RUNNING HEAD: Social Regulation of HPA Axis in Infants, Children and Adolescents

Social Regulation of the Adrenocortical Response to Stress in Infants, Children and Adolescents: Implications for Psychopathology and Education

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Introduction

In attempting to understand how social experiences impact both typical and atypical aspects of human social and emotional development, researchers have looked to the psychobiological stress response as a potential mediating and moderating mechanism (Chrousos & Gold, 1992). The neurological and physiological systems involved in the stress response are acutely sensitive to social events (Flinn & England, 1995; Dickerson & Kemeny, 2004). Individual differences in stress physiology have been related to social and emotional functioning within the normal range (e.g. temperamental variations; Gunnar, Sebanc, Tout, Donzella & van Dulman, 2003) and have also been associated with abnormal functioning (psychopathology) in children (Kaufman, Martin, King & Charney, 2001), adolescents (Klimes-Dougan, Hastings, Granger, Usher, Zahn-Waxler, 2001) and adults (Chrousos & Gold, 1992).

Inclusion in social groups and successful negotiation of intimate personal relationships are vital features of successful child, adolescent and adult functioning. It is therefore not surprising that social and interpersonal threats are among the most highly aversive of human experiences, serving to activate both negative emotion and stress-responsive physiological systems, including the sympathetic adrenal medullary (SAM) system and the hypothalamic-pituitary-adrenal (HPA) axis (Flinn & England, 1995; Dickerson & Kemeny, 2004). That social experiences may also have *long term* effects on the organization and functioning of these physiological stress systems is perhaps less obvious. A growing body of evidence suggests that social experience may have important short and long-term influences on the HPA axis in particular, especially in the developing organism (Gunnar & Vazquez, in press; Vasquez, 1998).

After a brief description of the historical foundations of HPA axis research, we review current evidence regarding the role of social experiences in the regulation of HPA axis

physiology. We describe research on how social variables influence HPA axis functioning in normal samples of infants, children and adolescents, and also describe variations in HPA axis functioning observed in children exposed to atypical social experiences such as institutional rearing, maternal depression, and abuse and neglect. Data on the associations between exposure to social stress, HPA axis functioning and the development of psychopathology are then reviewed. We end by briefly describing data on the associations between HPA axis activity and cognitive and memory performance, and consider the potential implications of social regulation of cortisol for understanding educational performance.

Social Influences on Stress Physiology: Historical Foundations

Stress research traces its history to Selye's 1936 publication in the British journal *Nature* in which he proposed that the body passes through three stages as it confronts and attempts to adapt to what he then termed *noxious agents* but later called *stressors* (Selye, 1936). While many details of Seyle's theory have been challenged and revised, the idea that a wide variety of stressors can produce illness as a result of the body's *physiological stress* response forged a new field, focused on biological stress and its effects. A young psychologist working in the newly minted field of neuroendocrinology forged the first links between stress biology and *development*, and directed attention to the modulation of HPA axis functioning and organization by social factors. In 1957, Seymour Levine demonstrated in *Science* that simply removing rat pups from their mother for a few moments daily (termed *handling)* permanently modified activity of what, then, was understood to be the core neuroendocrine system of the stress response, the HPA system (Levine, 1957). In the decades that followed, it became apparent that the brain was the primary site for the long term alterations in HPA axis functioning as a result of social experience, due in part to McEwen's landmark work demonstrating that glucocorticoids

(GC's; cortisol in humans and non-human primates, corticosterone in rats), the hormonal products of the HPA system, both sustain normal brain function and pardoxically endanger nerve cells (McEwen, Weiss, & Schwartz, 1968). More recently, the link between early experience, brain development, and both normal and disordered functioning has become increasingly evident and better understood, due largely to evidence that early experience (especially deprivation experiences) reduces neural plasticity to stress experienced later in life (e.g. Mirescu, Peters, & Gould, 2004) and even permanently silences genes critical to the regulation of the stress response (e.g., Weaver et al., 2004). Truly, there is no way that this remarkable field and its implications for our understanding of healthy and disturbed neurodevelopment can be reviewed in a short chapter. As a result, we will focus our review on evidence primarily on the human data on social influences on the regulation of the HPA axis during development; this human literature primarily relies on measurement of CORT rather than the CNS elements of HPA axis regulation. We will refer to rodent and non-human primate literatures where necessary to help interpret the human literature, particularly with regard to causation.

Overview of HPA Axis Physiology

The two effector arms of the mammalian stress system are composed of the sympathetic-adrenomedullary (SAM) system and the hypothalamic-pituitary-adrenocortical (HPA) axis (Gunnar & Vazquez, in press). Generally speaking, the SAM system supports rapid mobilization and response, often described as "fight/flight" reactions. In contrast, the HPA system, through modulation of its basal activity, supports the efficacy of the SAM and related CNS fight/flight responses. In addition, through elevation in response to stressors, it counteracts or suppresses these acute stress effects, including its own activation (Sapolsky, Romero, & Munck, 2000). The hormone produced by the HPA system, CORT (cortisol in humans, corticosterone in many

rodents), serves as a gene transcription factor, permitting sculpting of the neural systems involved in learning, memory, and emotion (De Kloet, 2003). Thus, one function of CORT in stress is to alter the way the organism responds to a stressor the next time it is encountered (Sapolsky et al., 2000).

The HPA system is depicted in Figure 1. Briefly, the cascade of events resulting in elevations in CORT begins with the release of corticotropin-releasing hormone (CRH) and vasopressin (VP) from the paraventricular nuclei (PVN) in the hypothalamus. CRH and VP travel through small blood vesicles to the anterior pituitary (AP), where they stimulate the production and release of adrenocorticotropic hormone (ACTH). Of the two releasing hormones, CRH is the more potent, but VP appears to enhance the capacity of CRH to affect increases in ACTH production and release. Released into general circulation, ACTH interacts with receptors on the cortex of the adrenal glands to stimulate the production and release of CORT.

Multiple pathways are involved in the activation and inhibition of the HPA axis through regulating GABA-inhibition of CRH- and VP-producing cells in the PVN (see for review Herman & Cullinan, 1997). With regards to activation, physical stressors which pose immediate threats to health and viability (e.g. cold stress, heat stress, blood loss, etc) activate the HPA axis largely through norepinephrine (NE) neurons ascending from the brainstem. Psychological stressors (sometimes called processive stressors) activate the HPA axis through cortico-limbic pathways, including pathways from the central nucleus of the amygdala (CEA). The HPA axis is under negative feedback control meaning that increases in CORT will result in inhibition of PVN CRH- and VP-production. This inhibition is effected by CORT-responsive cells in the hypothalamus, hippocampus, and it now appears, medial regions of the prefrontal cortex

(Herman, & Cullinan, 1997; Sullivan & Gratton, 1999). None of these pathways is direct (i.e. they are multi-synaptic); thus, HPA regulation is multi-factorial.

CORT acts by interacting with two classes of receptors: mineralo- and glucocorticoids receptors (MR and GR; note that both receptors are responsive to CORT in the brain) (de Kloet, Vreugdenhil, Oitzl, & Joels, 1998). MR are high- and GR are low-affinity CORT receptors. This means that when CORT is at low levels, MR are activated, while GR are only activated when CORT levels are high, as at the peak of the circadian cycle or during stress. MRs tend to mediate what have been termed "permissive" effects of CORT, including maintaining the responsiveness of neurons to their neurotransmittors, maintaining the HPA circadian rhythm, and maintaining blood pressure. GRs mediate most of the effects of stress elevations in CORT. Presumably related to MR and GR activation, both chronically low and chronically high levels of CORT are associated with non-optimal functioning. In contrast, moderate basal levels, a clear circadian rhythm in CORT, and rapid increases and then rapid re-establishment of basal levels in response to stressors tend to be associated with optimal physical and behavioral health.

Measurement, Analysis, and Interpretation of CORT Activity in Human Populations.

Assessment of the HPA axis in humans has been accomplished in many ways, but it is important to distinguish between measures obtained under non-stimulated or basal conditions and measures obtained in response to specific stressors.

Basal Activity. Researchers examining basal CORT activity are interested in identifying the typical, unstimulated level of CORT for individuals at a particular time of day, or their typical pattern of CORT across the whole day. While it has been common to use pretest measures of CORT in the laboratory as a basal or baseline measure (e.g., Vanyukov, Moss, Plail, Blackson, Messich & Tarter, 1993), recent evidence suggests that pretest measures are often significantly

different from measures obtained in familiar (e.g. home) settings (van Eck et al., 1996b; Walker, Walder, & Reynolds, 2001; Larson, Gunnar, & Hertsgaard, 1991). Increasing numbers of researchers are now taking advantage of the ease of having subjects collect home samples to examine basal CORT activity. Individual differences in CORT levels at particular times of the day, the pattern of CORT production across the waking day or across a 24 hour period (e.g., amplitude or slope of the diurnal rhythm) or the amount of within-person variability noted across multiple days are typical methods of assessing natural variation in basal cortisol activity. In some protocols, CORT is assessed at the same time of day across all subjects in an effort to control for the strong diurnal variability inherent in this neuroendocrine system. In other protocols, CORT is assessed at fixed periods following awakening in an effort to track activity of the HPA system in relation to the subject's own day-night behavior. There is some evidence that CORT levels obtained early in the morning, or in response to awakening reflect latent traits of the axis with high heritability quotients (e.g., Bartels, de Geus, Kirschbaum, Sluyter, & Boomsma, 2003). Conversely, there is some evidence that levels assessed in the afternoon and evening reflect larger, transient state characteristics of the system as it reacts to the cumulative challenges of the day. Nevertheless, the demarcation between state and trait contributions or the influence of environmental and biological systems is not distinct (e.g., Shirtcliff, Zahn-Waxler, & Klimes Dougan, 2005). Other factors like sleep, food, exercise, medication use, and menstrual timing (in women) also influence CORT levels, and need to be measured and controlled in analyses (Kirschbaum & Helhammer, 1989). Recent statistical approaches (reviewed below) allow the isolation of variance associated with assay error, control factors, diurnal rhythms, trait and state contributions to CORT activity. In general, researchers now recognize that single samples of CORT do not provide sufficient information to interpret CORT activity – multiple

samples across the day and across multiple days provide the best characterization of basal activity, and measurement of CORT responses to stressors in addition to basal CORT provides a more complete picture of CORT functioning.

Cortisol Reactivity to Stressors

Assessment of the HPA axis may also involve examining reactivity to pharmacological probes and/or environmental stressors; however, pharmacological probes are rarely used in studies of children. Developmental researchers tend to rely on laboratory stressor tasks or naturally-occuring stressors such as the first day of school. Regardless, the optimal sampling protocol involves some home basal assessments, measures prior to the stressor, and multiple measures (often at 20 to 30 minute intervals) after the onset of the stressor to examine both reactivity and recovery. The classic CORT stress response profile consists of moderate CORT levels at pretest, high CORT levels in response to a stressor, and a subsequent return to near-pretest levels within 40 to 60 minutes after stressor termination. Because elevations in CORT may represent normative stress responses, the challenge of defining disruptions in the stress reactivity cycle are considerable. Typically, researchers look at individual differences in elevations of CORT in anticipation of a stressor (*anticipatory stress reaction*), the degree of elevation in response to a stressor (*reactivity)*, and the degree of delay in returning to pretest levels following a stressor (*recovery)*. Exaggerated levels of anticipatory stress or stress reactivity, a longer delay in returning to baseline, or a failure to show an HPA reaction in response to known stressors have all been considered disruptions of the expected HPA axis response to stress. Recently, researchers have begun to note a potentially dysregulated pattern termed *declivity* in which rather than elevating, CORT decreases below not only pretest levels (which might be elevated in anticipation of testing) but also below home basal levels at the same

time of day (Shirtcliff et al., 2005; van Goozen, Matthys, Cohen-Kettenis, Gispen-de Wied, Wiegant, & van Engeland, 1998). There is as yet too little study of *declivity* to know whether it is associated with disordered functioning or is a normative pattern of response to laboratory stressors of a particular type.

Advanced Statistical Models

Advanced statistical approaches have recently been developed to help isolate and model separate aspects of HPA axis activity, including trait variation in basal CORT levels and diurnal CORT patterning, and day-to-day and moment-to-moment state variations in CORT in large samples. These approaches include Latent-State-Trait modeling, which uses a latent variable approach to isolate and predict variance in CORT that is stable within individuals across time, and is thus presumed to represent "trait" variance in CORT (Shirtcliff, Granger, Booth, & Johnson, 2005; Kirschbaum, Steyer, Eid, Patalla, Schwenkmezger & Hellhammer, 1990). Another approach, HLM growth curve modeling, allows researchers to derive a latent estimate of each individual's basal pattern of CORT production across the day (presumably trait cortisol variation), to predict individual differences in these basal CORT patterns from trait variables of interest (Hruschka, Kohrt & Worthman, 2005), and to model the effects time-varying (state) factors such as mood and activity level on within-person changes in CORT (Adam, 2005; Adam & Gunnar, 2001; van Eck, Berkhof, Nicolson, & Sulon, 1996a). Using these approaches, associations between CORT and other parameters of interest, such as psychopathology, are much more robust than when trait and state variance in CORT are not as effectively isolated.

Now that the basic physiology, typical activity, and basic methods of examining HPA axis activity have been described, research on the impact of social factors on HPA axis functioning during development will be reviewed.

Social regulation of the HPA axis in Infancy and Early Childhood

Studies in rats and monkeys indicate that the HPA axis is under powerful social regulation early in development (for review see Sanchez, Ladd, & Plotsky, 2001). In rats, shortly after birth the axis enters a period described as the "stress hypo-responsive period" or SHRP. This lasts until about post-natal day 14. During this time it is difficult to elevate CORT to many stressors, and it has been suggested that this period serves to protect the developing brain from adverse impacts of chronic CORT elevations. Removing the mother for 12 to 24 hours will produce elevated CORT levels, but mimicking her stimulation of the pups by stroking them with a wet paintbrush (e.g. licking) and providing milk through a canula will keep CORT levels at baseline during maternal separation (Suchecki, Rosenfeld, & Levine, 1993). Thus it is social stimulation that maintains the axis in a non-stress state during development in the rat. Importantly, maternal licking also seems to regulate methlyation of the GR gene in the brain, such that pups who receive a lot of maternal licking have more GR receptors for CORT compared to those who receive low levels of licking and grooming (Weaver et al., 2004). More CORT receptors confer better negative feedback control of the HPA axis and less stress vulnerability.

Rats are less mature than primates at birth; therefore, it is not clear whether the mechanisms that mediate early experience effects in monkeys and humans are similar to those that operate in rats. What is clear, however, is that not long after birth in monkey infants, maternal availability and responsiveness serve as powerful CORT buffers. Capturing mother and infant from their social group produces behavioral expressions of distress from both parties, but if the infant can maintain contact with the mother, it exhibits only small increases in CORT (Levine & Wiener, 1988). Separation of mother and infant results in large increases in CORT

and fear-related behaviors that may be regulated, at least in part, by CRH production in the amygdala and other extra-hypothalamic areas (Kalin, Shelton, & Barksdale, 1989). Thus, in some ways similar to rats, non-human primate infants maintain basal CORT levels throughout most of early development through contact and proximity to attachment figures. The primate work, however, makes it clear that in some species alloparents can serve similar functions. That is, if the infant is separated from the mother but is then "mothered" by another female during separation, this attenuates elevations in CORT and reduces behavioral distress (Levine & Wiener, 1988).

The human HPA axis also comes under strong social regulation or buffering during early development. In the early months of life, however, being held and soothed by the mother or other adults does little to reduce CORT responses to stressors such as being physically manipulated (e.g. during a doctor's exam) or experiencing a mildly painful stressor like an inoculation, even though these caregiving actions do reduce crying (Gunnar, Marvinney, Isensee, & Fisch, 1988). As these studies demonstrate, although crying and CORT elevations are sometimes correlated in infancy, actions that reduce crying do not necessarily reduce the CORT response, and visa versa. Nonetheless, over the course of the first year it becomes increasingly difficult to elevate CORT to stressors like brief separations (of a few minutes), wariness-eliciting stimuli, and inoculations (see for review, Gunnar & Donzella, 2002). The uncoupling of CORT responses and behavioral distress, which is often focused on eliciting contact with attachment figures, is particularly marked under acute threat conditions among toddlers who are in secure attachment relationships with the person who is available for immediate succor (Spangler & Schieche, 1998). Indeed, only in secure attachment relationships does the caregiver appear to be able to completely buffer CORT increases in distressed toddlers, as observed in laboratory (Nachmias, Gunnar,

Mangelsdorf, Parritz, & Buss, 1996) and in naturalistic contexts (Ahnert, Gunnar, Lamb, & Barthel, 2004). Insecurely attached toddlers show CORT responses to stressful events even with their attachment figure present, and toddlers who exhibit disorganized/disoriented attachment patterns may be particularly vulnerable to elevations in this hormone (Hertsgaard, Gunnar, Erickson, & Nachmias, 1995). Thus, over the course of the first year of life, the HPA axis comes under strong social regulation in human children and the social buffer is more potent if the child is securely attached to her caregiver(s).

As in non-human primates, alloparents do appear to be capable of buffering CORT elevations in young children. This has been noted in studies of babysitters and child care providers (see for review, Gunnar & Donzella, 2002). Babysitters were instructed to provide sensitive, responsive care or more distant, neglectful care for brief (i.e, 30 minute) separations. Sensitive and responsive care by a babysitter, even if she was a stranger to the child, buffered or prevented elevations in CORT at least for brief periods. When young children are in group care settings, the quality of care provided by the "alloparent" appears to determine whether CORT levels rise over or fall over the day. Typically, for young children, CORT levels average about the same in the mid-afternoon and mid-morning, in contrast to the mature rhythm which would exhibit a decline over this period. The more mature adult rhythm emerges as children begin to outgrow their afternoon nap (Watamura, Donzella, Kertes, & Gunnar, 2004). Nonetheless, rising levels of CORT over the day suggest loss of adequate regulation of the HPA axis. Daytime increases in CORT have been observed frequently when children are in group or congregate care, however CORT increases less in high quality than low quality settings (reviewed in Gunnar & Donzella, 2002). The pattern of CORT response in these settings, which is sometimes lower than home levels in the morning and then higher than home levels in the afternoon, suggests that

these responses are not acute separation reactions (Gunnar & Donzella, 2002). Furthermore, CORT levels have been noted to decrease over nap periods at child care, even for children who simply lie on their cots and do not appear to fall asleep (Watamura, Sebanc, Donzella, & Gunnar, 2002). Such data suggest whatever is happening while children are involved in activity at child care is responsible for stimulating the HPA axis. One reasonable possibility is *peer interactions*.

Over the toddler and preschool years, children become increasingly motivated to play with other children; meanwhile, their social skills are just emerging, making peer play challenging (Hartup, 1979). Social competence tends to be negatively correlated with the rise in CORT over the group care day, which is consistent with evidence that age correlates negatively with CORT when preschoolers are at child care, but not when they are at home (reviewed in Gunnar & Donzella, 2002). The importance of peer relations is also demonstrated by evidence that as early as the preschool years, peer rejection is associated with chronic elevations in CORT when children are with their peers (Gunnar, Sebanc, Tout, Donzella, & van Dulman, 2003). This may explain why exuberant, under-controlled as well as fearful, anxious children tend to be susceptible to producing higher CORT levels and rising CORT patterns over the child care day (Dettling, Gunnar & Donzella, 1999; Gunnar, Sebanc, Tout, Donzella & vanDulman, 2003; Watamura, Donzella, Alwin, & Gunnar, 2003). Thus, while temperament has been shown to correlate with CORT activity in infancy and early childhood, its associations may be both mediated by social relationships, as in exuberant, undercontrolled temperament influencing peer rejection that is more proximally related to elevated CORT, or moderated by social relationships, as when responsive caregiving prevents fearful children from activating the HPA axis.

Although parents can clearly serve as buffers of the effects of social environments on young children's HPA axis activity through positive, calming, parenting behavior, they can also

serves as a profound source of social strain if their behavior is threatening, or fails to provide appropriate comfort. Conflict between two parents may be an especially powerful form of threat, as it combines exposure to anger and even violence, simultaneous with reduced access to parents who may be too preoccupied with their own problems to offer attention or comfort to the child. In a group of kindergarten-aged children and their parents, Pendry and Adam (2005), found that children living in homes characterized by higher levels of interparental conflict had significantly higher evening CORT levels, while less effective parenting, defined by low levels of warmth and involvement, was independently associated with higher evening CORT.

Social Regulation of the HPA axis in Middle Childhood and Adolescence

Although less evidence is available on the social regulation of CORT in the middle childhood and adolescent years, the evidence that does exist suggests that family and peer influences continue to play an important role. Beyond the results for young children mentioned above, several studies have found conflict in the family environment to be a powerful activator of CORT during middle childhood and adolescence, while a positive, stable, supportive home environment is associated with lower CORT levels (Flinn & England, 1995; Pendry & Adam, 2005; see also Repetti, Taylor & Seeman, 2002). In a sample of Caribbean children and adolescents, Flinn and England (1995, 1999) noted that high levels of family and peer conflict were among the most powerful activators of CORT; interparental conflict was also a strong predictor of CORT levels in a group of middle-class North American adolescents (Pendry & Adam, 2005). In terms of positive social influences, in the Caribbean study, the degree of support available to mothers in the home environment was also an important determinant of CORT levels in the children. Children in single mother homes without kin support or those living with distant relatives or in stepparent homes with non-related siblings had higher average

CORT levels than those in biological parent homes or those living with biological mothers who had additional kin support.

Very few studies have examined social factors influencing HPA axis activity specifically in adolescents, which is surprising given the importance of changing peer and family relationships, combined with the many other changes in physical appearance, physiology, sexuality, and social roles of this age period. The convergence of all these changes in a short period of time is thought to contribute to the experience of high levels of stress in adolescence. Recent evidence also implicates ongoing brain development as a factor in the increased emotionality and risk taking during the adolescent years (Dahl, 2004). In addition, a number of studies now suggest that a small increase in basal CORT levels occurs across mid- to late-adolescence, perhaps especially in adolescents girls (Elminger, Kuhnel & Ranke, 2002; Jonetz-Mentzel & Wiedemann, 1993; Kiess, Meidert, Dressendorfer, Scheiver, Kessler & Konig, 1995; Kenny, Gancayo, Heald, & Hung, 1966; Kenny, Preeyasombat, & Migeon, 1966; Lupien, King, Meaney & McEwen, 2001; Netherton, Goodyer, Tamplin, & Herbert, 2004 [in girls only]; Tornhage, 2002; Walker, Walder & Reynolds, 2001). The functional consequences of increasing basal CORT levels during adolescence are not yet known.

The combination of increased exposure to stressful circumstances and the ability of adolescents to reliability report on their own social experiences make adolescence an attractive period during which to study the impact of social events on the HPA axis. Utilizing the experience sampling method (ESM), in which adolescents were signaled to complete diary reports as they go about their daily lives (see Larson, 1989), in conjunction with repeated sampling of salivary CORT, Adam (2005) found that adolescents' HPA axes were responsive to moment-to-moment changes in social and emotional experiences in their everyday environments.

Controlling for the effects of time of day, momentary within-person increases in negative emotion were associated with significant within-person increases in CORT levels. In addition, being alone, rather than with other people at the time of sampling was also associated with higher momentary CORT levels. Interestingly, being alone appeared to elevate CORT only for younger and not older adolescents.

In another sample of late adolescents, individuals who had recently experienced high levels of negative life events were found to have higher average CORT levels, and those who were experiencing chronic strain in their interpersonal relationships (including family, peer and romantic), were found to have flatter diurnal CORT curves (Adam, Mineka, Zinbarg & Craske, 2005). Thus, as with infants and young children, important social relationships in the lives of children and adolescents, both within the immediate family environments and also outside the home, are associated with individual differences in CORT activity.

HPA Axis Activity in Children Exposed to Abnormal Social Environments

Situations in which extreme deviations from the expected social environment occur provide unfortunate illustrations of the importance of the environment for HPA axis functioning. Studies of children reared in institutions or orphanages have provided important insights. Notably, infants and toddlers living in such institutions appear to lack the normal diurnal rhythm in CORT production (see for review, Gunnar, 2000). In particular, CORT levels are low early in the morning and fail to decline in the late evening. This atypical pattern has also been observed in rhesus infants raised on cloth surrogates (Boyce, Champoux, Gunnar & Suomi, 1995). Lack of a consistent and supportive caregiver may be what disrupts the normal diurnal CORT rhythm, as similar disturbances have been noted in many young children placed in foster care (Fisher, personal communication). In contrast, permanently placing children in supportive adoptive

families appears to allow the normal diurnal CORT rhythm to be re-established (Gunnar, 2000). Several studies, however, suggest that not all children adopted from severely depriving conditions will re-establish completely normal patterns of HPA axis regulation. Many years after adoption, several studies now show elevated basal CORT levels in post-institutionalized children (e.g. Gunnar, Morison, Chisholm, & Shuder, 2001). However, there is some evidence that long-term elevations in basal CORT levels may be restricted to children who experienced the most adverse early care, resulting in severe growth failure (Kertes, Gunnar & Madsen, under review).

In addition to children reared in institutions, researchers have also examined physically- and sexually-abused children who have experienced catastrophic failure of their caregiving system. There is some evidence of elevations in basal CORT among these children, particularly if they exhibit chronic post-traumatic stress (PTSD) symptoms (Carrion, Weems, Ray, Glaser, Hessl & Reiss, 2002; De Bellis et al., 1999). However, not all studies have reported altered HPA axis activity, raising critical questions about the nature, duration, and severity of abuse necessary to produce long-term alterations in HPA axis functioning (Cicchetti & Rogosh, 2001). Furthermore, the finding that PTSD pursuant to early abuse is associated with elevated basal CORT levels in childhood stands in contrast to the suppressed CORT levels reported for adults with PTSD. Some have suggested that the duration of PTSD symptoms may account for this discrepancy, with elevated CORT levels characterizing PTSD early in the disorder and suppressed levels emerging over time as the HPA system “down-regulates” or adjusts to chronic CORT elevations (Yehuda, Halligan & Grossman, 2001). Taken together, the data on children exposed to severe deprivation early in life and those exposed to severe abuse suggest that such conditions increase the risk for long-term alterations in HPA axis functioning. However, the pattern of effects observed also raises

important questions about developmental changes in stress reactivity and regulation and individual difference factors that may determine whether and how long-term impacts are expressed.

Data presented thus far offer strong evidence of the influence of current social relationships on current HPA axis activity, and present the intriguing possibility that variations in social experience early in life may have organizational effects on HPA axis activity in humans, supplementing the already convincing body of evidence on the long-term effects of early experience on the HPA axis in rodents and non-human primates. A critical question, however, is whether activity of the HPA axis mediates the impact of social environments on the development of psychopathology.

Social Environments, HPA Axis Functioning, and Internalizing Psychopathology

Theoretical models. Disruptions in the social environments of children are not only implicit to theories of HPA axis functioning in abusive and neglectful family environments; they are also central to some of the core etiological theories of depression. Although dependent in part on the individual's psychological resources, chronic exposure to stressful life events has long been considered an important risk factor for the development of depression (Tafet & Bernardini, 2003). Additionally, HPA axis dysregulation among adults with Major Depressive Disorder (MDD) is one of the most consistent findings in biological psychiatry (Chrousos & Gold, 1992; Pariante, 2003). Models pertaining to childhood depression have been largely based on a downward extension of research with clinically depressed samples of adults. A more developmental approach, and the approach taken in the current chapter, is to subsume anxiety and depressive symptomatology and disorders under the more inclusive class of internalizing problems (see Zahn-Waxler, Klimes-Dougan, & Slattery, 2000). This is justified in part based on evidence that rates of comorbid anxiety and depression are high, they have core negative

affect features in common, and anxiety disorders often precede the development of depression. It is even possible that in childhood, disruptions in the HPA axis are more closely linked to anxiety than depression (e.g., Granger, Weisz, & Kauneckis, 1996; Feder et al., 2004). Indeed, there are many parallels in the etiological models of anxiety and depression, and theories of stress and HPA axis reactivity may be central to understanding the development of both.

Developmental models of depression and internalizing symptomatology focus on the effects of early experience on HPA axis activity, and the implications of normative variations in anxiety and fear reactions (Gunnar, 1992; Gunnar & Vasquez, in press). The long history of early experience-stress studies in animals provides the basis for attempts to understand how variations in care early in life may impact individual differences in stress resilience and vulnerability, leading to psychiatric disorders (see Gunnar, in press, for a recent review). Findings suggest that early experiences related to the quality of maternal care cause changes to extra-hypothalamic, cortico-limbic circuits that influence activity of the HPA axis. Briefly, this etiological model suggests that hippocampal alterations produced by prolonged stress and elevated cortisol cause an impairment of the negative feedback loop, and could account for alterations in basal cortisol and stress reactivity in patients with MDD.

A second developmental approach focuses on individual differences. Pathological anxiety in animals and humans may reflect inhibited temperament, and an exaggeration of normal anticipatory HPA responses (Rosen & Schulkin, 1998) may be most characteristic of this group. In the presence of elevated GCs and CRH, a cascade of biomolecular events that include increased expression of immediate-early genes (Makino, Gold, & Schulkin, 1994), increases the sensitivity of central fear circuits, heightens anxiety to distal danger cues and supports the transition from normal to pathologically anxiety. Thus, early social experiences, either on their

own or in interaction with temperamental vulnerability, are thought to contribute to alterations in HPA axis functioning associated with depression. What evidence exists for altered HPA axis activity in children and adolescents with internalizing problems, and for the contribution of social environments to the emergence of these differences?

Basal / Diurnal Functioning. In contrast to the studies conducted with adults, children with internalizing problems are less likely to exhibit distortions in basal CORT or the HPA rhythm. Here the conclusions are based primarily on reviews by others (e.g. Brooks-Gunn, Auth, Peteren, & Compas, 2001; Dahl & Ryan, 1996; Goodyer, Park, & Herbert, 2001; Ryan, 1998) although more recent findings are duly noted. In clinical samples, children and adolescents with clinical levels of anxiety and depression do not consistently show alterations in their basal CORT. Disruptions are more likely to be noted for diurnal patterns, particularly with regard to sleep onset (Carrion et al., 2002; DeBellis et al, 1999; Feder et al, 2004; Klimes-Dougan et al., 2001; for recent exceptions Luby et al., 2003; Martel et al, 1999; Ronsaville et al., in press). In addition, certain types of depression including melancholic depression or suicidal symptoms are more likely to be linked with elevated basal cortisol levels (e.g., Dahl et al., 1991; Luby et al., 2004; Klimes-Dougan, Zahn-Waxler, & Shirtcliff, 2005).

Some researchers have considered within-person variability, a sign of erratic basal output, to be an important indicator of HPA axis dysregulation and have examined this in relation to MDD (Yehuda, Teicher, Trestman & Siever, 1996; Peeters, Nicholson, & Berkhof, 2004). In one study examining adolescents, more highly variable early morning basal CORT levels (in particular, a spiking of these levels) across days predicted which adolescents would experience their first bout of clinical depression over the next months (Goodyer, Herbert, Tamplin & Altham, 2000a).

Several other studies suggest that premorbid differences of the axis precede and predict the

development of depression in high-risk samples. Essex and colleagues (Essex, Klein, Cho, & Kalin, 2002; Smider et al., 2002) obtained salivary CORT samples in the afternoon when children were 4.5-years of age and these measures predicted internalizing problems in kindergarteners a year later and both internalizing and externalizing problem behavior in first grade. Similar findings have been reported in studies of young adolescents (Granger, Weisz, & McCracken, 1996; Susman, Dorn, & Chrousos, 1991; Susman, Dorn, Inoff-Germain, Nottelman, & Chrousos, 1997). Higher CORT levels and higher CORT to DHEA (an adrenal androgen with effects that often counter those of CORT) ratios may also predict longer illness duration (Goodyer, Herbert, & Althan, 1998).

To what extent do early social experiences contribute to elevated cortisol levels and variability, and hence to risk of developing internalizing symptoms? In the Essex et al. (2002) study, the elevations in cortisol at age 4.5 that were found to predict internalizing and externalizing problems were in turn predicted by levels of maternal stress. Notably, however, concurrent maternal stress predicted high child CORT levels only if the currently stressed mother had also been highly stressed during the child's infancy. Furthermore, most of the association with maternal stress was carried by the effects of maternal depression symptoms. These results are similar to those of Dawson and Ashman (2000) mentioned earlier. Maternal depression during the child's early years may seriously compromise the mother's capacity to provide sensitive, responsive, and supportive care to her child. However, in the Essex et al (2002) study, it is not clear whether children with higher CORT levels had mothers who had been consistently depressed over the child's whole life. Work by Halligan and colleagues (2004) suggests the importance of maternal depression in the child's early years in particular. They found that adolescent children of mothers who were depressed post-natally had higher morning CORT

levels and more variability in these levels (Halligan, Herbert, Goodyer, & Murray, 2004), even after controlling for current life events and mothers' current levels of depression. Child internalizing symptoms added to the prediction of early morning CORT variability.

Stress Reactivity.

Like the research on basal functioning, research on stress reactivity suggests that MDD in children and adolescents is less associated with endogenous dysregulation of the HPA axis than it is in adults. Nonsuppression of CORT to dexamethasone is rare in MDD children and adolescents and ACTH and CORT responses to CRH are also typically normal, at least in depressed children who have not also been physically abused (see Ryan, 1998). In contrast, clinically anxious children show elevations in CORT in responsive to some types of stressors, including air puff startle (Ashman, Dawson, Panagiotides, Yamada, & Wilkinson, 2002).

Using experimental paradigms that involve some type of social stressor has also yielded mixed findings with regard to anticipation and reaction to stress. Granger and his colleagues (e.g., Granger, Stansbury, & Henker, 1994; Granger, Weisz, & Kauneckis, 1994) used a conflict paradigm to assess stress reactivity with a clinic-referred sample of children and adolescents. They found that increased CORT reactivity was concurrently associated with higher levels of a number of internalizing symptoms including social withdrawal, social anxiety, task inhibition, and low levels of perceived contingency. Using a similar conflict paradigm, Klimes-Dougan et al (2001) found moderate levels of CORT reactivity were associated with fewer internalizing and externalizing symptoms. A commonly used paradigm is the Trier Social Stress Test (TSST; Kirschbaum, Pirke & Helhammer, 1993) in which the participant gives a speech followed by solving mathematics problems. Various adaptations of this procedure have also been used with children and adolescents. Although elevations in CORT are typically documented using this

procedure, most studies have failed to find group differences in stress reactivity between children with internalizing disorders and comparison groups (e.g., Dorn et al., 2003; Klimes-Dougan et al., 2001; Martel et al., 1999). However when parameters of stress reactivity and stress recovery were considered separately, the greatest increase in CORT reactivity patterns for girls was associated with the highest levels of internalizing problems (Klimes-Dougan et al., 2001).

In addition to activation, understanding of how children at risk for internalizing problems recover from a stressor is critical. In a few studies repeated CORT samples after a stressor have been considered (e.g., Klimes-Dougan et al., 2001). Another aspect of recovery, failure to habituate to novel situations, may be associated with internalizing symptomatology (Gunnar & Vasquez, in press). Increasing CORT levels to novel stressors may not be unique to shy, inhibited or anxious children and indeed may initially be associated with assertion and dominance, as more assertive children are often the first to approach challenging and uncertain circumstances. However, shy, inhibited or anxious children may be less likely to habituate CORT responses as the situation becomes more familiar, and they may be less able to turn off the CORT response once they have left the novel situation. Several researchers have noted higher CORT levels among more anxious, introverted children, but only once the peer group setting was familiar (e.g., Granger, Stansbury, & Henker, 1994; Legendre & Trudel, 1996; Bruce, Davis, & Gunnar, 2002; Davis, Donzella, Krueger, & Gunnar, 1999). Failure to habituate, and the more frequent or prolonged elevations in CORT that go along with lack of habituation to stressors, may in turn increase risk for developing anxiety and depression (e.g., Pruessner et al., 1997; van Eck, Berkhof, Nicolson, & Sulon, 1996a, 1996b).

In addition to being associated cross-sectionally with symptoms of anxiety, CORT reactivity has also been shown to predict subsequent internalizing symptoms. Clinic referred children

participated in a conflict paradigm and were assessed for internalizing problems at the time of the conflict paradigm and also 6 months later (Granger, Weisz, & McCracken, 1996). Those who exhibited high CORT reactivity at the time of the first assessment exhibited more internalizing symptoms at the second time point. Also, increases in internalizing problems were associated with higher CORT reactivity at the follow-up.

If disruptions in the HPA axis system are related to internalizing symptomatology, attempts to normalize the HPA axis may provide us with critical information for diagnostic, preventive, and therapeutic purposes (Tafet & Bernardini, 2003). There is some preliminary evidence with adult samples to suggest that HPA axis activity may be modified indirectly through amygdala regulated, psychotherapeutic processes including cognitive-behavioral stress management (e.g., Gaab, Battler, Menzi, Pabst, Stoyer, & Ehlert, 2003) and social support (e.g., Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Kirschbaum, Klauer, Filipp, & Hellhammer, 1995) Given the importance of supportive peer affiliation, particularly in adolescence, more research is needed that examines the effects of support beyond the caregiving environment.

Thus, while evidence suggests that negative aspects of social circumstances may potentially place individuals at greater risk for the development of internalizing disorders through increased basal levels, variability, or CORT reactivity, positive social relationships may also offer the potential to protect against HPA dysregulation and the development of internalizing disorders.

Disruptive Behavioral Disorders (DBD) / Externalizing Problems

Etiological models regarding HPA axis functioning for externalizing problems center on core, biological disruptions in the physiological response system. Raine (1996) suggests that systems implicated in HPA axis functioning (e.g., CNS, ANS) are underaroused for some individuals (partially assumed to be genetically determined) and these response patterns may

predispose some individuals to criminality. Thus, the implication is that the HPA system will be blunted or hyporesponsive in children with externalizing problems or disruptive behavior disorders (DBD). Consistent with this hypothesis, studies of DBD children's response to serotonergic challenges have shown that these children exhibit blunted CORT reactions to fenfluramine (Soloff, Lynch, & Moss, 2000) and sumatriptan (Snoek et al., 2002), both of which typically elevate cortisol, suggesting that serotonergic regulation of the HPA axis is compromised.

There are various mechanisms that may account for low basal and reactivity CORT levels. Some possibilities include an unresponsive stress-reactivity system or a down-regulation of the axis following periods of elevated CORT. This latter hypothesis has been invoked by those suggesting that a chaotic and threatening family life may produce a down-regulated stress system in the children of antisocial parents, consistent with evidence of low basal cortisol in sons of substance abusing fathers (Hardie, Moss, Vanyukov, Yao, & Kirillovac, 2002; Pajer, Gardner, Kirillova, & Vanyukov, 2001). Overregulation of the HPA axis may contribute to low basal CORT production. Alternatively, an increased threshold for stress reactivity may account for low levels of CORT reactivity. Finally, those exhibiting externalizing problems may be under-reactive to threat stimuli, resulting in impaired avoidance learning and under-arousal, which may encourage sensation seeking as a means of increasing arousal.

"Nonstressed" or Resting HPA axis functioning: Basal, Pretest and Diurnal

Although low basal CORT has been observed in some samples of DBD children (McBurnett, Lahey, Rathouz, & Loerber, 2000; van de Wiel, van Goozen, Matthys, Snoek, & van Engeland, 2004; van Goozen et al., 1998), this finding has not been consistent (Dabbs, Jurkovic, & Frady, 1991; Scerbo & Kolko, 1994; vanGoozen, Matthys, Cohen-Kettenis,

Buittelaar, & van Engeland, 2000; Granger, Weisz, Kauneckis, 1994; Azar et al. 2004; Susman et al. 1999). Unfortunately, these studies vary in the time of day when CORT levels were examined, as well as in the conditions under which samples have been obtained. Most do not involve sampling CORT under highly familiar conditions (e.g. at home), but rather when children come to the laboratory for testing, limiting our ability determine whether basal activity of the HPA axis is lower for children with distruptive behavior problems. Nevertheless, subgroup analyses within those studies documenting basal or, more accurately, baseline differences in CORT for children with DBD in comparison to low-risk groups may be instructive. Thus, van de Weil and colleagues (van de Wiel, van Goozen, Matthys, Snoek, & van Engeland, 2004) only noted lower baseline CORT levels for DBD children who exhibited the most significant problem behavior. Similarly, McBurnett and colleagues (e.g. McBurnett, Pfiffner, Capasso, Lahey, & Loerber, 1997; McBurnett et al., 1991) found that DBD boys who had the lowest CORT levels were described as the meanest by their peers, as the most aggressive by adults, and were more overtly rather than covertly aggressive. These results seem to suggest that only the most disordered DBD children may exhibit abnormally low basal or baseline CORT.

Given this possibility, it is surprising to find that in both risk and community samples, CORT has been found to correlate with scores of externalizing behavior (e.g. Pajer, Gardner, Kirillova, et al., 2001; Scerbo & Kolko, 1994; Vanyukov et al., 1993) and aggression (Flinn & England, 1995; Spangler, 1995; Tennes & Kreye, 1985; Tennes, Kreye, Avitable, & Wells, 1986; Oosterlaan, Geurts, Knol, & Sergeant, 2005). Many of these studies, however, have assessed CORT in the early morning when levels are typically high, perhaps increasing the sensitivity to associations between externalizing problems and lower basal HPA activity. For example, using a very large community sample of children and adolescents, Shirtcliff, Granger, Booth, and

Johnson (2005) applied latent state-trait modeling techniques to identify the trait component of early morning salivary CORT production. For boys, but not girls, they found a significant negative relation between trait CORT shortly after awakening and externalizing problems. In addition to these cross-sectional associations, several studies have demonstrated that low basal CORT levels predict heightened disruptive behavior several months or years later (e.g., Granger, Weisz, and McCracken, 1996; McBurnet, Lahey, Rathouz & Loeber, 2000; Shoal, Giancola & Kirrilova, 2003). Thus, in all, the data are suggestive but not definitive regarding low basal CORT activity and more work is needed. This is particularly the case as low basal CORT could contribute to low ANS and CNS reactivity, as one function of basal cortisol is to maintain the responsiveness of neurons to their neurotransmittors (Sapolsky et al., 2000).

Stress Anticipation, Reactivity, and Recovery

Some have even suggested that disturbances in the HPA activity in externalizing disorders may be most evident under stress as compared to baseline conditions (Snoek, Van Goozen, Matthys, Buitelaar, & Engeland, 2004). In examining this hypothesis it is necessary to distinguish between failure to respond in anticipation of a threatening event, smaller elevations in CORT in response to such events, and/or more rapid return to baseline following termination of the event, as these distinctions could reflect different causes of low CORT reactivity. In this regard, there is growing evidence of blunted anticipatory responding. Specifically, in a number of studies, DBD children or those at risk for DBD tend to exhibit low pretest CORT levels that do not change after exposure to a mild stressor, while non-risk children tend to show higher pretest CORT levels that actually decrease over the period of stressor exposure (Hardie et al., 2002; King, 1998; Moss, Vanyukov, & Martin, 1995; Moss, Vanyukov, Yao, & Kirillova, 1999; Pajer, Gardner, Rubin, Perel, & Neal, 2001). The challenge in interpreting these findings is that

in most cases the testing has been conducted early in the morning; thus it is not clear whether DBD children fail to exhibit an anticipatory response or simply have low early morning basal CORT levels. Clearly, these studies would have benefited from assessment of basal levels on non-test days (e.g., Klimes-Dougan et al., 2001).

There is also some evidence that DBD children show less of a CORT increase in response to mild stressors (e.g., Jansen et al., 1999; Moss et al., 1995; Targum, Clarckson, Magac-Harris, Marshall, & Skwerer, 1990; Snoek et al., 2002). The implications for these findings are not clear however for in most of the studies the non-risk group fails to elevate CORT to the stressor or actually shows decreasing CORT reactions over the stressor period (for an exception see Snoek et al., 2002). To adequately examine whether DBD children show a blunted CORT stress response, the paradigm should elevate CORT for the non-risk comparison children. Van Goozen and colleagues (1998) have employed such a paradigm that involves a frustration/provocation task during which a peer (on audiotape) denigrates the target child's performance. They reported that children with oppositional defiant disorder (ODD), and those comorbid with attention deficit disorder (ADD), showed decreased CORT in response to the provocation task, while non-risk children tended to show an increase. However, not all children with disruptive behavior problems exhibited blunted CORT reactivity; ODD children comorbid for anxiety problems actually exhibited the highest CORT reactivity. This study suggests that blunted CORT reactivity may only be seen for DBD children who are not comorbid for anxiety disorders, an interpretation also offered by McBurnett and colleagues (1991) and Snoek et al. (2004).

Finally, there is a paucity of research regarding CORT recovery following a stressor for children with externalizing problems. Van Goozen et al. (2000) found that although non-anxious DBD and non-risk children only tended to differ in CORT in the immediate post-stress period,

DBD children continued to show CORT decreases during a recovery period, ending up with significantly lower CORT levels than controls by the end of the testing period. Because the DBD children did not show an elevation in CORT to the task, it is unlikely that this reflects a difference in negative feedback regulation of the HPA axis, as in PTSD (Yehuda et al., 2001).

As there is some evidence of lower basal CORT and blunted CORT reactivity to frustration/provocation, this begs the question of whether these differences are meaningful. One way to address this question is whether they have implications for responsivity to treatment. In a recent follow up study, van del Wiel and colleagues (2004), examined the effectiveness of treatment for DBD children as a function of CORT baseline and reactivity using a 9 month treatment window and multifaceted (medication, individual, and family therapy) intervention. Although pretest or baseline differences were not predictive and CORT reactivity was similar with regard to symptom severity at the pretest assessment, boys with more elevated CORT levels following the frustration/provocation paradigm were significantly more responsive to therapeutic intervention than were those with low CORT stress responsivity. A related question is whether CORT reactivity also can be altered by therapeutic interventions in children at risk for externalizing problems. A recent prevention study on low-income preschoolers who experienced the familial risk factors for conduct disorder addressed this question. Using a randomized prevention trial, Miller and colleagues (Miller, Brotman, Gouley, Pine, & Rafferty, 2002) increased CORT reactions during a peer entry/interaction task among the children in the intervention group. As this intervention focused on social-cognitive processes, this pattern of results suggests that low CORT reactivity among children at risk for DBD, at least, may not reflect dysregulation of the HPA axis, as much as disturbances in psychological processes operating over cortico-limbic circuits that activate the HPA axis. However, this conclusion is

extremely tentative given that it is based on only one study that was conducted on a risk group, rather than children with DBD.

Summary of HPA Activity in Child Clinical Disorders

This brief review of research on HPA axis activity in children with clinical disorders and subclinical behavior problems yields evidence of associations between internalizing and externalizing symptoms and CORT levels in children and adolescents. It also lends supportive evidence, but not universally so, of associations between internalizing disorders and CORT hyperactivity, and externalizing disorders and CORT hypoactivity. The control provided in animal studies and the growing literature on correlational studies with children and adolescents has enabled us to draw speculative conclusions that social-environmental factors play a role in regulating CORT levels and activity, and hence may place a role in the emergence and course of clinical symptoms and disorders associated with dyregulated HPA axis activity.

Social and Nonsocial Contributions to HPA Axis Functioning: A Model

As illustrated by the above discussion of the literatures on externalizing and internalizing disorders, associations between psychopathology and HPA axis activity are not straightforward, and inconsistencies abound. One explanation for these inconsistencies is that the design and measurement of most studies of psychopathology and CORT do not take into account the multiple influences on current HPA axis functioning that exist, including influences of both a social and non-social nature. Figure 2 depicts some of the known influences on HPA axis activity in humans, as measured by salivary CORT levels. Some of these influences are ongoing at the time of CORT assessment, while some are historical factors that have previously affected the organization of the HPA axis. We do not have time to review each component of the model

in detail; the major point of Figure 2 is to illustrate the multiplicity of influences on current CORT levels and activity, and hence the complexity of the task of predicting it.

Historical influences are critical (Figure 2, Column 1). Recent research has suggested that prenatal stress exposure may play a role in the organization of the HPA axis and thus in CORT activity (Bertram & Hanson, 2002; Matthews, 2000; Wadhwa, Dunkel-Schetter, Chicz-DeMet, Porto & Sandman, 1996); early postnatal influences have also been shown to play a critical role, particularly in animal models, but also now in humans (Halligan et al., 2004). As noted in this review, one's prior history of stress exposure and of supportive relationships can modify current CORT activity (Essex et al., 2002; Pendry & Adam, 2005); although less studied, one's health and lifestyle history also likely plays a role in regulating current CORT activity.

Current influences on cortisol activity (Figure 2, Column 2) include mood and cognitive biases present at the moment or on the days of testing (Adam, 2005), exposure to recent negative life events (Adam et al., 2005), recent food, exercise, medication, nicotine or caffeine intake (Kirshbaum & Helhammer, 1989, 1994), and in the case of women, menstrual timing (Kirshbaum, Kudielka, Baab, Schommer, & Helhammer, 1994). A variety of other physiological systems are in constant interaction with the HPA axis, including the activity of sympathetic nervous system, immune and inflammatory systems, and other adrenal, gonadal, and ovarian hormones (Heinrichs, Baumgartner, Kirschbaum & Ehlert, 2003; Rosmond, 2005).

To complicate matters further, the effects of these multiple influences on HPA axis functioning may change with ontogeny. In addition to age- and pubertal stage-related changes in cortisol levels (Netherton et al., 2004, Stroud, Papandonatos, Williamson & Dahl, 2004), changes in other hormone systems (Cameron, 2004), and changes in the maturity and functioning

of neural systems that interact with the HPA (Dahl, 2004; Spear, 2000; Stroud, 2004, Young & Altemus, 2004) have the potential to modify how experience and HPA axis activity interrelate.

Basal cortisol levels and reactivity to stressors have been found to be modified by gender (Taylor, Klein, Lewis, Gruenewald, Gurung & Updegraff, 2000; Kudielka & Kirschbaum, 2004; Stroud, Salovey & Epel, 2002) and by temperament or personality characteristics (Gunnar et al, 2003; Nachmias et al., 1996; Kirschbaum, Bartussek, & Strasburger, 1992). Both behavioral genetic and molecular genetic studies have noted moderate to strong genetic contributions to aspects of basal CORT and also to CORT reactivity (Bartels, Van den Berg, Sluyter, Boomsma & de Geus, 2002; Wüst, Federenko, Hellhammer & Kirschbaum, 2000; Wüst et al., 2004 a, b), providing evidence for a partial genetic basis for preexisting HPA axis differences and differences in the reactivity and modifiability of the HPA with experience.

It is also important to note that the various influences identified in Figure 2 may have differential degrees of impact on different parameters of CORT measurement, such as average levels, diurnal slopes, and the size of the CORT response to awakening or reactivity to a lab stressor. For example, genetic predispositions may make a larger contribution to the size of the CORT response to awakening than to evening CORT levels (e.g. Wüst, Federenko, Hellhammer & Kirschbaum, 2000), social-environmental contributions may have a larger acute impact on evening CORT levels than they do on morning levels (e.g. Pendry & Adam, 2005), and a history of trauma or childhood chronic stress may be more likely reflected in a current flattening of the diurnal rhythm, rather than an overall elevation of levels (Gunnar & Vazquez, in press).

Rather than being discouraged by this complexity, our goal is to suggest that thorough measurement of each (or at least several) of these factors, in relation to multiple parameters of CORT functioning, should lead to better characterization and understanding of CORT activity,

which should in turn reveal stronger and more consistent associations between CORT, behavior or pathology. At the very least, it should make us more forgiving when only a proportion of the variation in cortisol levels is accounted for in any one study.

Also apparent in Figure 2 are many places in which *social variables* enter the model to influence both the developmental course, and current activity of the HPA axis (see the more darkly shaded boxes in the model). For example, social environments that influence the mothers' emotional wellbeing and the hormonal environment of the pregnancy may alter the organization of the fetal HPA axis (Avishai-Eliner, Brunson, Sandman, Baram, & 2002; Wadhwa, Dunkel-Schetter, Chicz-DeMet, Porto & Sandman, 1996; Wellberg & Seckle, 2001). In a sophisticated set of rodent experiments (Weaver et al., 2004), early maternal-pup interactions were shown to produce organizational effects on the structure and functioning of the offspring hippocampus, through permanent changes in the phosphorylation of a portion of the DNA responsible for glucocorticoid receptor development. The long term effects of early maternal depression (Halligan et al., 2004) and institutionalization (Gunnar et al., 2001) discussed previously suggest the possibility of similar early social influences on the organization of HPA axis functioning in humans.

Given the continuing plasticity and growth of the brain, however, it is likely that social experiences may continue to have organizational influences on the development of the HPA axis in early childhood, and even into the adolescent years. Examining the cumulative effects of one's lifelong history of social stress and support on HPA axis activity, health and functioning using longitudinal data on social, behavioral and physiological functioning, is a critical direction for future investigation. This need is beginning to be addressed by the incorporation of stress

biomarkers in large-scale longitudinal studies in which social influences on biomarkers will be studied from the prenatal period onward.

Another rich direction for future research involves the investigation of the impact of *macrosocial or macrosystemic* factors such as poverty, lack of opportunity and discrimination on stress physiology, with racial and SES differences in stress-exposure and stress-system activation hypothesized to partially account for group disparities in adult functioning and health (Flinn & England, 1997; Lupien, King, Meaney & McEwen, 2001; Sapolsky, 2004). Indeed, beyond its clear effects on socio-emotional functioning, the known impacts of CORT on cognition, memory, immune-system functioning and physical health suggest possible pathways by which stress may jeopardize one important pathway to prosperity: educational performance.

Implications of Social Influences on HPA axis Activity for Education

Research on the potential implications of individual differences in HPA axis activity for educational functioning are only just beginning to be examined, but represent a ripe area for future investigation. Existing research shows strong associations between experimental manipulations in CORT levels and cognition and memory processes in adults (Lupien, Gillin, Hauger, 1999; Lupien & McEwen, 1997; Wolf, Schommer, Helhammer, McEwen, & Kirschbaum, 2001). Associations between CORT levels and cognitive and memory functioning are thought to follow a reverse U-shaped curve, with too low and/or too high levels associated with impaired performance (note the similarity to CORT associations with emotional and physical health -- in all cases, moderate, and effectively regulated levels of this hormone are considered advantageous). More recently some work on cortisol and memory in children has suggested that negative effects of elevated cortisol on memory are also present in preschool age children (Heffelfinger & Newcomer, 2001; Lupien & McEwen, 1997).

In addition to direct effects on cognitive functioning, individual differences in HPA axis functioning may have the potential to disrupt achievement through several indirect pathways. CORT levels may influence the ability to fall asleep and sleep quality (Gillin, Jacobs, Fram, & Snyder, 1972). Decrements in number of hours of sleep have been shown to have strong effects on educational performance in middle-school children (Sadeh, Gruber, & Raviv, 2003). In adults, high levels of cortisol during sleep have been shown to impair declarative memory consolidation processes that typically occur during slow wave sleep (Born & Wagner, 2004).

Another indirect pathway by which HPA axis activity may influence educational performance is through its effects on physical and mental health. It seems likely that increased absenteeism associated with the presence of physical health problems, and absenteeism and social problems associated with the presence of depression and anxiety may contribute to and interact with poor cognitive, attentional and memory processing to cause additional impairments in educational functioning. Problems in classroom functioning and educational performance may then feed back to cause additional strain and cortisol elevations, as failure experiences (at least in adults) have been shown to be important activators of the HPA axis, particularly among individuals with low self-esteem (Pruessner, Hellhammer & Kirscbaum, 1999).

Due to the relative lack of research in this area on children, much of our discussion on the potential educational implications of increased cortisol has been based on extensions of experimental animal work and research with adult humans in laboratory settings. What do we know of how CORT levels relate to educational functioning in naturalistic academic settings? Initial findings by Adam and Snell (2005) show that CORT levels are typically lower when adolescents are productively engaged in academic activities than when they are engaged in non-academic tasks (controlling for the effects of time of day and of being alone on CORT levels).

Whether low CORT levels facilitate attention, focus and achievement, or whether positive engagement in academic activities lowers CORT levels remains unclear from these correlational data; experimental research on CORT, attention, and performance in school age children and adolescents is required to further explore these associations.

Another important implication for education emerges from Gunnar and colleagues' findings (Gunnar & Donzella, 2001) that individual differences in the quality of day care settings are important in determining the extent to which children will display increased HPA activation in these environments. Whether this in turn relates to the degree of intellectual and social benefits children obtain from their day care settings remains to be examined, and whether the quality of elementary school, middle-school and high-school classroom environments also influence CORT levels is another important direction for future research. Child attentional processes and readiness to learn upon entering the first grade are important determinant of later success in school (Alexander, Entwisle & Dauber, 1993; Duncan et al., 2005; McClelland, Morrison & Holmes, 2000). If elevated adrenocortical activity due to low quality child care or learning environments does contribute to impairments in attention and social functioning in the classroom, this would provide another important reason why the quality of these environments needs to be closely regulated, both in terms of the intellectual stimulation they offer and the quality of socioemotional environment they provide.

In general, research on social influences on the HPA axis leads us to conclude what should already be obvious – that providing children with supportive social environments that promote positive emotion and feelings of safety and security is good for children and their development -- and that adverse social environments can cause wounds that cut far beneath the skin, influencing children's mental and physical wellbeing and their cognitive potential.

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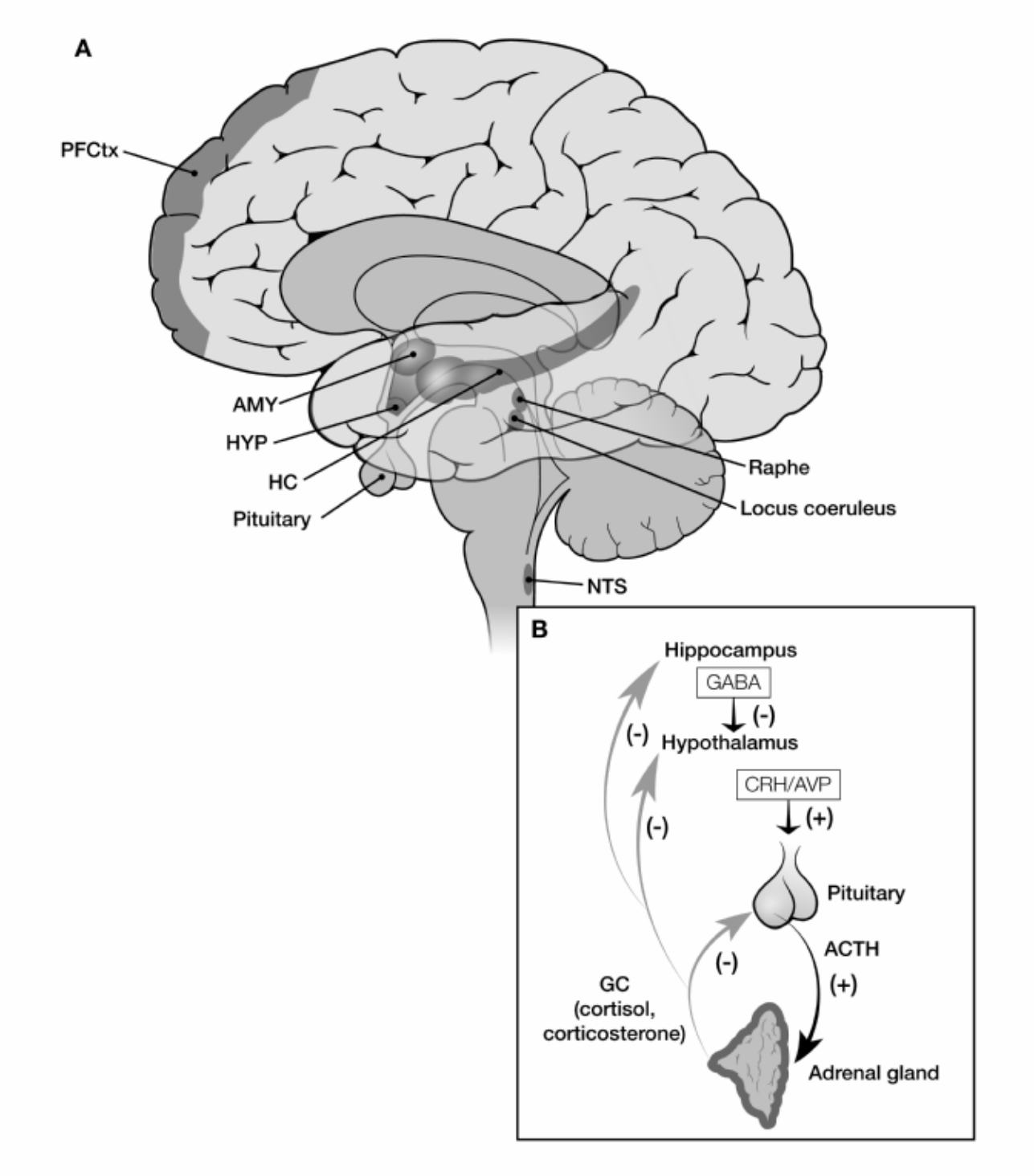
Figure Captions

Figure 1. The Limbic Hypothalamic Adrenal Pituitary Axis.

Figure 2. Historical and current influences on HPA axis functioning as indexed by salivary cortisol levels, highlighting the role of social factors.


A
PFCtx
AMY
HYP
HC
Pituitary
Raphe
Locus coeruleus
NTS
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GABA
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CRH/AVP
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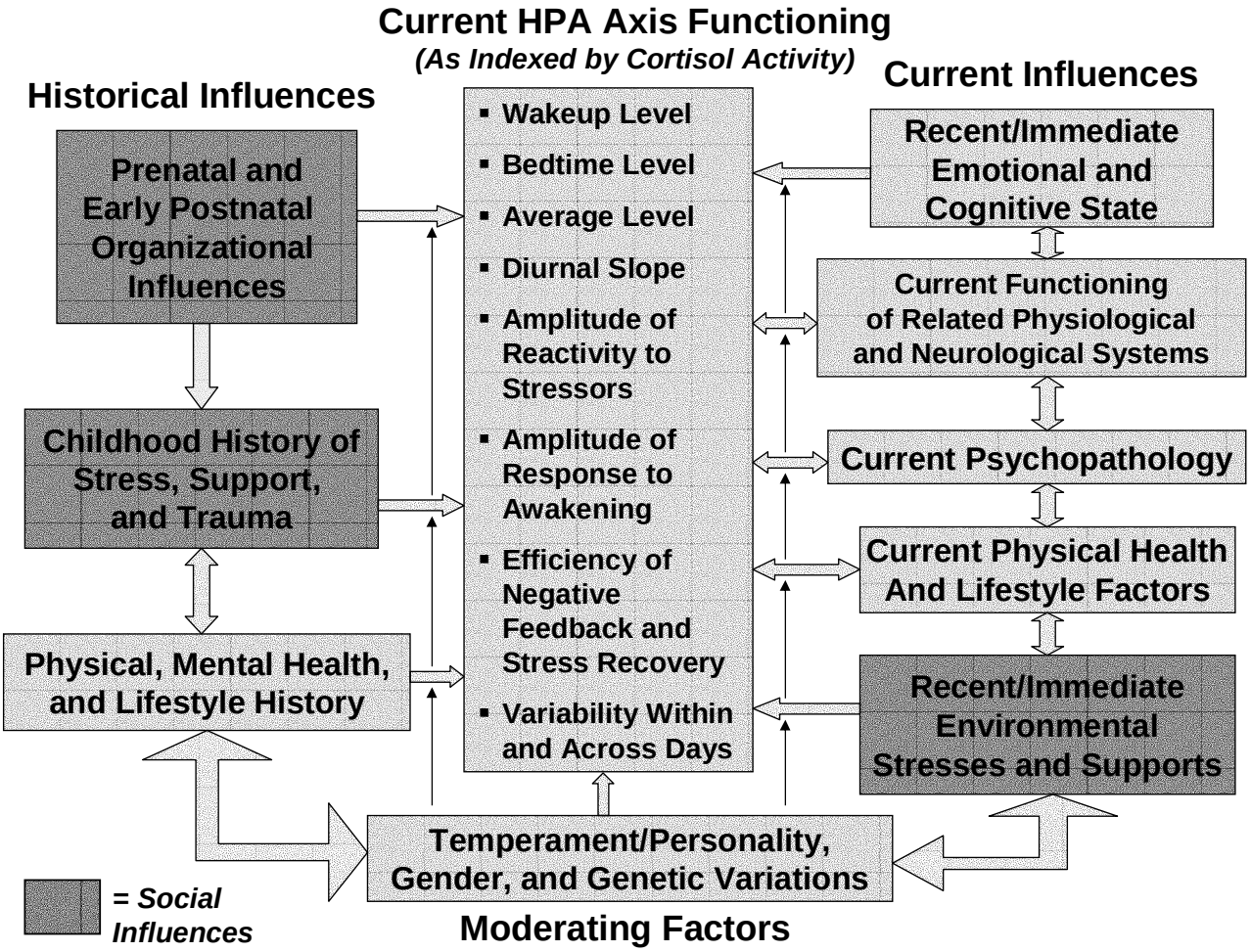
Pituitary
ACTH
(-)
(+)
GC
(cortisol,
corticosterone)
Adrenal gland


Current HPA Axis Functioning
(As Indexed by Cortisol Activity)
Historical Influences
Current Influences
Prenatal and Early Postnatal Organizational Influences
Childhood History of Stress, Support, and Trauma
Physical, Mental Health, and Lifestyle History
Wakeup Level
Bedtime Level
Average Level
Diurnal Slope
Amplitude of Reactivity to Stressors
Amplitude of Response to Awakening
Efficiency of Negative Feedback and Stress Recovery
Variability Within and Across Days
Recent/Immediate Emotional and Cognitive State
Current Functioning of Related Physiological and Neurological Systems
Current Psychopathology
Current Physical Health And Lifestyle Factors
Recent/Immediate Environmental Stresses and Supports
Temperament/Personality, Gender, and Genetic Variations
= Social Influences
Moderating Factors