), past exposure to stress, and current mental and physical health status to obtain a multilevel understanding of human development.

The last decade has seen examination of polymorphisms in genes influencing activity of the HPA axis. The development of genetic analyses has allowed researchers to probe the stress system by examining polymorphisms in genes that regulate the HPA axis and related systems. Studies of specific polymorphisms in relation to hormonal, behavioral, and psychiatric outcomes have supplemented vast literatures by providing genetic mechanisms that may contribute to individual differences in observed phenomena. Caspi et al. (2003) focused a great deal of attention on the serotonin transporter linked polymorphic region gene polymorphism, and variations in this serotonin transporter gene have been linked to depression, especially in the presence of significant life stress. A recent study found that girls with the short/short genotype had greater HPA reactivity to a laboratory stressor than did girls with the short/long or long/long genotype (Gotlib, Joorman, Minor, & Hallmayer, 2008). Such studies are critical to understanding the effect of genotype on psychiatric outcomes, especially when examined longitudinally to test the hypothesis

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that genotype and stress reactivity translate to actual risk for disorder.

Genetic variations in the CRH receptor 1 (*CRHR1*) gene have been associated with depressive symptoms and clinically relevant outcomes, sometimes moderating the effects of child trauma (Cicchetti, Rogosch, & Oshri, 2011; Gillespie, Phifer, Bradley, & Ressler, 2009). For example, several single nucleotide polymorphisms (SNPs) in *CRHR1* interacted with child maltreatment to produce increased depressive symptoms, but not posttraumatic stress disorder (PTSD) symptoms, in adults (Bradley et al., 2008). A number of studies have linked *CRHR1* polymorphisms to depression and suicidality (Licinio et al., 2004; Liu et al., 2006; Wasserman, Wasserman, Rozanov, & Sokolowski, 2009). *FKBP5*, a component of the GR heterocomplex that regulates GR sensitivity, has shown associations with PTSD symptomology, including peritraumatic dissociation in children who have been seriously injured (Koenen et al., 2005), which has been shown to increase the risk of PTSD as adults (Ozer, Best, Lipsey, & Weiss, 2003). In addition, researchers have examined *FKBP5* polymorphisms that are significantly associated with GR resistance in depressed individuals (Binder et al., 2004) and somatic, sensory, and behavioral symptomology in maltreated children (Dackis, Rogosch, Oshri, & Cicchetti, 2012). Reduced *FKBP5* expression has been demonstrated in individuals with concurrent PTSD (Yehuda et al., 2009), and altered expression has been shown to predict PTSD diagnosis in traumatized individuals (Segman et al., 2005). It could be that *CRHRI* and *FKBP5* moderate the development of emotion regulatory systems, especially the interaction between the amygdala and stress-responsive systems, which prime responses to stress and risk for psychopathology throughout the life span (Gillespie et al., 2009).

GR (e.g., ER22/23EK, N363S, BclI, A3669G) and MR (−2 G/C, MR I180V) gene SNPs have both been associated with alterations in HPA axis reactivity, and these MR SNPs (but not GR SNPs) have been simultaneously related to autonomic reactivity to stress (DeRijk, van Leeuwen, Klok, & Zitman, 2009). Perhaps the most intriguing findings in relation to HPA axis related polymorphisms have been the observed relationships between genetic variation and treatment response for psychological disorders. For example, in depressed patients, those who carried the GR-related BclI-site and had a high ACTH response to challenge showed lower treatment response rate compared to noncarriers (Brouwer et al., 2006). Such studies will further our understanding of the mechanisms by which treatment improves symptomology and may improve interventions aimed at ameliorating the outcomes of those suffering from psychiatric illness.

New research trajectories show promise to inform the study of human development and stress physiology. First, recent research points to the importance of understanding monoamine, neuropeptide, and steroid hormone receptor systems when interpreting how an individual responds to stress. The location, concentration, sensitivity, and function of receptors throughout physiological systems exert a substantial impact on homeostatic regulation. Understanding these effects and how receptor systems develop will be of utmost importance when examining the interrelation of biology and behavior. Second, research on the development of PFC regulation of the HPA system should be a top priority. Although we have made progress on understanding the nature of top-down stress system regulation, much work needs to be done regarding how the PFC develops in concert with the HPA, SAM, and other systems to interact spatially and temporally in a "neuro-symphony of stress" (Joëls & Baram, 2009). Third, future psychobiological research must become more developmental and process focused. Instead of relying on biological measures at one point in time, researchers must understand what mechanisms produced this outcome and how this will affect future stress system regulation. For example, cortisol output is the result of several systems operating in unison with regulatory processes working at each level. Only with research that examines the inputs, mechanisms, and outcomes of stress-mediating systems will we be able to accurately interpret how they develop and affect health and behavior.

Methods and Statistics

Until the latter part of the 1980s, the only way to sample cortisol was via urine or plasma. Early in that decade there were studies of cortisol in newborns that capitalized on blood draws taken routinely to screen for metabolic disorders (e.g., Gunnar, Fisch, & Malone, 1984). There were also a few studies using urinary cortisol measures in preschool and school-age children that were published (e.g., Lundberg, de Chateau, Winberg, & Frankenhaeuser, 1981), but this method did not prove successful in bringing physiological assessment to psychologists. The opening of the field awaited the ready availability of salivary cortisol assay techniques. There were 22 articles using salivary cortisol assays in 1989; in 2011 nearly 350 papers were published using salivary cortisol. In addition, the shift from primarily radioimmune assays, which must be conducted in facilities equipped to manage radioactive material, to enzyme assays, which can be conducted outside of such facilities, has advanced the field and made saliva analysis more accessible.

Along with improving the ease of collection and assaying, the last 25 years have seen real progress in understanding how to collect salivary cortisol accurately. We have realized that we need to be very cautious in our use of citric acid based flavored stimulants to encourage young children to accept sampling because the pH of the sample affects many assays (Schwartz, Granger, Susman, Gunnar, & Laird, 1998). Collection on cotton dental swabs is being replaced by collection on swabs made of synthetic material in order to avoid interference from vegetable steroids in the cotton that affect some assays and the possibility that some steroid molecules *stick* to cotton. Because the timing of samples is critical, studies sometimes employ track-cap methodology that time–date stamps when vials are opened to retrieve saliva sampling materials (Kudielka, Broderick, & Kirschbaum, 2003). Because morning levels are very dynamic in the first hour after

awakening, actigraphy to assess sleep quality and awakening time is being used in some studies (e.g., Stalder et al., in press).

Although most studies of cortisol in humans use salivary measures, today a new method is quickly gaining popularity: the measurement of cortisol in hair. Unlike plasma or saliva, which capture real-time fluctuations in cortisol levels, hair cortisol measures the accumulation of cortisol over time (Russell, Koren, Rieder, & Van Uum, 2012). Cumulative cortisol measurements can be obtained for specific time periods, as each 1-cm length of hair represents roughly 1 month of development. However, further research on hair cortisol analysis is needed to verify its routine use in clinical and nonclinical samples. In addition, the estimate of hair length and time period is based on hair growth in adults, and we need to verify that these estimates also apply to hair growth early in development.

Future scientific developments that aim to advance the field should allow for less invasive measurement of higher levels of the HPA axis and other systems. Although the measurement of cortisol and other downstream products of stress mediating systems are informative starting places, they do not provide insight into neural processes. Researchers who want to understand CRH activity at the level at the hypothalamus in children, for example, are unable to do so because of the invasiveness of a spinal tap. In addition, pharmacological challenges performed on adults to understand feedback mechanisms of the HPA axis are not ethical for use in children. Thus, higher order stress system processes are not understood in childhood, when potentially lifelong patterns of activity are being set. Methods that allow for valid yet less invasive measurement of higher order mechanisms will be invaluable tools to advance the fields of developmental psychopathology and stress physiology. However, whether they could ever be produced is questionable. Because of this, it is essential that researchers study human development work closely with those studying development in other species where more invasive procedures can be used, as we discuss later in the section on translational research.

The scientific innovations of the past 25 years have been paralleled by similar advancements in statistics. New statistical tools have allowed for complex, longitudinal data modeling and better methods of measuring error. Specifically, multilevel growth curve and group-based trajectory modeling have been used to analyze cortisol change over time. Multilevel growth curve approaches model an expected cortisol pattern over time and test whether the hypothesized variables predict divergence from that pattern (e.g., Doane & Adam, 2010). Group-based trajectory modeling instead describes patterns of cortisol change in data over time and identifies factors associated with each identified pattern (e.g., Van Ryzin, Chatham, Kryzer, Kertes, & Gunnar, 2009). Both procedures account for missing observations and unequal spacing of observations using maximum likelihood techniques. In addition, study designs that incorporate multiple days of cortisol assessment reduce error by allowing the model to better account for day-to-day cortisol variability.

A methodological challenge that arises from differential reactivity to stressors across development involves finding out what situations activate the HPA axis and how to challenge the system based on this knowledge. Many studies intend to measure stress reactivity in children, yet the paradigms they use produce no elevations in cortisol. A review by Gunnar, Talge, and Herrera (2009) addresses this issue by compiling studies that use different stress paradigms (e.g., handling, novelty, public speaking, threat to relationship) across childhood to help researchers choose tasks that reliably activate the stress system to better understand factors that affect HPA axis reactivity. Paradigms that tax available coping resources and, especially for older children, those that threaten the social self tend to be most effective at activating the HPA system (Gunnar et al., 2009). Understanding human development is crucial to the measurement of physiological systems as the same stressor can elicit diverse responses in a child at different time points.

The next 25 years should bring better ways to conceptualize and analyze the joint action of the HPA axis and other stress sensitive and responsive systems. Cortisol is often measured along with activity of the autonomic nervous system, including vagal tone (respiratory sinus arrhythmia); preejection period, which largely measures epinephrine impacts on the heart; galvanic skin response, a measure of norepinephrine (NE) activity; and salivary α-amylase, an indirect measure of NE activity. A well-documented problem that has arisen over the last 25 years is that measures of autonomic activity and measures of cortisol are often poorly correlated. Cortisol is more highly correlated with measures responsive to epinephrine produced by the adrenal medulla (Goldstein & Kopin, 2008) but often completely uncorrelated with measures responsive to acetylcholine (i.e., vagal tone) and measures responsive to NE (e.g., galvanic skin response and α-amylase).

Nonetheless, we know that how cortisol impacts the brain and body depends, in part, on the activity of other stress-sensitive systems, including the SAM system. Animal studies indicate that emotional memories require actions of NE on cells in the amygdala along with the permissive presence of cortisol. There is also increasing evidence that associations between cortisol and behavior are strengthened in the presence of high SNS activity, underscoring the importance of multiple system measurement in predicting psychopathology (Bauer, Quas, & Boyce, 2002). Studies indicate that behavior problems are associated with concurrent SNS and HPA hypoactivity (Gordis, Granger, Susman, & Trickett, 2006) as well as hyperactivity (El-Sheikh, Erath, Buckhalt, Granger, & Mize, 2008). Recently, considerable attention has been paid to the role of asymmetry in the HPA and SAM systems in the development of psychopathology. Failure to coordinate the arms of the stress system may statistically mediate a pathway between early stressful experiences and subsequent pathological outcomes. For example, a recent study reported that childhood sexual abuse predicted an asymmetric profile of vagal tone and cortisol reactivity and that this profile in turn predicted higher levels of externalizing and internalizing

symptomology in adulthood (Shenk, Noll, Putnam, & Trickett, 2010). However, there is still much to learn about the mechanisms by which HPA and SAM hypoactivity, hyperactivity, and asymmetry may mediate or moderate the development of psychopathology. In order to progress, we need biologically plausible models of how and under what conditions activity of various stress-sensitive systems may work together or separately as stress mediators to impact neurobehavioral development and psychological health.

Sensitive Periods, Development, and Psychopathology

Because we need salivary measures of cortisol in order to study the HPA axis noninvasively in children, nearly all of the research on the axis in children has been conducted since 1989 (for a review, see Hostinar & Gunnar, 2013). Several critical questions have guided that work. First, do we see developmental changes in reactivity and regulation of the HPA axis, and are those changes related to sensitive periods for shaping its regulation? Second, what are the critical regulators of axis reactivity and regulation during development? Third, how are measures of cortisol reactivity and regulation related to the development and expression of psychopathology?

We have learned a great deal about development. The HPA axis becomes responsive to signals during fetal development (Gitau, Fisk, Teixeira, Cameron, & Glover, 2001; Kempnå & Flück, 2008). However, the axis is immature during this time and open to shaping by the fetal milieu (Gunnar & Davis, in press). It is now widely understood that the fetus continuously receives not only nutrients, but also biological signals from the mother, and there is increasing evidence that this information produces physiological and epigenetic changes with long-lasting consequences for physical and mental health (Sandman, Davis, Buss & Glynn, 2011). These "predictive adaptations" may facilitate survival if the environment of the womb accurately presages the nature of the postnatal environment but impair health if there is a mismatch (Barker, 1998).

In the last 25 years we have learned that the HPA axis continues to develop after birth (for a review, see Gunnar & Quevedo, 2007). Because the liver is immature at birth, its production of the protein that binds and inactivates circulating cortisol (i.e., cortisol-binding globulin) is low and only gradually increases to mature levels over the first months of life. This means that the same amount of free or biologically active cortisol can be maintained with only low levels of HPA axis activity and that, when the axis is triggered, small increases in cortisol production may mean large increases in biologically active hormones. Reactivity of the HPA axis also decreases over the first months postnatal, perhaps due to the maturation of receptors and fast feedback regulation of axis activity (Gunnar & Vazquez, 2006). As a result, during the first three months even small variations in caregiving are reflected in axis reactivity (e.g., Albers, Riksen-Walraven, Sweep, & de Weerth, 2008). Although this developmental progression is now quite clear, what we do not know is whether this degree of responsivity makes these first months a sensitive period during which normal variations in care "get under the skin" and shape the reactivity and regulation of this system and/or other systems that are responsive to variations in glucocorticoids. What we do know is that as the child moves into the fourth and fifth months after birth, the axis becomes more regulated and less reactive to minor changes in stimulation. We then move into a period of time when it becomes difficult to produce elevations in cortisol: when children have immediate access to adults with whom they have a secure attachment relationship or, if such individuals are temporarily unavailable, to surrogate caregivers who provide sensitive care.

What we do not yet know is how early this buffering effect of secure attachment relationships can be discerned. We do know that it is apparent by one year of age and extends at least until the second birthday and probably beyond (Hostinar & Gunnar, 2013). We also do not understand mechanistically how the presence and availability of trusted adults block activity of the axis (Hostinar, Sullivan, & Gunnar, 2013). This is a critical gap that needs to be filled. As argued by Hostinar and colleagues, there are likely multiple pathways mediating the buffering effect of the attachment figure. These may extend from the hypothalamus to the prefrontal cortex. Moriceau and Sullivan (2006) showed that in 10- to 12-day-old rat pups, the mother's presence buffered HPA axis response to a mild shock by blocking the release of NE in the PVN of the hypothalamus, thus reducing the CRH response and shutting down the axis's reaction. Although complex, it is also likely that attachment figures buffer the HPA axis via their effect on oxytocin levels in the central nervous system. As reviewed in Hostinar et al. (2013), it appears oxytocin may be able to translate the presence of the attachment figure into reduced stress responding via effects at the level of the pituitary (i.e., ACTH) as well as at higher levels of the central nervous system. In a brilliant series of studies, Seth Pollak's research group demonstrated that girls who phoned or interacted with their mothers immediately after going through a speech stressor task produced higher levels of urinary oxytocin and lower levels of salivary cortisol than did girls who did not have the opportunity to talk with their mothers (Seltzer, Prososki, Ziegler, & Pollak, 2012). Note that if the girls were only allowed to send a text message, this did not do the trick. Something about the mother's voice was critical to releasing oxytocin and buffering the axis. Thus, it is likely that oxytocin plays some role in allowing attachment figures to buffer children's stress systems. There is also evidence that opiate systems may be stimulated by parental contact and may be necessary for the comfort that contact provides when young children are distressed (Gray, Watt, & Blass, 2000; Panksepp, Nelson, & Siviy, 1994). Understanding the mechanisms transducing the stress-buffering effect of attachment is important if we are to understand what systems go awry when attachment figures fail to fulfill their stress-regulating role or when they become critical sources of fear and stress.

Although the prenatal and infancy periods may be sensitive periods for organization of the HPA axis, it is increasingly

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likely that puberty opens another window during which the system may be particularly sensitive to the level of threat and support the child experiences. The first indications that puberty might reorganize the axis came from evidence that cortisol increases with puberty (for a review, see Gunnar & Vazquez, 2006). Spear (2000) suggested that heightened activity of the axis with puberty may increase the brain's vulnerability to stress during early adolescence and help explain the increase in depression and other emotional problems at this time. Recent studies have confirmed the pubertal increase in HPA-axis reactivity (e.g., Gunnar, Wewerka, Frenn, Long, & Griggs, 2009) and have supported the possibility that puberty ushers in a period during which heightened stress reactivity makes early adolescence a vulnerable period for psychopathology (Andersen & Teicher, 2009; Dahl & Gunnar, 2009).

There is much we need to understand about puberty and stress. Most critical is our need to better understand the relation between heightened HPA axis activity and increased gonadal activity and sexual differentiation of patterns of stress responding and regulation. Prior to puberty, there are remarkably few differences between boys and girls in their patterns of HPA axis responding; however, there are well known adult differences in neuroendocrine regulation (Kudielka & Kirschbaum, 2005) and in responsiveness to social buffering (Kirschbaum, Klauer, Filipp, & Hellhammer, 1995), and it is likely that these differences begin to emerge with the pubertal transition. This is an area of study that is only just beginning to be mined but which promises to be a rich vein of information critical to our understanding of gender differences in vulnerability to different forms of psychopathology (see, e.g., Natsuaki et al., 2009).

The last 25 years have seen the development of a much better understanding of the critical features of contexts that elicit stress responses of the HPA axis. In addition to physical threats to life and limb, which are potent stress activators, it is now clear that threats to the social self among adults are potent triggers of HPA axis activity (Dickerson & Kemeny, 2004). These threats are nicely embodied in the Trier Social Stress Test, a paradigm that involves giving a speech before a judgmental audience and performing mental arithmetic out loud at a level that necessarily involves making public mistakes. The Trier Social Stress Test has been adapted for children, but it does not always reliably provoke cortisol elevations prior to the pubertal transition (Gunnar et al., 2009). What we do not understand is whether contexts that constitute threats to the social self change across development, leading to different types of evaluative threats being more or less potent at different ages, or whether children's sensitivity to social evaluative threat changes as they get older. Both seem likely, and understanding both in relation to stress system responding would provide important insights in work on children at low and high risk for psychopathology.

It has become quite clear that the most potent stressors for children are threats to their connection with attachment figures. Animal studies first demonstrated the massive increases in stress hormone production occasioned by forcibly separating infant monkeys from their mothers (e.g., Coe, Mendoza, Smotherman, & Levine, 1978). Those of us studying stress in young children quickly learn that, although we could produce elevations in cortisol by brief separations of parents and children, we could in no way mimic the conditions in monkey studies, and thus our milder separations produced smaller responses (for a review, see Gunnar & Donzella, 2002). Nonetheless, naturalistic studies revealed that, even in supportive day care homes, young children produced marked increases in cortisol throughout the day when separated from home and parents. When parents express high anger, and particularly when they threaten abandonment, the axis responds intensely (Flinn, 2006). Even everyday family conflict has been linked to lower morning cortisol levels and a flatter diurnal cortisol slope, a pattern of diurnal activity indicative of chronic stress (Slatcher & Robles, 2012). Conversely, affectionate contact in families has been shown to reduce cortisol levels (Flinn, 2006). What we need to understand better is the relation between the child's sense of safety or threat within the family and the child's social self as an object whose status determines stress and coping and how these sources of stress and coping change with development.

The last 25 years have also seen a tremendous change in our understanding of the nature of the interaction between psychopathology and HPA-axis reactivity and regulation. Work during this period has shown that emotional and physical stressors (e.g., maltreatment, poverty, family conflict, malnutrition, illness) are potent moderators of the HPA axis. Chronic overactivation of the HPA axis may contribute to hippocampal cell atrophy, increased activation of the amygdala, immune system suppression, and cognitive and physical deficits. Individuals experiencing significant stress are also at an increased risk for psychopathology and health problems throughout life (Edwards, Holden, Felitti, & Anda, 2003; Felitti et al., 1998). Research in the past 25 years has revealed that different forms of psychopathology often have unique physiological profiles in clinical populations and are affected by individual differences in experience. These profiles may change across development, operating as a risk factor at one point and a correlate of the disorder at another. For example, increased ACTH reactivity and cortisol levels and reduced glucocorticoid feedback inhibition are commonly reported in depressed adults (for a review, see Pariante & Lightman, 2008). Postpubertal depressed adolescents show similar cortisol patterns to depressed adults, but prepubertal children tend to be hyporesponsive to stress, and this hyporesponsiveness is a predictor of later depression (see Hankin, 2012, for a review). Puberty may be an important developmental milestone as the HPA axis becomes more highly reactive to stressors and risk for depression increases significantly (Andersen & Teicher, 2009). Prospective research that examines physiological risk factors for depression across development will be vital in order to study associations over time.

This quarter century has also seen research proliferate on children and adults who have been exposed to trauma, and physiological measurement has aided the examination of the links between adversity and psychopathology. Consistent

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with other research in developmental psychopathology, one of the clearest messages of research on early life stress and trauma is that not all individuals who have these early experiences exhibit hyperresponsivity of the HPA axis as adults; many exhibit hypoactivity of the axis (Gunnar & Vazquez, 2001). It appears that the best way to distinguish those with hyper and hypo cortisol levels is to sort them according to various forms of affective pathology. Those who suffered abuse as children but appear to be symptom free as adults produce lower than typical levels of cortisol and smaller cortisol responses to stressors, whereas those with clinical depression produce elevated levels and reactivity (e.g., Carpenter et al., 2007; Heim, Ehlert, & Hellhammer, 2000). Such patterns may even be apparent in childhood (Cicchetti & Rogosch, 2001; Cicchetti, Rogosch, Gunnar, & Toth, 2010). What we do not know and need to know is which came first: the hyper versus hypo pattern of HPA axis activity or the propensity for affective pathology. Are children who are abused but who do *not* develop affective pathology less stress responsive to begin with, or is it the case that healthy functioning involves downregulating the axis in response to chronic stress or abuse (e.g., Miller, Chen & Zhou, 2007)? Does this mechanism not function well, thus allowing the axis to remain hyperactive among those with the propensity to become clinically depressed in response to early abuse? Ultimately, questions like this will benefit from genetic and epigenetic studies, as it seems likely that gene–environment interactions are involved in these differing patterns of stress reactivity and psychopathology following early trauma and abuse.

Another question that research on traumatized children raises is whether stress patterns change with development. For example, children with PTSD as a result of maltreatment have demonstrated higher cortisol levels than did controls, although low cortisol has typically been reported in adults with PTSD who experienced maltreatment as children (Carrion et al., 2002; De Bellis et al., 1999). Children with major depressive disorder (MDD) studied in sleep lab settings do not appear to display the dysregulated pattern of HPA activity typically observed among adults with MDD (e.g., Feder et al., 2004). To date, no one has studied whether such modifications are made abruptly or gradually, nor has it been determined whether reorganization may occur at a specific developmental stage or after a certain period of time following trauma exposure (e.g., Trickett, Noll, Susman, Shenk, & Putnam, 2010). This is another question that really needs to be addressed if we are to understand the developmental processes relating stress system activity to disorder.

From a developmental standpoint, there is much we still need to know about the ontogeny and regulation of the stress system and its contribution to psychopathology. The existence of sensitive periods during which experiences may exert maximal effects on development and risk for psychopathology has been investigated in relation to an array of disorders in the field. However, coming to conclusions on the existence and timing of potential sensitive periods has been difficult. Physical and psychological stressors have long been recognized to have differential effects based on developmental timing. Early childhood has been considered a sensitive period for the development of multiple systems because it is a time of rapid growth and development, including maturation of the central nervous system (Rutter, 1991). Evidence in rat and primate models indicates that prenatal, perinatal, and early life stress may alter HPA axis reactivity and regulation through adulthood (Meaney et al., 1991; Schneider, Coe, & Lubach, 1992). Studies of abuse victims also point to early trauma as a potent regulator of the HPA axis in humans (De Bellis et al., 1994; Heim et al., 2002). However, we do not know if there is a specific period in which trauma must occur to produce these deleterious effects or whether a window also exists for recalibration of the HPA axis following early adversity. Although periods of increased risk for psychopathology have been identified (Leckman & Yazgan, 2010), the field lacks prospective research that might target sensitive periods for the etiology of disorder years before onset.

Mechanistic studies of how early stress programs physiological systems while also influencing behavior and cognition will be needed to understand how trauma can get under the skin to influence health and contribute to psychopathology years later. Theories that attempt to explain the intervening years between adversity and onset of disorder must be inherently developmental in nature. A recent model proposed by Miller, Chen, and Parker (2011) integrates biological and behavioral research to explain how experiences across the life span impact allostasis and health. The model posits that experiences are programmed into macrophages of the immune system via epigenetic markings, posttranslational modifications, and tissue remodeling. Behavioral and hormonal responses, which have also been shaped by the environment, exacerbate cytokine reactivity and disrupt negative feedback processes. As a result, the autonomic, HPA, and immune systems continuously interact in relationship to the current environment and with respect to the individual's past experiences. Such interdisciplinary models will be necessary in the future as the relationships between previously separate domains are further clarified. Integrative, longitudinal research conducted at multiple levels of analysis is essential if we are to advance our knowledge of stress-mediating systems, psychopathology, and development.

Resilience, which is the process by which an individual attempts to rebound after significant stress, has piqued the interest of researchers in stress physiology and developmental psychopathology (Cicchetti, 2010; Masten, 2011). Factors such as genetics and the developmental timing and duration of stress play a role in the physiological response and the ability to recover after stressor onset (Cicchetti & Rogosch, 2012; Lupien, McEwen, Gunnar, & Heim, 2009). Researchers have questioned whether previous traumatic experiences sensitize individuals to or inoculate them from the deleterious effects of future stressors, but most evidence indicates that previous exposures increase the likelihood of maladaptation (Masten & Narayan, 2012), likely due to an increase in

allostatic load on the individual. Further, dose–response gradients suggest that higher doses of stress are correlated with increased trauma symptoms. However, a significant amount of variation in clinical symptomology occurs within groups who have experienced the same dosage of stress. The context of the stressor (e.g., ongoing family violence) and the availability of internal and external coping resources (e.g., social support) must be considered when studying resilience in the face of a new traumatic event (Hostinar & Gunnar, 2013). Psychological risk factors, such as threats to the self or loved ones, observing traumatic events in person or through media, and self-blame must also be considered when understanding adaptation across development (Masten & Narayan, 2012). In addition, physical dangers, including malnutrition, toxins, injury, and detrimental effects on parenting that may follow extreme adversity, are more direct pathways to maladaptation (Masten & Narayan, 2012), and future research must uncover how these factors relate to psychological influences and history of trauma to impact risk and resilience.

There is a vast literature on individual differences that moderate responses to stress, including personality, emotion regulation, social support, and genetics. Endophenotypes that may be subclinical predictors of future psychopathology will be helpful in teasing apart which factors have effects on various domains of functioning. For instance, research on schizophrenia has yielded multiple cognitive factors associated with genetic risk for disorder that are present at different levels in clinical and nonclinical populations (Braff, Freedman, Schork, & Gottesman, 2007). Using the endophenotype approach, researchers hope to identify specific cognitive, emotional, and physiological domains affected by trauma and focus on predictors of maladaptation and recovery in each. In addition, it is hoped that by comparing these endophenotypes in clinical and nonclinical populations we will obtain a better understanding of adaptive functioning and factors that lead to psychopathology.

Theoretical Perspectives on Stress and Development

Although often defined as dysregulation, adaptions made during stress may not necessarily reflect failures in regulation. They may instead reflect stress systems responding in a regulated fashion to a repeated or chronic challenge or stressor. Although this may result in different levels or patterns of stress system activity from that observed under low-stress conditions, this may be the way the system evolved to respond. Failure to exhibit the stress-regulated pattern would actually reflect dysregulation. This is a point of contention among the various theoretical perspectives available to organize our understanding of stress and development, and it is to these theories that we turn next.

Developmental work on the neurobiology of stress was being conducted 25 years ago within a developmental psychobiology framework, which holds many of the same tenets as developmental psychopathology (see Michel & Moore, 1995). Thus, the neurobiology of stress and development was being studied from a systems perspective and dynamic and nonlinear relations among systems were anticipated, as were self-righting and self-regulating properties of the organism in relation to its context. However, developmental psychobiology is not a theory but a multidisciplinary framework for understanding development. The theories that we had to draw upon 25 years ago were not developmental.

Stress held a central role in our understanding of psychopathology in 1989. Some period of intense or heightened stress was known to precipitate first episodes of many psychiatric illnesses (Andrews, 1978). Diathesis–stress models of vulnerability to psychopathology were widely accepted, with the assumption that genetics and/or experiences during development created the diathesis for disorder (e.g., Monroe & Simons, 1991; Rende & Plomin, 1992). With regard to the HPA axis and stress neurobiology, we knew that early experiences mattered from the work in the animal literature that we have already cited in this article (e.g., Levine, 1957; Meaney & Szyf, 2005). However, research using animal models and human research on stress and development were still quite separate in 1989, with generally little cross talk. This was to change over the next 25 years and profoundly impact our theorizing about stress, development, and psychopathology.

During the last 25 years, research findings pushed the field beyond the bounds of existing theories and models. First, our understanding of the systems that are involved in the stress response has expanded along with our recognition that responses of these systems are typically not highly correlated with one another. The lack of "lockstep" response in the stress system has challenged us to understand and model a distributed stress system that reacts uniquely to different types of stressors and whose patterning of responses changes over time and development (Joëls & Baram, 2009). Second, we have become acutely aware that elevations in cortisol, once almost synonymous with stress, may be only one way the axis exhibits its response to stressors. Chronic activation of the axis, we now know, is followed by adjustments in the axis that bring cortisol down to normal or even hypo levels of activity (Fries, Hesse, Hellhammer & Hellhammer, 2005). Downregulation at the level of the pituitary and adrenal results, even though hyperresponding, may continue to prevail at higher levels of the axis (e.g., hypothalamic CRH) and stress-responsive regions in the limbic system. Nonlinear relations in the activity of different components of the stress system were part of what inspired the development of the allostatic load model (ALM) of stress and disease.

In 1993, McEwen and Stellar proposed a new formulation of the relationship between stress and disease that emphasized the "hidden cost" of adapting to stressful life conditions over long periods of time. The model argued that the neural, endocrine, and immune systems that are responsive to stressors maintain the constancy of the body through fluctuations or reactions that meet external and internal demands, a concept termed *allostasis*. Nonlinear associations among multiple stress-mediating systems were described. Chronic exposure to heightened neural and/or neuroendocrine responses (allostatic

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reactions) were predicted to produce an *allostatic load* that produced wear and tear on cardiovascular, immune, and endocrine systems over time, which results in dysregulation of these systems and pathology. Although not developmental, Danese and McEwen (2012) have recently argued that the available evidence suggests that the ALM can be applied to the impact of chronic stress experienced in childhood, and in 2011 two issues of this journal were devoted to articles applying the ALM to the study of developmental psychopathology (Cicchetti, 2011a, 2011b).

As noted, although the ALM addresses changes occurring over time, there is nothing explicitly developmental in the model. Nonetheless, in the last 25 years a good deal of information has accumulated indicating that stressors have differential impact depending on when during development they are experienced. Beginning with the work of Levine (1957), the first weeks of a rat pup's life were shown to be a sensitive period for shaping reactivity and regulation of the HPA axis, a shaping that we now know is at least partially explained by methylation of the GR gene in the hippocampus (Meaney & Szyf, 2005). However, the time period in the rodent's life when this occurs is roughly equivalent to the last trimester of human pregnancy, raising the possibility that an equivalent period in humans might be prenatal rather than postnatal. Although this issue is by no means settled, the Barker hypothesis (see review, Barker, 2007) clearly sent researchers back to considering the very early origins of the type of adult disorders (e.g., metabolic syndrome, cardiovascular disease) that are the bread and butter of the ALM. As such, this would argue that the ALM is not sufficient, and models that are more explicitly developmental are needed.

Diathesis–stress models, which are ever popular, are also not explicitly developmental. These models postulate that certain factors (e.g., polymorphisms or temperament), when present in individuals, serve as latent vulnerabilities that are activated in poor environments to produce worse outcomes than in individuals without that factor (McEwen, 1998). Although diathesis–stress models are helpful when considering factors that may moderate individual's outcomes in particular environments, they are often inadequate for studying factors that may lead to differential effects depending on one's environment. In the contrast, differential susceptibility theory (Belsky & Pleuss, 2009) and biological sensitivity to context theory (Boyce & Ellis, 2005) recognize that individuals are differentially susceptible to environmental influences but posit that certain factors may promote maladaptation in some contexts and enhance adaptation in others. Differential susceptibility theory proposes that factors should not be seen as diatheses but rather as plasticity agents that increase one's susceptibility to environmental influences (Belsky, 1997). Biological sensitivity to context theory argues that all ranges of reactivity are adaptive in some contexts (Boyce & Ellis, 2005), in line with differential susceptibility theory's focus on traditional risk factors as plasticity agents that affect reactivity to the environment. The theory also posits that reactivity to contextual factors can be measured and used to predict future developmental outcomes, and it especially argues the evolutionary adaptiveness of an individual's reactivity in responding to future contexts. Recent work has attempted to unite the theories while strengthening the evolutionary and developmental arguments for the differential susceptibility to the environment theory (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011). At the same time, new statistical suggestions have been made for researchers testing the diathesis–stress and differential susceptibility models in reference to how particular factors operate in a range of environments (Roisman et al., 2012).

The sensitivity to context and diathesis–stress models both reference evolutionary theory to provide grounding. The latest model that strives to address gaps in current theories using evolutionary principles is the adaptive calibration model (Del Giudice, Ellis, & Shirtcliff, 2011), which proposes that all patterns of response to stressors that are commonly observed exist to increase inclusive fitness and are adaptive as a result. Furthermore, life history theory argues that the stress response undergoes changes during multiple periods of development as life history demands change. Beginning with adrenarche, the stress response becomes increasingly different for the two sexes, again, because the life history demands on males and females have differed throughout our evolutionary histories. Finally, this model posits that moderate stress produces improved regulation of stress systems during development whereas intensely stressful/adverse rearing environments produce adaptive response patterns that differ for males and females. Specifically, males will become hypostress responsive, callous, and aggressive whereas females will become hyperstress responsive, anxious, and withdrawn. However, there is evidence that this gender response pattern may not hold for children who have experienced highly pervasive maltreatment (Doom, Cicchetti, Rogosch, & Dackis, 2013).

Although the ACM is very developmental, with the exception of evolutionary mechanisms (e.g., inclusive fitness, life-history stages), the more proximal mechanisms producing development and individual differences are poorly specified. Future theoretical work needs to be more explicitly developmental, particularly with regard to proposed proximal mechanisms for stability and change over time in highly interrelated systems. These theories must be able to explain the reciprocal processes by which the environment impacts the individual and the individual alters his or her own environment across development, producing a unique set of physiological and behavioral outcomes. Theories must also address the developmental problem of sleeper effects, in which certain influences on the individual are not readily detected until many years later. The question of how the individual and the environment interact across development and possibly program future physiological reactivity is still in need of theoretical and empirical work.

Specifically, one consistent research finding that needs to be addressed in current theories is that high cortisol levels and reactivity are not always associated with disorder (Hellhammer, Buchtal, Gutberlet, & Kirschbaum, 1997). Low cortisol

levels and reactivity may be just as detrimental as high cortisol levels (Gunnar & Vazquez, 2001). ALM has tried to explain both instances as *dysregulation*, although dysregulation is not clearly defined. It is more likely the case that each represents "differential regulation." Future theoretical models must be able to explain these anomalies while using terms that underscore the difference between physiological measures and adaptive (or maladaptive) functioning. The relationships between cortisol, emotion, and behavior are not always clear; and theoretical explanations of these associations are greatly needed.

Biologically plausible mechanisms that explain the relationships between environmental influences, physiological outcomes, and behavior will be essential to future theoretical accounts. Unfortunately, the brain and its complex influences on physiology and behavior are rarely given appropriate attention. More detailed explanations of how the brain regulates itself and other physiological systems are needed, and developmental neuroscience needs to be better integrated into future theoretical work. Finally, due to the heterogeneous influences of context and timing on physiology and behavior, better modeling of context and timing in our research is essential to capturing the multifaceted nature of human development. Looking to the next 25 years, we hope to see a truly developmental model of stress and development.

Translational Issues

Translational issues are at the forefront of challenges stress researchers face when planning, interpreting, and disseminating research (Gunnar & Cicchetti, 2009). The first translational hurdle involves the integration of the animal and human developmental literatures. Twenty-five years ago, virtually all research on the HPA axis, stress, and development was conducted in animals, but the expectation and hope was that this research held implications for our understanding of human development. Since that time, the work in animal models has been groundbreaking; meanwhile, we have developed a human literature. However, integration between the two has been modest, as most researchers who include HPA axis measures in human work have only a cursory knowledge of the animal literature. The result is often rejection of the importance of animal models or an oversimplified direct application of the animal findings to humans.

Animal models are necessary because invasive work cannot be done in children, but understanding anatomical, physiological, and developmental timing differences between species, as well as disparities in the ecology and evolutionary history of the model species, are all factors crucial to drawing correct inferences from the animal work. On the whole, the most important influence of animal models in early life stress research has been in telling us what questions to ask as we probe human development, more so than providing us with answers. The animal work has also allowed us to infer that a finding in humans is plausibly causal, even though based on correlational findings, when in animal studies the causal direction has been verified through well-controlled experimental manipulations. It is often overlooked that one value in more closely integrating animal and human research is to provide guides to animal researchers in the types of questions they need to ask to build more solid translational bridges to human work. For example, animal studies of early life stress rarely examined the diurnal rhythm in cortisol until it was found to be affected by stressors in humans. Then, probes of stress and diurnal cortisol activity revealed evidence of the impact of experimentally manipulated stressors on the diurnal rhythm of young monkeys (Sánchez et al., 2005). Researchers are increasingly realizing that in order to understand how early experiences influence neurobehavioral development, we need to communicate regularly across disciplinary boundaries.

Large-scale efforts by a number of organizations and individuals have encouraged multidisciplinary research in stress physiology. The National Institute of Mental Health supported research networks and developing centers around questions of stress and mental health in the late 1990s and early 2000s. For example, in 1998, the National Institute of Health put out a request for applications entitled HPA Regulation: Cross-Disciplinary Research Networks, and this funding led to a great deal of crosstalk among researchers from various domains. Similarly, the Canadian Institute for Advanced Research supported a program on experience-based brain and biological development that brought together animal and human researchers studying stress and development with epidemiologists, pediatricians, and developmental psychologists to help to explain how social experiences early in life get under the skin to affect lifelong behavioral and physical health. The MacArthur Foundation network on socioeconomic status and health was critical in advancing concepts like allostatic load that have helped to close the gap among the various disciplines whose methods and theories are needed to explain stress–health relations across development.

Editors committed to interdisciplinary research also have profound impacts on the field. For example, this issue and other special issues of *Development and Psychopathology* showcase research from a number of domains that focuses on topics of interest to scholars in numerous areas of study. In addition, the importance of training future developmental scientists to integrate research across disciplines cannot be overstated. Organizations that sponsor interdisciplinary training opportunities and mentors who encourage research spanning multiple levels contribute to the future of developmental science by investing in young scholars. Large-scale and individual efforts to integrate and disseminate multidisciplinary research are both essential to uniting fields once thought to be disparate.

The second translational issue facing those interested in stress physiology is how to use neurobiological measures to inform prevention and treatment (Cicchetti & Gunnar, 2008). Neurobiological measures of the stress system are currently used to identify differences between individuals or groups, but no standards exist for identifying psychopathology or maladaptive patterns of stress responsivity using physiological measures. Further, it is unclear whether such standards are

even possible given significant variation in stress responsiveness within and between individuals, the problem with identifying adaptive versus maladaptive responses to stress, and the role of context in determining health and maladaptive patterns. This variability and uncertainty has made knowledge of the stress system particularly difficult to incorporate into prevention and treatment interventions. However, notable exceptions exist in the literature and should be models for future prevention and treatment efforts. Dozier and colleagues (Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008) created a relational intervention called the Attachment and Biobehavioral Catch-up that aims, among other things, to normalize HPA axis activity in children living in foster care. In a randomized clinical trial, children in the treatment group had cortisol activity that was brought to levels similar to the non–foster-care group, unlike the continued high levels observed in the control group (Dozier et al., 2008). In similar fashion, an attachment-theory-informed preventive intervention with maltreated infants (child–parent psychotherapy) normalized cortisol regulation relative to children in the comparison group (Cicchetti, Rogosch, Toth, & Sturge-Apple, 2011). Both of these interventions were conducted in families of infants. Family-focused interventions for preschool-aged children in foster care also found that the treatment group had diurnal cortisol rhythms more similar to the non–foster-care group over the course of the study whereas the treatment control group exhibited a more flattened diurnal cortisol pattern (Fisher, Stoolmiller, Gunnar, & Burraston, 2007). Understanding mechanisms behind these interventions will allow researchers to identify effective components of treatment that promote psychological and physiological adaptation following significant stress.

Although measures of HPA axis activity are currently used in research as correlates of risk and disorder or as predictors of future maladaptation or psychopathology, not much is known about the clinical utility of HPA axis measures for psychiatric assessment. Extensive research will be needed to assess whether markers of the HPA axis can be used for clinical applications despite significant between- and within-subject variability. Developing standards of measurement that provide clinical information may be a useful tool for clinicians and researchers (if such measurement is even possible).

As the animal and human literatures rapidly grow, increased emphasis must be placed on the translation of information between disciplines to inform theory and future research. Communication is essential to this process, and large- and small-scale efforts are needed to encourage interdisciplinary research and theory. Collaboration is also crucial between basic and applied researchers in order to translate findings from the basic sciences to prevention and treatment interventions. We can no longer afford to focus solely on our own discipline, as collaboration across disciplines is needed to fully understand development and to ask important questions that will propel the field forward.

Concluding Remarks

There have been remarkable developments in the study of stress neurobiology and developmental psychopathology in the last 25 years. We are now well poised to truly understand biologically, as well as psychologically, how adverse life conditions get under the skin and affect risk for psychopathology, why some individuals are affected more than others, and how to intervene at different developmental time points to support healthy outcomes for children. Just as the advent of salivary assays for cortisol opened the doors in earnest to psychoendocrine research on children, so it is likely that technical innovations as yet unknown will have tremendous impacts on how we address developmental studies of stress and psychopathology in the years to come. However, the more things change, the more the fundamentals of science and theory remain critical to our progress. No matter which tools we bring to bear, our advancement will depend on our ability to integrate biological and psychological models. Physiological measures are not simply indices of psychological processes; they are the means through which psychological processes impact our body and critically, our brain. As human beings, we make sense of our environment, form concepts, and attempt to create a coherent narrative for our experiences. Thus, we can never understand stress–health linkages without bringing psychological constructs to bear. Because we attempt to do this for the developing child, our biological and psychological processes must be understood with an eye to developmental processes. Because what may seem maladaptive is often the result of adaptive responses to adverse contexts, we also need a balanced approach to studying normative and atypical patterns of development, especially for situations in which the context changes and makes prior adaptations maladaptive. The fundamentals of developmental psychopathology have been and remain critical as we look forward to the next 25 years of progress in understanding processes that link stress and health across development.

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