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Early Adverse Care, Stress Neurobiology, and Prevention Science: Lessons Learned

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Abstract

There is growing evidence that some of the difficulties observed among children who have experienced early adverse care (e.g., children internationally adopted from institutional care and maltreated children in foster care) involve experience-induced alterations in stress-responsive neurobiological systems, including the hypothalamic-pituitary-adrenocortical (HPA) system. Thus, incorporating stress neurobiology into prevention research could aid in identifying the children most in need of preventive intervention services, elucidating the mechanisms of change in effective interventions, and providing insight into the differential responses of children to effective interventions. However, integrating stress neurobiology and prevention research is challenging. In this paper, the results of studies examining HPA system activity in children who have experienced early adverse care are reviewed, the implications of these results for prevention research are discussed, and critical steps for successfully incorporating stress neurobiology into prevention research are identified.

Keywords

stress neurobiology; hypothalamic-pituitary-adrenocortical (HPA) system; early adverse care; prevention science

Children who have experienced early adverse care (e.g., abuse, neglect, and multiple caregiver transitions) often demonstrate compromised physical, cognitive, and psychosocial development (Pears & Fisher, 2005; Rutter & The English and Romanian Adoptees Study Team, 1998; Verhulst, Althaus, & Versluis-Den Bieman, 1990; Zima et al., 2000). Although improvements in care are often followed by improved functioning, difficulties persist and sometimes increase for a subsample of these children (Casey Family Programs, 2005; Morison & Ellwood, 2000; O'Connor et al., 2000). Inspired by studies examining the impact of early adverse care in rodents and nonhuman primates (e.g., Sánchez, Ladd, & Plotsky, 2001), several prevention researchers have suggested that experience-induced alterations in stress-responsive neurobiological systems underlie individual differences in the impact of and recovery from early adverse care (Cicchetti & Gunnar, 2008; Fishbein, 2000; Gunnar,

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Fisher, & The Early Experience Stress and Prevention Network, 2006). Thus, incorporating stress neurobiology into prevention research might help to identify the children most in need of preventive intervention services. Measures of stress neurobiology collected within the context of randomized controlled trials might also serve as indicators of intervention effectiveness and elucidate the mechanisms of change in effective interventions. Moreover, assessing the activity of stress-responsive neurobiological systems might provide insight into differential responses to these interventions.

Despite the impetus for incorporating measures of stress neurobiology into prevention research, this endeavor is not without its challenges. The stress response is multifaceted, involving changes in and interactions between multiple neuroendocrine, autonomic, immune, and metabolic systems (Sapolsky, Romero, & Munck, 2000). To date, much of the research with children who have experienced early adverse care has concentrated on one such system, the HPA system. Thus, the HPA system and its hormonal endproduct, cortisol, are the focus of this paper. We first review the results of studies examining HPA system activity in children who have experienced early adverse care and discuss the implications of the results for prevention research. We then identify steps for integrating measures of HPA system activity into prevention research.

Implications of Stress Neurobiology for Prevention Research

Associations Between HPA System Activity and Mental Health Disorders

Dysregulation of the HPA system has been implicated in the etiology of a number of mental health disorders, including posttraumatic stress disorder (PTSD), depressive disorders, and disruptive behavior disorders (De Bellis, 2001; Kaufman & Charney, 2001; Repetti, Taylor, & Seeman, 2002). For instance, Heim, Plotsky, and Nemeroff (2004) argued that alterations in the HPA system mediate the relation between early adverse care and depression in adulthood. Indeed, there is extensive evidence of altered HPA system activity, particularly elevated diurnal cortisol levels and reduced negative feedback of the HPA system, among adults with depression (Plotsky, Owens, & Nemeroff, 1998). In contrast, reduced diurnal cortisol levels and enhanced negative feedback of the HPA system have been observed in adults with PTSD (Yehuda, 2001). The associations between HPA system activity and mental health disorders have been less consistent among children, possibly because these associations only emerge over time (Kaufman, Martin, King, & Charney, 2001; van Goozen, Fairchild, Snoek, & Harold, 2007). For example, the results from a longitudinal study have shown that postnatal maternal depression predicts elevated morning levels in early adolescence, but these elevations are not associated with concurrent measures of adolescent depression (Halligan, Herbert, Goodyer, & Murray, 2004). Nevertheless, these elevated morning cortisol levels predict increased symptoms of depression 3 years later (Halligan, Herbert, Goodyer, & Murray, 2007). In a study with young children, similar results were obtained, with elevated afternoon cortisol levels predicting increased internalizing behaviors 18 months later despite being unrelated to concurrent measures of internalizing behaviors (Smider et al., 2002). Consistent with results that the HPA system adjusts to chronic stress by decreasing its activity over time, there is also evidence that childhood internalizing disorders and externalizing disorders are associated with elevated diurnal cortisol levels at one age and reduced diurnal cortisol levels at a later age (Alink et al., 2008; Ruttle et al., 2011). Thus, cortisol–behavior associations assessed at one point might provide an incomplete picture of the dynamic relations between HPA system activity and mental health disorders.

This literature has a number of implications for prevention research. However, it is critical to recognize the intricate associations between HPA system activity and mental health disorders. That is, there is evidence that elevated and reduced HPA system activity are both

maladaptive, being related to (and perhaps contributing to) different mental health disorders (e.g., elevated diurnal cortisol levels in adults with depression and reduced diurnal cortisol levels in adults with PTSD). These associations are further complicated by factors such as an individual's developmental stage and mental health history (e.g., disorder subtype and comorbidity; Gunnar & Vazquez, 2006; Heim et al., 2004). This complex pattern of results complicates the design and interpretation of prevention research employing measures of HPA system activity. It also highlights the need for additional longitudinal research on HPA system activity and the development of mental health symptoms in typically developing and at-risk populations. This vein of research might prove to be particularly informative for prevention researchers because HPA system activity might provide insight into the onset, developmental course, and diagnostic classification of mental health disorders such as PTSD, depressive disorders, and disruptive behavior disorders. There is also evidence that dysregulation of the HPA system predicts later mental health symptoms such as depressive behaviors in adolescence (Halligan et al., 2007). Therefore, measures of HPA system activity might serve as indicators of risk for future mental health disorders, which would permit for the delivery of preventive intervention services prior to the onset of mental health symptoms in adolescence or adulthood.

Impact of Early Adverse Care on HPA System Activity

Prior research findings have shown that early adverse care has a profound effect on the subsequent functioning of the HPA system (Sánchez et al., 2001; Tarullo & Gunnar, 2006). However, the directionality of the effect appears to be inconsistent. Elevated diurnal cortisol levels have been observed among children who experienced multiple caregiver transitions, children who experienced multiple types of maltreatment, and maltreated children with PTSD (Blair, Raver, Granger, Mills-Koonce, & Hibel, 2011; Carrion et al., 2002; Cicchetti & Rogosch, 2001), whereas reduced diurnal cortisol levels have been seen among rhesus monkeys exposed to repeated maternal separations, maltreated children in foster care, and children raised in institutions (Bruce, Fisher, Pears, & Levine, 2009; Carlson & Earls, 1997; Dozier et al., 2006; Sánchez et al., 2005). Thus, it has been speculated that specific aspects of early adverse care such as the type, chronicity, and developmental timing of the stressor and the length of time since the stressor occurred determine the impact on the HPA system (Heim, Ehlert, & Hellhammer, 2000; Miller, Chen, & Zhou, 2007; Sánchez et al., 2001). In fact, although foster children have been shown to display lower morning cortisol levels than nonmaltreated children, there is a great deal of variability within foster children and individual differences in morning cortisol levels are associated with different maltreatment experiences (Bruce et al., 2009). Specifically, severe physical neglect is related to low morning cortisol levels and severe emotional maltreatment is associated with high morning cortisol levels. Similarly, while individuals who have experienced early adverse care often demonstrate altered cortisol responses to psychological stressors (Fisher, Kim, Bruce, & Pears, 2012; MacMillan et al., 2009), specific aspects of early adverse care explain some variability in this response. For instance, children prenatally exposed to cocaine are more likely to show a blunted cortisol response than nonexposed children (Lester et al., 2010). However, among the prenatally exposed children, children who have also experienced domestic violence are the most likely to show a blunted cortisol response.

This research has several implications for prevention research. First, measures of HPA system activity might aid in identifying the subsample of children most in need of preventive intervention services due to early adverse care. For instance, researchers have found that approximately 22% of children who were maltreated in childhood demonstrate positive outcomes in adulthood (McGloin & Widom, 2001). Similarly, although the foster children, as a group, were characterized by low morning cortisol levels, a number of these children displayed morning cortisol levels that were comparable to the nonmaltreated

children. Second, these results might explain the heterogeneity in the negative outcomes among children who have experienced early adverse care. Research findings suggest that reduced and elevated morning cortisol levels are dysfunctional, but these patterns of cortisol production seem to be related to different physical and mental health problems (Chrousos, 2009; Heim et al., 2000). For instance, foster children who experience severe physical neglect and display low morning cortisol levels might be at risk for PTSD, whereas foster children who experience severe emotional maltreatment and display high morning cortisol levels might be at risk for depression. Importantly, early identification of the children at risk for specific mental health disorders would permit the delivery of services in a more efficient and cost-effective manner. However, a number of issues must be addressed before measures of HPA system activity can be used to identify at-risk children. For example, there are no established norms specifying typical (or atypical) diurnal cortisol levels in the literature and it is difficult to compare cortisol levels across studies owing to different sampling and assaying techniques. Additionally, although morning cortisol levels have been shown to predict later mental health symptoms, the effect sizes tend to be modest (Halligan et al., 2007; Smider et al., 2002). Therefore, it is likely that multiple measures of the activity of the HPA system and other stress-responsive neurobiological systems will be needed to accurately identify at-risk children.

Effects of Preventive Interventions on HPA System Activity

Given the impact of early adverse care on HPA system activity, researchers have become increasingly interested in the plasticity of this system in response to psychosocial preventive interventions. There is evidence that such interventions can impact the diurnal cortisol patterns and cortisol responses to psychological stressors of children who have experienced early adverse care (Cicchetti, Rogosch, Toth, & Sturge-Apple, 2011; Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008; Luecken et al., 2010). For example, Multidimensional Treatment Foster Care for Preschoolers (MTFC-P) is a preventive intervention that emphasizes the use of consistent, contingent parenting strategies to promote child psychosocial development. MTFC-P has been shown to reduce the risk of placement disruptions and increase secure attachment-related behaviors (Fisher, Burraston, & Pears, 2005; Fisher & Kim, 2007). In addition, over a 12-month period, foster children who receive services as usual have been shown to exhibit increasingly blunted diurnal cortisol slopes, whereas foster children who receive MTFC-P demonstrate more typical diurnal cortisol slopes (Fisher, Stoolmiller, Gunnar, & Burraston, 2007). Interestingly, results have also shown that MTFC-P prevents increased caregiver stress in response to child behavior problems and that higher caregiver stress is associated with the increasingly dysregulated diurnal cortisol slope observed among foster children who receive services as usual (Fisher & Stoolmiller, 2008). These results suggest that the intervention buffers foster children from the negative effects of caregiver stress on the HPA system. Furthermore, the Incredible Years Series was adapted to prevent externalizing behaviors by improving parenting practices and child social competence in preschool-aged children with siblings adjudicated for delinquent acts. This preventive intervention has been shown to positively affect parenting practices and reduce child aggression (Brotman et al., 2008). Additionally, children who receive the intervention display an increased cortisol response to a social challenge compared to children who do not receive the intervention (Brotman et al., 2007). Notably, the results from a follow-up study of this sample have revealed that the increased cortisol response mediates the effects of the intervention on child aggression among families with low parental warmth (O'Neal et al., 2010).

Of particular interest to prevention researchers, the results of these studies indicate that measures of HPA system activity collected within the context of randomized controlled trials can serve as additional indicators of intervention effectiveness and can illuminate the

underlying mechanisms of change in effective interventions. These preventive interventions were designed to improve parenting practices and child psychosocial outcomes. However, the results of these studies demonstrate the effectiveness of the interventions in preventing increasingly dysregulated activity of the HPA system among at-risk children, which suggests that the HPA system maintains a degree of plasticity following early adverse care. These results also provide insight into the therapeutic components of these interventions. For example, the results from MTFC-P suggest that providing caregivers with strategies for managing child behavior problems reduces caregiver stress and mitigates the effects of caregiver stress on foster children's diurnal cortisol slope. Importantly, the results with the siblings of adjudicated youths identify the cortisol response to a stressor as an important target for preventive interventions. That is, the intervention effects on child aggression are largely explained by change in child cortisol response among low warmth families. These results suggest that interventions that normalize (or at least prevent increasingly dysregulated) HPA system activity among children who have experienced early adverse care have the potential to reduce the risk for mental health disorders such as PTSD, depressive disorders, and disruptive behavior disorders. However, additional research is clearly needed: few researchers have examined HPA system activity as a mediator of intervention effects on psychosocial outcomes.

Role of Stress Neurobiology in Differential Responsivity to Interventions

Researchers have speculated that certain aspects of stress neurobiology moderate the impact of preventive interventions on key outcomes such that some children are more or less likely to benefit from an intervention (Cicchetti & Gunnar, 2008; Gunnar et al., 2006). For example, children who are less responsive to psychological stressors might also be less responsive to psychosocial preventive interventions. To date, the effects of stress neurobiology on the response to intervention have not been examined in children who have experienced early adverse care. However, research findings in other populations suggest that this line of research might prove fruitful. For example, Van de Wiel, Van Goozen, Matthys, Snoeck, and Van Engeland (2004) found that children displaying a blunted cortisol response to a psychological stressor responded poorly to a group-based intervention designed to reduce disruptive behavior disorders. Similarly, autonomic functioning (i.e., heart rate variability and skin conductance response) has been shown to moderate the response to interventions designed to reduce behavior problems and substance use (Beauchaine, Gartner, & Hagen, 2000; Fishbein, Hyde, Coe, & Paschall, 2004). Clearly, additional research on the associations between stress neurobiology and differential responses to intervention is needed. Such research might aid in identifying subsamples of children who will not respond to standard interventions and in developing targeted interventions for these children.

Roadmap for Incorporating Stress Neurobiology Into Prevention Research

Understanding the Basic Neurobiology of Stress

The first step to integrating stress neurobiology and prevention research is to gain an understanding of the neurobiology of stress. Unfortunately, this is not a simple task; stress neurobiology involves the dynamic interaction of multiple neurobiological systems. We outline some basic information about stress neurobiology, with a focus on the HPA system, but more in-depth knowledge is needed to collect, analyze, and interpret measures of stress neurobiology.

Stressors and the stress response—Stress is the result of real or perceived threats to an individual's physical or psychological viability (Levine, 2005; McEwen, 2000). Physical stressors such as pain do not require interpretation (or even consciousness), whereas psychological stressors depend upon an individual's appraisal of the threat within the

context of the available coping resources (Gunnar & Vazquez, 2006; Herman & Cullinan, 1997). Thus, a psychological stressor might not produce a stress response in every individual or in the same individual in every circumstance (Lazarus & Folkman, 1984). Interpreting individual differences in the stress response is one of the challenges of stress neurobiology. Also, there is not a single stress response or a single pathway for activating stress responses. Many different stressors activate stress-responsive neurobiological systems, but they do so via different input pathways and patterns of responding. The common element across these responses is the maintenance of viability by changing the levels of functioning of many neurobiological systems. This maintenance of stability through change is termed *allostasis*, and the wear and tear that allostasis causes on the body and brain over time is termed *allostatic load* (McEwen, 2000, 2006).

The HPA system—The HPA system, which produces steroid hormones called glucocorticoids (cortisol in humans), is a critical part of the body's response to stressors. As discussed below, basal functioning requires cortisol, which is produced at varying levels over the day. Elevating cortisol levels above basal levels begins with signals indicating the detection of threat being sent through the brain to the paraventricular nuclei of the hypothalamus (Gunnar & Vazquez, 2006). Signals that are strong enough stimulate the production and release of arginine vasopressin and corticotropin-releasing hormone (CRH). These hormones travel through small blood vesicles between the hypothalamus and the anterior lobe of the pituitary gland, where they stimulate the cleaving of a prohormone into adrenocorticotropic hormone (ACTH). ACTH is released into general circulation, activating cells in the cortex of the adrenal glands to synthesize and release cortisol into general circulation. Although some effects of cortisol are mediated in the cell membrane and are rapid, most effects are slower because they involve gene transcription. Cortisol regulates genes by binding to receptors that lie within the cytoplasm of many cells throughout the body and brain. The activated hormone–receptor complex migrates to the nucleus of the cell, where cortisol binds to glucocorticoid receptive elements in the promoter regions of different genes. Cortisol participates in regulating the activity of these genes and the production of their proteins. The impact of elevated cortisol levels is realized when the genes are transcribed and the availability of their proteins increases or decreases. From the detection of the threat, cortisol reaches peak levels in blood in 20 min and other fluids such as saliva in 27 min. It might then take minutes or hours to impact the body and brain and continue to exert effects for a prolonged period of time. Unlike the sympathetic system that supports the immediate, short-lived fight-or-flight response to stressors, the HPA system supports longer term adjustments.

Cortisol serves multiple roles in the survival of stressors, including the mobilization of energy, modulation of immune function, and inhibition of systems that require energy but serve long-term functions (Sapolsky et al., 2000). Cortisol also plays a complex role in the adaptation to stressors. Cortisol is a gene-transcription factor that changes gene expression throughout the body, with one effect being to alter the experience of and response to future stressors. Chronic activation results in longer term adjustments that down-regulate the activity of the system to help maintain cortisol levels within normal bounds. Thus, exposure to chronic stressors might initially result in elevated cortisol levels, followed by reduced basal cortisol levels, a blunted cortisol response to stressors, or both (Gunnar & Vazquez, 2001; Heim et al., 2000; Miller et al., 2007).

Activity of the HPA system also follows a circadian rhythm (Kirschbaum & Hellhammer, 1989; Schmidt-Reinwald et al., 1999). In humans, cortisol levels rise before awakening and peak 30–45 min after awakening, declining across the day and reaching their nadir 30 min after the onset of sleep. Basal levels of cortisol are important for maintaining the body in a state of health and for preparing the body to mount a stress response. Extremely low cortisol

levels impair the ability to maintain appropriate blood pressure and respond with increased blood pressure to a surge of adrenaline. In contrast, chronically elevated cortisol levels negatively affect memory and attention, impair immune functioning, and contribute to the development of metabolic disorders, diabetes, and stroke (McEwen, 2000, 2006). Hence, chronically reduced and elevated cortisol production bear risks to physical and mental health (Chrousos, 2009; Heim et al., 2000).

Regulation of the HPA system is partially determined by the type of receptor that cortisol occupies. Cortisol occupies glucocorticoid receptors in the body and glucocorticoid or mineralocorticoid receptors in the brain. Glucocorticoid receptors mediate the stress-related functions of cortisol and are critical for terminating HPA system activation by detecting cortisol levels and signaling the hypothalamus to inhibit production of CRH (i.e., negative feedback). Mineralocorticoid receptors mediate the basal functions of cortisol and are critical for regulating the circadian rhythm. Chronic stress impacts both type of receptors, resulting in dysregulated negative feedback and circadian rhythms (Oitzl, Champagne, van der Veen, & de Kloet, 2010).

Specifying a Biologically Plausible Conceptual Model With Clearly Defined Hypotheses

As described above, multiple neurobiological systems are involved in the stress response and these systems have widespread effects throughout the body and brain. Thus, there is not a single biomarker of stress. Indeed, it has been argued that the patterns of activity across these systems is more informative than the activity within any one system (Gordis, Granger, Susman, & Trickett, 2006). Because different measures of stress neurobiology provide different information, selecting the most appropriate measure must be guided by the study's conceptual model. That is, the second critical step to incorporating measures of stress neurobiology into prevention research is to develop a theoretically driven conceptual model with specific hypotheses. For example, van Goozen and colleagues (2007) proposed a model of childhood externalizing behaviors in which the effects of early adverse care on externalizing behaviors are mediated through neurobiological deficits—primarily alterations in the HPA system and other stress-responsive neurobiological systems—and disinhibited cognitive problems. Of particular relevance to prevention research, they hypothesized that the cortisol response to psychological stressors must be normalized to enhance the response to interventions and reduce externalizing behaviors. The authors proposed a pharmacological method for restoring typical HPA system activity; however, the results of the randomized controlled trials reviewed above suggest that psychosocial preventive interventions that address parenting practices positively affect HPA system activity in at-risk children. In sum, because the relations between HPA system activity and mental health disorders and early adverse care experiences are complicated, prevention researchers must carefully consider the impact of specific aspects of early adverse care and the intervention's mechanisms of change on stress neurobiology to select the most appropriate measure of stress neurobiology. To highlight the complexity in selecting measures of stress neurobiology, we briefly review different measures of HPA system activity below.

Methods for measuring cortisol levels—Salivary cortisol samples, which measure the amount of unbound (or biologically active) cortisol, can be collected noninvasively and repeatedly, making them ideal for assessing diurnal cortisol patterns and cortisol responses to naturalistic or laboratory stressors. Cortisol levels in saliva are highly correlated with, though lower than, cortisol levels in blood (Vining, McGinley, Maksvytis, & Ho, 1983). Urine samples can be used to provide integrated measures of unbound cortisol excretion over longer sampling periods (e.g., nighttime cortisol levels; Yehuda, Bierer, Andrew, Schmeidler, & Seckl, 2009). Researchers have also begun to use hair samples to measure accumulated cortisol over several weeks or months (Kirschbaum, Tietze, Skoluda, &

Dettenborn, 2009). Thus, hair samples might be particularly informative for examining cortisol levels in response to a chronic stressor.

Salivary cortisol measures—Salivary cortisol samples collected over the course of the day provide information about the diurnal pattern of cortisol production. The diurnal cortisol pattern in humans—an early morning peak and a late evening nadir—can be observed as early as age 6–12 weeks (Larson, White, Cochran, Donzella, & Gunnar, 1998); however, diurnal cortisol levels tend to fluctuate in early childhood due to naps and feedings (Watamura, Donzella, Kertes, & Gunnar, 2004). In adults, dysregulated diurnal cortisol patterns (e.g., blunted cortisol slopes, reduced morning cortisol levels, and/or elevated evening cortisol levels) have been associated with a host of physical and mental health problems (Chrousos, 2009; Heim et al., 2000).

In addition to the diurnal cortisol pattern, researchers have become interested in the cortisol awakening response (CAR). The CAR is characterized by a sharp increase in salivary cortisol levels, peaking 30–40 min after awakening and returning to awakening levels 60–75 min after awakening (Clow, Thorn, Evans, & Hucklebridge, 2004; Fries, Dettenborn, & Kirschbaum, 2009). Although the function of the CAR is not clear, its role and regulation appear to be distinct from the diurnal cortisol pattern. Interestingly, a blunted CAR has been observed in adults with physical and mental health problems such as depression and work overload (Clow et al., 2004; Wüst, Federenko, Hellhammer, & Kirschbaum, 2000). However, among at-risk adolescents, a heightened CAR has been found to predict the onset of depression (Adam et al., 2010).

Saliva samples can also be collected during a stressor to examine the cortisol response to and recovery from physical or psychological stressors. Cortisol levels tend to peak 20–40 min after the onset of the stressor and gradually return to baseline levels 40–60 min after the end of the stressor (Dickerson & Kemeny, 2004). However, not all stressful experiences activate the HPA system. Based upon their meta-analysis, Dickerson and Kemeny concluded that a stressor must threaten an adult's physical (e.g., pain) or psychological preservation (e.g., social-evaluation) to produce a cortisol response. Tasks that merely require mental effort or produce negative emotions do not elevate cortisol levels. In a review of the developmental literature, Gunnar, Talge, and Herrera (2009) also concluded that tasks that threaten the physical or social self tend to be effective in activating the HPA system. However, the ability to elicit a cortisol response in children is complicated by factors such as child age and presence of a supportive caregiver. For example, stressors such as minor medical procedures produce elevations in cortisol levels prior to 12 months of age but generally cease to produce elevations, at least in children with supportive caregivers, beyond that age (Gunnar, Brodersen, Krueger, & Rigatuso, 1996). Researchers have also found that the Trier Social Stress Test, a psychological stressor that activates the HPA system in adolescents and adults, fails to produce elevated cortisol levels among children transitioning into adolescence (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009; Stroud et al., 2009). Unfortunately, researchers often use tasks of convenience as stressors, find a decrease (rather than an increase) in cortisol levels, and interpret a smaller decrease in cortisol levels as evidence of a stress response. To avoid this implausible interpretation, researchers should determine whether a task activates the HPA system in the sample of interest prior to use.

Other measures of HPA system activity—Despite our focus on cortisol levels, it is important to recognize that cortisol only assesses one level of the HPA system. As such, this peripheral measure provides an incomplete view of the regulation (or dysregulation) of the HPA system. Although these tests are not usually conducted with healthy children for ethical reasons, there are pharmacological challenge tests that permit researchers to examine higher levels of the HPA system, including tests to examine the sensitivity of the HPA

system to negative feedback, responsiveness of the pituitary to CRH, and responsiveness of the adrenal cortex to ACTH.

Recognizing Critical Data Collection Issues

The next step for integrating stress neurobiology and prevention research is to ensure accurate data collection. Measures of stress neurobiology can be affected by a number of factors that can obscure or complicate the interpretation of results. Therefore, it is important to identify potential confounding factors and to determine the most appropriate course of action depending upon the impact of the factor, specific research question, and characteristics of the sample. We provide a few examples below to illustrate factors that can affect salivary cortisol levels.

Data collection methods—Although this method is not feasible with certain populations, saliva samples should be obtained via unstimulated, passive drool because some stimulants and collection devices can have unintended consequences. For example, substances such as powdered drink mix crystals have been used to stimulate saliva flow, but previous research findings have shown that substances that lower the pH of saliva samples artificially inflate or deflate cortisol levels depending upon the type of assay used (Schwartz, Granger, Susman, Gunnar, & Laird, 1998; Talge, Donzella, Kryzer, Gierens, & Gunnar, 2005). Collection devices, including braided cotton dental ropes, inert polymer swabs, and hydrocellulose microsponges, have also been used to obtain saliva samples. However, some devices make it difficult to recover an adequate amount of saliva and/or retain a percentage of cortisol (Donzella, Talge, Smith, & Gunnar, 2008; Harmon, Hibel, Rumyantseva, & Granger, 2007). Thus, if a stimulant or collection device is required, its effects should be tested prior to data collection using the intended assay and the same method should be subsequently employed with every participant.

Physical health—Because the HPA system responds to physical stressors, researchers typically avoid collecting salivary cortisol samples from participants who are acutely injured or ill. Additionally, participants with chronic illnesses such as endocrine disorders and autoimmune disorders are often excluded because of the impact of these disorders on the HPA system (e.g., Buske-Kirschbaum et al., 1997). Relatedly, a number of medications have an effect on HPA system activity or the measurement of cortisol in saliva (Granger, Hibel, Fortunato, & Kapelewski, 2009). For example, infants taking acetaminophen have been shown to display a reduced cortisol response to a series of stressful tasks (Hibel, Granger, Kivlighan, Blair, & The Family Life Project Investigators, 2006). The use of oral contraceptives, which increase the production of corticosteroid-binding globulin, is also associated with a blunted cortisol response to a psychological stressor (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999). However, given the unknown effects of most medications, Granger et al. (2009) provided a framework to guide decisions about the inclusion of medications in stress neurobiology research.

Collaborating With an Expert in Stress Neurobiology

The provided examples are not intended to be an exhaustive review of the issues that might arise when incorporating measures of stress neurobiology into prevention research. Thus, prevention researchers are strongly encouraged to collaborate with experts in the particular measure(s) of stress neurobiology. It is critical that this collaboration extends from the initial planning through the interpretation of the results. A knowledgeable collaborator will provide insight into the complex nature of the neurobiological systems involved in the stress response and will aid in formulating a theoretically driven conceptual model. A collaborator will offer guidance on data collection issues such as determining the number of samples needed to characterize the diurnal cortisol pattern (Hruschka, Kohrt, & Worthman, 2005) or

selecting a stressor that is likely to elicit a cortisol response (Dickerson & Kemeny, 2004; Gunnar, Talge, et al., 2009). Finally, a collaborator is a valuable asset when analyzing the data and interpreting the results. Therefore, a knowledgeable collaborator will be useful in navigating the possibilities and pitfalls of integrating stress neurobiology and prevention research.

Conclusions

Similar to all multidisciplinary research, incorporating measures of stress neurobiology into prevention research poses a number of challenges. We have provided a roadmap to increase the likelihood of successfully integrating stress neurobiology and prevention research. We have also attempted to illustrate that assessing stress neurobiology in children who have experienced early adverse care, particularly within the context of randomized controlled trials, has great potential to move prevention science forward. This type of research should result in the development of increasingly effective preventive intervention services for these at-risk populations. Thus, the challenges associated with this type of research are clearly worth the effort.

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