



THE HYPOTHALAMIC–PITUITARY–ADRENOCORTICAL SYSTEM AND EMOTION: CURRENT WISDOM AND FUTURE DIRECTIONS

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Measures of the hypothalamic–pituitary–adrenocortical (HPA) axis can help us understand emotional development. However, to use these measures effectively, we must remember that the HPA system evolved to serve multiple essential functions, including regulation of glucose and carbohydrate metabolism and modulation of the immune and cardiovascular systems (Sapolsky, Romero, & Munck, 2000; Schulkin, 1999). While emotions do influence the HPA axis, this system is also capable of responding when the individual is comatose. Emotions are, thus, neither necessary nor often sufficient to account for increases and decreases in HPA activity. Nonetheless, when approached with an understanding of the complexity of its regulation, HPA activity can provide insights into emotions and their role in neurobehavioral development. This chapter provides an overview of some of the critical issues and current advances in using measures of HPA activity, particularly cortisol, in developmental studies of emotion. Because the HPA axis forms one arm of the mammalian stress system, this chapter should be read in conjunction with the chapter by Obradović and Boyce in this volume, which includes discussion of the other major arm, the sympathetic-adrenomedullary system.

The basic anatomy and physiology of the HPA axis and of the extra-hypothalamic corticotrophin-releasing hormone (CRH) system are covered in detail in other reviews (Gunnar & Quevedo, 2007; Joëls & Baram, 2009; Korosi & Baram, 2008; Papadimitriou & Priftis, 2009; Ulrich-Lai & Herman, 2009) and will not be covered here. The remainder of the chapter is written as if the reader has a full grasp of this information. Indeed, we argue that without grounding in the biology of these systems, researchers will be unable to make much headway in using activity of the HPA axis to illuminate understanding of emotional development.

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With this caveat in mind, we first turn to a discussion of advances in methodological issues in the study of the HPA axis and emotion, followed by a discussion of new directions in HPA axis–emotion research. Throughout we highlight cross-cutting themes of this monograph, by paying close attention to: the time course of emotion–HPA associations; the importance of social context in contributing to and modifying HPA axis responses; examining the specificity of associations between HPA axis activity and emotion; and considering how the coordination of, and interactions between, multiple stress-sensitive systems might help us to better understand associations between HPA axis activity and both typical and atypical emotional functioning.

ADVANCES IN ASSESSING STRESS REACTIVITY OF THE HPA AXIS

Many studies of emotion and stress focus on relations between the dynamics of cortisol production in response to acute stressors. There have been a number of advances recently in understanding how to measure, analyze and interpret such acute responses.

What Activates the HPA Axis?

The literature on stress and the HPA axis is replete with laboratory paradigms in adults (Dickerson & Kemeny, 2004) and children (Gunnar, Talge, & Herrera, 2009) that while effective in provoking emotional responses fail to provoke increases in cortisol. Dickerson and Kemeny (2004) argued that these paradigms address the wrong emotion–motivational system, that the HPA axis evolved to respond to threats to self. Situations that create a significant threat to the physical self are difficult to create in the laboratory and, in any case, would not be ethical to use with children. Threats to the social self, they argued, engage the HPA axis, especially if the threat is perceived as uncontrollable and unpredictable. Their meta-analysis of the adult literature supported their contention. No similar meta-analysis has been performed on the child literature; however, there is evidence that situations that elicit self-evaluative emotions (embarrassment, shame) do produce elevations in cortisol among even in very young children (reviewed in Gunnar, Talge et al., 2009). Social rejection, another form of threat to the social self, also increases cortisol activity in young children (Gunnar, Sebanc, Tout, Donzella, & van Dulmen, 2003) and adolescents (Stroud et al., 2009). Identifying the correct emotion–motivational system to activate the HPA axis is critical in stress–emotion research. Given developmental changes in the self-system, further research is needed to identify developmentally appropriate situations that ethically create threats to the social self.

Creating situations that activate the axis can be challenging in the laboratory, hence researchers have sought to capture naturally occurring stressors by assessing the axis as children go about their everyday lives. Measurement in naturalistic environments allows an assessment of how typical social and emotional experiences relate to basal cortisol rhythms, and also cortisol reactivity to specific social or affective events. Several naturalistic studies have identified family conflict, parent marital problems, and parenting styles as potent influences on children's and adolescents' average cortisol levels in the home setting (Flinn & England, 1995; Pendry & Adam, 2007). Other studies relating diary reports of adolescent mood across the day to cortisol levels measured shortly thereafter have found that cortisol levels are significantly higher following adolescents' experiences of negative mood states, such as anger, worry, and loneliness (Adam, 2006; Doane & Adam, 2010). Thus, naturalistic studies support the notion that the HPA axis is strongly regulated by social emotions and social experience.

Researchers need to ensure they are assessing the correct emotion–motivational system to examine cortisol–emotion relationships and should move beyond considering cortisol as a general stress hormone responding to all levels and types of perceived stress and emotional experiences. Future research needs to continue to hone in on the specific socio-affective dimensions that contribute to the cortisol stress response at various ages.

Advances in Thinking About Baseline

In laboratory studies, the magnitude of the cortisol stress response is typically determined by comparison of poststressor values to measures of prestress baseline. Unfortunately, simply coming to the laboratory perturbs the system such that levels are either lower (often in infants and very young children; e.g., Larson, Gunnar, & Hertsgaard, 1991) or higher than the individual's nonstimulated levels. Because of negative feedback regulation, when levels are initially elevated, mild activation typically does not override negative feedback control, and as a result cortisol levels decrease over the stressor period. One way of overcoming this problem is to adapt the participant to the laboratory for a prolonged period (e.g., 30 to 60 min) and sample several times during that period to assure that cortisol levels have recovered to baseline prior to the imposition of the stressor task. Another method is to use a control day when the participants return to the laboratory knowing that they will only engage in nonchallenging activities (Lovallo, Farag, & Vincent, 2010; Stroud et al., 2009). Yet a third way to identify baseline is to collect a home baseline over the same time period as the laboratory assessments (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009).

The bottom line is that without carefully identifying baseline activity of the system, measures of stress reactivity will not likely reflect the true reactivity of the system to

whatever stressor the researcher is interested in. When most of the participants show declining values over a brief period in the laboratory, it is highly unlikely that this simply reflects the normal diurnal decrease and much more likely that the laboratory stressor was imposed on an already activated system.

Advances in Quantifying the Cortisol Stress Response

Early studies of the cortisol response to stressors in children and adolescents often relied on two measures: pre and post. Newer work involves multiple measures allowing much richer examination of the dynamics of cortisol reactivity and regulation. The use of multiple measures, though, requires attention to the timecourse of the HPA system in order to relate these measures to dynamic changes in emotion. Once the hypothalamus has received signals to produce a response, it takes about 5 min to observe elevations in ACTH and about 20–25 min to observe peak cortisol levels in plasma, with about 2 more min before levels peak in saliva (Gunnar & Tagle, 2007). *Thus, emotion–cortisol associations in response to acute stressors should be offset by about 20–25 min, with cortisol levels measured at a particular time reflecting affective experiences occurring roughly 20–25 min earlier.* Moreover, once produced, it takes time to clear cortisol from circulation, and, because of negative feedback regulation of the axis, once a significant response has been produced, the system is resistant to further responding, making it difficult to differentiate the impact of multiple stressors in the context of the same experimental session. Simply sampling one pretest and one posttest measure of response is inadequate to fully examine the response pattern of this system, as individuals differ in both rise time and time to return to baseline (Ramsay & Lewis, 2003). *Whenever possible, multiple samples leading up to the onset of the emotional stressor event and multiple samples following it, obtained at 10- to 20-min intervals, are advisable.*

When multiple measures were obtained, researchers used to rely on examining the total amount of cortisol produced in response to a stressor by calculating the area under the curve either with respect to ground or to initial level (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). Because interest has risen in examining the dynamics of changes over time in cortisol, newer studies have taken advantage of multilevel growth curve approaches and group-based trajectory modeling. While these statistical procedures have most often been applied to studying changes in cortisol across the waking day, they are equally applicable to studying the stress response and its relation to emotional reactions and coping processes. Briefly, in multilevel growth curve approaches, the investigator models an expected pattern of cortisol change over time, and examines whether variables chosen a priori cause deviations from that expected pattern (e.g., Doane & Adam, 2010). By contrast, group-based trajectory models identify and describe the patterns of cortisol

change that exist within the data and then identify which variables are most associated with membership in each (e.g., Van Ryzin, Chatham, Kryzer, Kertes, & Gunnar, 2009). Both these approaches, unlike ANOVA (e.g., Van Goozen Matthys, Cohen-Kettenis, Buitelaar, & van Engeland, 2000), use maximum likelihood techniques that allow for missing observations and unequal spacing of observations.

Social Support and Self-Regulation

Relevant to both laboratory and fieldwork, and illustrating a major theme of this monograph (the importance of context), is evidence that social support, or its lack of, moderates relations between stressor exposure and HPA activity. Especially in young children who use their emotional behavior to solicit support from attachment figures and other adults, the presence of an adult with whom the child has a secure or trusting relationship may buffer or block elevations in cortisol even when the child appears to be quite emotionally frightened or otherwise distraught (see review, Gunnar & Donzella, 2002). With the development of self-regulatory competence, associations between individuals' emotional appraisals of stressful situations and their HPA responses begin to reflect regulatory strategies and competencies (Smeeckens, Riksen-Walraven, & van Bakel, 2007). Indeed, cognitive-behavioral stress management training can produce dissociations between emotional appraisals of threat and HPA responding (e.g., Gaab, Sonderegger, Scherrer, & Ehlert, 2006). *Thus, children's social contexts, and their internalization of those contexts in the form of self-regulatory strategies, play an important role in modifying associations between emotion and HPA axis activity. Indeed, measures of HPA activity can provide a way of assessing the effectiveness of social support and self-regulatory competencies in preventing or reducing HPA responses to emotionally evocative and threatening situations.*

Recent Work on Chronic Stress and HPA Reactivity

Past or recent exposure to chronic stress can modify the impact of current or acute stress on HPA axis activity. This is because in response to chronic elevations in cortisol activity, the axis undergoes modifications that tend to bring activity to lower levels (Fries, Ziegler, Kurian, Jacoris, & Pollak, 2005; Miller, Chen, & Zhou, 2007). For example, chronic elevations in cortisol can down-regulate or reduce CRH activity in the hypothalamus, reducing ACTH and cortisol reactivity, while these same elevations produce an up-regulation or increase of CRH activity in the amygdala potentially increasing fearful or anxious responses to threat (Makino, Gold & Schulkin, 1994a, 1994b). As a result, chronic stress can produce heightened

autonomic activity, accompanied by blunted HPA activity (Evans & Kim, 2007). Not all individuals respond to chronic stress with a blunting of the HPA system; some appear to increase the HPA set point exhibiting increased basal levels and larger stress responses. Lower basal and response levels following chronic childhood stress appear to be more commonly observed among psychiatrically healthy individuals (Carpenter et al., 2007; Elzinga et al., 2008); elevated basal levels and hyper-responsivity are more often observed among individuals with depression or internalizing problems (Ashman, Dawson, Panagiotides, Yamada, & Wilkinson, 2002; Heim & Nemeroff, 2001). Extreme blunting of the HPA axis to chronic stress, however, is associated with a variety of somatic disorders (Fries et al., 2005) and post-traumatic stress disorder (Yehuda, 2002). These patterns are noted among adults, and may be related early life stressors altering the development of the axis (Heim, Plotsky, & Nemeroff, 2004). Their expression may vary with the developmental period of assessment and duration of stressor exposure (De Bellis, 2001; Gunnar & Quevedo, 2007). Thus, without awareness of developmental histories of stress exposure (particularly exposure to severely stressful conditions), the current behavior of the HPA axis in relation to emotion is more difficult to explain. This theme is mirrored throughout this monograph, with multiple other chapters making note of the importance of developmental histories as modifiers of current emotion–biology associations (see, e.g., chapters in this volume by Adam; Feldman; Strang, Hanson, and Pollack; and Cicchetti and Rogosch). *The bottom line is that researchers interested in studying emotion–HPA axis relations in chronically stressed populations should be aware that chronic stress alters both basal activity and acute reactivity to stress.*

NEW DIRECTIONS IN HPA AXIS RESEARCH

There are a number of new directions in research on the HPA axis and emotions. Here we highlight several that we believe are likely to have the largest impact on developmental research on emotion and emotion regulation.

ADVANCES IN MEASUREMENT

Salivary and plasma cortisol reflect moment to moment changes in cortisol production. When questions of chronic stress are the focus, the researcher is interested in cortisol production over a longer time frame. The production of cortisol over longer time frames can be measured in hair. Cortisol and other endogenous substances accumulate in hair with their location on the

hair shaft reflecting their production levels at the time the hair was formed. This has allowed researchers to collect hair, divide the hair shaft into lengths (e.g., 3 cm to assess every 3 months of cortisol production; 50 mg per segment needed), and use hair analysis as a way of creating a calendar of cortisol production (see Kirschbaum, Tietze, Skoluda, & Dettenborn, 2009). Recent evidence suggests that variables such as hair color, curvature, or number of washes per week do not confound measurement (Kirschbaum et al., 2009). Furthermore, studies in rhesus macaques have shown high correlations between hair measures and repeated samples of cortisol collected over a chronic stress period (Davenport, Tiefenbacher, Lutz, Novak, & Meyer, 2006). To our knowledge, so far the only published report using hair cortisol measures in children was an analysis of stress in the neonatal nursery (Yamada et al., 2007). Nonetheless, this technique is highly promising for the study of longer periods of stress–emotion exposure.

PUBERTY AND PLASTICITY

Activity of the HPA axis changes with development (Gunnar & Quevedo, 2007). While changes during infancy and early development are certainly of import, there is increasing interest in the changes that occur during puberty. With puberty, basal cortisol levels begin to rise and there is increasing evidence that over the pubertal transition, pubertal maturity is associated with heightened cortisol reactivity (Gunnar, Wewerka et al., 2009; Stroud et al., 2009). Animal studies suggest that marked changes in HPA axis reactivity during pubertal development open up a second sensitive period, with prenatal and infancy being the first one (see discussion of epigenetics, later), when the HPA axis is especially sensitive to being programmed or reprogrammed by experience (Romeo, 2010). Puberty is also associated with marked alterations in the functioning of neural systems involved in emotional responses to threat and reward (Dahl, 2004; Dahl & Gunnar, 2009). The confluence of developmental changes in neuroendocrine and emotion systems over the course of puberty may help explain why puberty is associated with marked increases in stress-related psychological and behavioral disorders. This confluence, plus the opportunity to use neuroimaging techniques to study the developing brain in later childhood and adolescence, provides a unique opportunity to study HPA axis–brain–emotion dynamics across a period of great significance for the understanding of developmental psychopathology. Furthermore, there is increasing interest in understanding how early experience effects on the developing stress–emotion system interact with experiences during the pubertal period to influence both adolescent and adult outcomes (e.g., Halligan, Herbert, Goodyer, & Murray, 2007).

NEUROIMAGING STUDIES OF THE HPA AXIS AND EMOTION

With advances in neuroimaging, there has been a rise in interest in using functional imaging to interrogate the relations between HPA axis activity and emotion. Some of this work focuses on the impact of stress on emotional learning and memory (van Stegeren, 2009), while other work focuses on developing a better understanding of the neural correlates of cortisol regulation in response to stress (Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009). To our knowledge, none of this work has involved children or adolescents, although some of the procedures would be highly appropriate for use in these populations, with appropriate attention to the methodological issues in hormone-imaging studies (King & Liberzon, 2009). Key findings from stress-imaging research include evidence that activity of the HPA axis, in conjunction with central (brain produced) norepinephrine (NE), plays complex roles in emotional learning that may vary with age and gender (Stark et al., 2006; van Stegeren, 2009). The amygdala, hippocampus, and several regions of the prefrontal cortex are targets of NE and cortisol in producing these effects. Findings from this literature reveal differential impacts of stress on emotional learning by gender (Merz et al., 2010; Stark et al., 2006) that may have significant implications for our understanding of adolescent-emergent sex differences in affective pathology (see also, Goldstein, Jerram, Abbs, Whitfield-Gabrieli, & Makris, 2010).

Studies attempting to understand the correlates of brain activity during a stressor and activity of the HPA axis (Dedovic et al., 2009; Dedovic, Wadiwalla, Engert, & Pruessner, 2009) have also highlighted the importance of gender, puberty, and the impact of stressor type and stress anticipation, on the neural correlates of stress experiences and HPA axis activity. There is also growing interest and some evidence that experiences in early in life, at least when retrospectively reported, influence both the patterning of neural activity and the magnitude of response to stressor tasks in adulthood (Buss et al., 2007).

Genetics and Epigenetics

Examining genetic variations relevant to HPA axis functioning and their interactions with experience is a noninvasive approach to moving “beyond cortisol” to gain insights into the role of other levels of the axis in emotional functioning. HPA axis polymorphisms, such as CRH receptor, and glucocorticoid and mineralocorticoid receptor polymorphisms have been linked to individual differences in reactivity to laboratory-based stressors (Thode et al., 2008; Wüst et al., 2004; Wüst, Federenko, Hellhammer, & Kirschbaum, 2000) and to individual differences in risk for development of depression and post-traumatic stress disorder (Gillespie, Phifer, Bradley, & Ressler, 2009). Recent

studies have found that interactions between HPA axis polymorphisms and measures of early life adversity provide the best prediction to stress reactivity, depression, and PTSD (Binder et al., 2008; Gillespie et al., 2009; Tyrka et al., 2009).

Additional genetic approaches have focused on epigenetic changes, rather than differences in gene sequence. Epigenetic changes are experience-driven, semipermanent alterations to portions of the DNA that can serve to either turn up or turn down expression of particular genes. Recent research supports the possibility of experience-based epigenetic programming of the GR gene in humans. Epigenetic changes to the GR promoter region have been observed in postmortem hippocampal tissues of suicide victims exposed to child abuse, and in lymphocytes in the cord blood of infants exposed to prenatal maternal depressed mood (McGowan et al., 2009; Oberlander et al., 2008). In the latter study, the observed epigenetic changes had functional consequences, predicting greater infant cortisol reactivity to a challenge task at 3 months of age. Epigenetic changes are however tissue specific, such that changes seen in peripheral cells may not reflect epigenetic changes and gene expression in other sites of interest, such as cortico-limbic circuits involved in emotion. As a result, interpretations of epigenetic data need to be specific to the particular cell type (e.g., lymphocytes) examined). *Genetic and epigenetic approaches, particularly when used in combination with functional measures of HPA axis activity and examined in relation to histories of stress exposure, are likely provide important insights into how activity at multiple levels of the HPA axis relate to typical and atypical emotional functioning.*

INTERACTIONS BETWEEN HPA AXIS ACTIVITY AND OTHER STRESS-SENSITIVE BIOLOGICAL SYSTEMS

Another new direction for research on the HPA axis research and emotion is to examine interactions between the HPA axis and other stress-sensitive biological systems. A key theme of this monograph is that no one biological system acts in isolation. Newer research, rather than simply giving a nod to the fact that we know multiple systems are involved, attempts to measure multiple systems, examine cross-system interactions, and consider their implications for understanding emotional processes.

HPA/ANS Interactions

One set of studies includes simultaneous measures of autonomic nervous system activity (sympathetic and parasympathetic activity; see Obradović & Boyce and Fox et al. chapters in this volume) and HPA axis activity and

examines how these systems interact to predict internalizing and externalizing disorders in children and adolescents (Bauer, Quas, & Boyce, 2002). For example, Gordis and colleagues found that low cortisol reactivity predicted higher levels of aggressive behavior in adolescents, but only in the presence of low sympathetic reactivity, as indicated by lower reactivity of salivary alpha amylase (a proposed surrogate marker for sympathetic activation) (Gordis, Granger, Susman, & Trickett, 2006). Attenuated responses of both the HPA and SAM are hypothesized to reflect low arousal, and low inhibition, fear, and anxiety, making risk taking and aggression more likely (Gordis et al., 2006). In a study of 8- to 9-year-olds El-Sheikh, Erath, Buckhalt, Granger, and Mize (2008) found that the combination of *high* basal SNS activity (alpha amylase or skin conductance) and high basal cortisol was associated with higher levels of internalizing and externalizing symptoms; on its own, without consideration of level of SNS activity, cortisol was not a significant predictor of child adjustment. Thus, in several studies, consideration of HPA/SNS interactions shed greater light than considering either variable alone.

HPA Interactions With Immune/Inflammatory Activity

Another set of studies examines interactions between emotion, HPA axis activity, and immune/inflammatory system activity. For example, studies of children examine the impact of day care and school experiences on cortisol levels and, in turn, the impact of variations in cortisol for immune function and illness (see, e.g., Boyce & Ellis, 2005; Watamura, Coe, Laudenslager, & Robertson, 2010). Other adolescent research examines the impact of early adverse experience on the ability of glucocorticoids to regulate inflammatory responses to stress (see Miller & Chen, 2010). Collectively, these studies show a strong impact of social context and emotional experience on both HPA axis activity and inflammation. On the other side of the causal coin, the potential *impact* of stress-related alterations in immune functioning and inflammation on emotion needs attention. Theoretical models and meta-analytic findings suggest that elevations in cytokines such as IL6 contribute to “sickness behavior” and elevated depressive symptoms and diagnoses in adults (Dowlati et al., 2010). The extent to which stress-related alterations in inflammatory processes contribute to internalizing symptoms and behaviors in child and adolescent populations remains to be examined. *These studies suggest that the HPA-axis/inflammation interplay is a potential mechanism by which socioemotional experiences may be translated into health outcomes and raise the possibility that immune and inflammatory activity, and individual differences in the ability of the HPA axis to contain such activity, may also be important contributors to individual differences in emotional experience.*

CONCLUSIONS

Measuring cortisol does not provide a simple read-out of child and adolescent emotional states. As Seymour Levine cautioned years ago (Levine & Wiener, 1989), it is not the “emotion juice.” Yet the activity of the HPA axis can be used to examine emotions and emotion-regulatory functioning when the research is conducted with attention to the neurobiology of the system, its development, and the regulatory systems that impact its activity. Studies incorporating measures of this system have burgeoned in recent years. We are, however, just beginning to tap the potential of what we can learn by close examination of how this endocrine system functions in both typically developing, low-risk children and those at risk for developing emotional disorders. We are also just beginning to understand how the HPA axis interacts with other stress systems to help explain both normal and atypical emotional functioning. While many of the new directions in HPA–emotion research so far have involved primarily adult populations, this work offers promising avenues for developmental studies of stress and emotion.