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PSYCHOLOGICAL AND STRESS HORMONE CORRELATES IN EARLY LIFE: A KEY TO HPA-AXIS DYSREULATION AND NORMALIZATION

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Abstract

Substantial recent research has focused on examining hormone indicators of psychosocial stress and on how relationships between stress and hormone changes might be linked to chronic illness. Particular attention has been paid to disease progression in cancer and HIV/AIDS. This focus has generated a plethora of research which has contributed both theoretically and clinically to the understanding of disease experience and the rate of disease progression. Measurement of salivary cortisol levels and diurnal variation has substantially advanced research methodology. Applying the unifying concept of allostasis and accumulated lifetime stress, this review attempts to assess the relevance of psychological and stress hormone correlates to disease resistance and health, through an examination of such correlates on the experience and outcomes of stress during childhood. Focus is on the role and importance of naturalistic social stress experiences such as school transition in healthy children, with emphasis on salivary cortisol as an endocrine marker of HPA-axis activation. It is argued that differing research perspectives offer valuable insight into the often assumed but largely unexplored links between early life experience and subsequent physical health outcomes in adulthood. Longitudinal studies incorporating measures of acute physical health outcome and of learning and memory are clearly needed.

PSYCHOLOGICAL AND STRESS HORMONE CORRELATES IN EARLY LIFE: A KEY TO HPA-AXIS DYSREULATION AND NORMALIZATION?

Some of the most notable research in psychoneuroimmunology over the last decade and a half has been focused on the role of hormonal indicators of psychosocial stress and their link with chronic illness. There has been a focus on how relationships between stress and hormone changes might be linked to chronic illness such as cancer and HIV/AIDS (for reviews see Balbin et al, 1999; Garssen & Goodkin, 1999; Turner-Cobb, 2002). Furthermore, recent research has seen an increasing interest in the role of early life experience as applied to psychobiological and health consequences (e.g. Coe & Lubach, 2003; Gunnar & Donzella, 2002; Gunnar & Vasquez, 2001). In this review article an attempt is made to assess the relevance of psychological and stress hormone correlates to disease resistance and health through an examination of such correlates on the experience and outcomes of stress in childhood. Evidence is presented which aims to draw together lines of research from different perspectives which support the notion that early life experiences and individual differences can impact HPA-axis responding to influence health outcomes in later life. Measurement of salivary cortisol levels and diurnal variation has substantially advanced research methodology across both areas of research. The concept of allostasis and accumulated lifetime stress is used to draw together the relevance of psychological and stress hormone correlates to disease resistance and health with such correlates in the experience and outcomes of stress during childhood. Focus is on the role and importance of naturalistic social stress experiences such as school transition in healthy children, with emphasis on salivary cortisol as an endocrine marker of HPA-axis activation. It is argued that differing research perspectives offer valuable insight into the often assumed but largely unexplored links between early life experience and subsequent physical health outcomes in adulthood. Furthermore, subtle differences in healthy children experiencing normal life transitions can provide theoretical evidence of neuroendocrine changes and the opportunity for intervention both pre and post puberty. It is concluded that longitudinal studies incorporating measures of acute physical health outcome such as upper respiratory infection and of learning and memory as transitory markers are called for, in addition to more long term measures of health symptomatology.

Cortisol in Chronic Illness

At one extreme of chronic illness, attention has been paid to disease severity and progression in cancer and HIV/AIDS. A full review of this literature is not intended here as it is covered extensively elsewhere (for a fuller review refer to Turner-Cobb, 2002). Of particular importance in this research has been the elevation in levels of the hormone cortisol, the end product of the hypothalamic-pituitary-adrenal (HPA) axis, measured in saliva, as a reliable indicator of increased physiological stress arousal (Kirschbaum & Hellhammer, 1989). Cortisol is linked to suppression of some parts of the immune response and an overall dysregulation of immune function (Kirschbaum & Hellhammer, 1989; Kirschbaum & Hellhammer, 1994). It is worth noting that as mentioned later in the review the relationship between stress, cortisol and immune function is not always linear and evidence for upregulation of immune function has been demonstrated under acute stress (Dhabar & Mcewen, 1997). Under normal conditions cortisol reveals a circadian rhythm with a diurnal decline from awakening to evening levels (Smyth et al., 1997) from approximately three months of age (Gunnar, 2002).

Amongst the most well documented research involving psychosocial effects on chronic illness is that of Spiegel and colleagues (Spiegel et al, 1989) which reported a survival effect of 18 months for women with metastatic breast cancer who attended group therapy compared that a wait list control. Subsequent studies of women with metastatic breast cancer by this research group have pointed to the role of social support in influencing cortisol (Turner-Cobb et al, 2000), to baseline diurnal cortisol decline as an indicator of subsequent survival time (Sephton et al, 2000) and to flatter diurnal cortisol rhythms in patients compared to healthy controls (Abercrombie et al., 2004). Following this landmark study, replication trials continue yet so far have failed to find a survival prolonging effect for group therapy (Llewelyn et al., 1999), however, supportive-expressive group therapy has since been further associated with an improvement in mood and reduction in pain, especially in those with greater distress at baseline (Goodwin et al., 2001). Similarly, in the area of HIV/AIDS, more severe life event stress and lack of social support have been linked to higher cortisol levels and greater disease progression (Leserman et al., 2000; Leserman et al., 2002).

The focus of the chronic illness literature has been on health outcomes in adults. Studies have implicated a number of psychological correlates including life event stress, both current and prior, although in the majority of studies these assessments only extend to a limited period of time such as one or two years prior to the health outcome under investigation. The study by Evans et al (Evans et al., 1997) is exceptional in this respect, assessing life events at six month intervals over a period of up to four years. Depending on the age of the sample under investigation, there are obvious reliability issues when assessing life stress retrospectively over a period of many years. Yet, incorporating more of a lifespan approach by measuring accumulated lifetime stress encapsulates the essence of explanatory theories such as that of allostasis by enabling an assessment of allostatic load (McEwen, 1998; Sterling & Eyer, 1988) as discussed later in this review.

Cortisol Responses and Early Life Experience

Activation of the stress response system in early childhood, most notably the part of this bimodal interactive system known as the hypothalamic-pituitary-adrenal (HPA)–axis (cf sympathetic adrenomedullary system SAM), has been linked to a range of psychological factors and physiological alterations during childhood and adolescence. For example, the importance of maternal attachment is one of the earliest areas of interest within the field of developmental psychology and one that has yielded a vast amount of research. More recent work has linked the importance of maternal attachment in animals and in child studies with neuroimmunological consequences and examined critical periods in relation to health (for recent review see (Coe & Lubach, 2003). Similarly, the negative mental and physical health outcomes of 'risky' family environments, characterized by social conflict and aggression have also been recently reviewed and a detailed explanatory model put forward in the literature (Repetti, 2002). Episodes of human maternal separation under experimental conditions in healthy nine month old children has been found to elicit HPA-axis activation (Gunnar et al, 1992). These infants demonstrated raised salivary cortisol levels in the presence of an unfamiliar sitter who responded only when the infant fussed or cried. This physiological effect resulting from the social challenge of separation was reduced to a level similar to the no separation condition when the sitter offered a nurturing and stimulating environment, demonstrates the importance of a positive social environment for neuroendocrine adjustment. It is worth noting that this type of HPA axis activation reflects a predictable and normal transient raise in cortisol with no resulting dysfunction. If repeated or continued over time in a chronic fashion however, a state of dysfunction could plausibly emerge. Parental loss during childhood (at an average age of 12 years) has also been linked to higher diurnal cortisol levels in adult men, demonstrating the long term neuroendocrine effects of early experience (Nicolson, 2004).

In terms of psychopathological development, a number of different patterns of alteration in cortisol levels and diurnal regulation have been observed. A number of studies have cross sectionally examined the influence of early life trauma covering a range of maltreatment in children. Cichetti & Rogosch (2001) report a variety of morning cortisol levels in children, varying with type and severity of maltreatment. The most severely maltreated children revealing significant elevations in morning cortisol levels sampled at 9am. The majority of recent research in children with PTSD symptoms, following trauma such as separation and loss, has focused on developmental psychopathology, with only a limited number of studies including physiological stress response measures. A study by Carrion et al (2002) reports HPA-axis alteration in a group of children with PTSD symptoms, as evidenced by a significantly raised salivary cortisol profile on late afternoon/evening measures (pre dinner and pre bed samples) compared to controls. Within the PTSD group, girls also showed significantly higher prebed cortisol levels than the boys (Carrion et al, 2002). Similarly, this pattern in cortisol elevation has also been seen in 6-12 year old adopted children who spent at least the first eight months of life reared in Romanian orphanages (Gunnar et al, 2001). In a study by King et al (2001) in girls aged 5-7 years old who had experienced sexual abuse in the previous two months, lower morning cortisol levels were found compared to controls under experimental conditions (King et al, 2001). Some work suggests that responses within maltreated children may differ depending on state of affective functioning (Hart et al, 1996). Thus the literature is somewhat ambiguous concerning cortisol levels and diurnal patterns in maltreated children although a disruption or dysregulation of the system is consistently reported. Whilst hypocortisolism predominates in adults with PTSD (e.g. for review see Yehuda et al, 2002) the children's literature represents an even greater puzzle. Indeed, as Gunnar and Vazquez (2001) point out, the concept of hypocortisolism, suppression of HPA-axis resulting in low cortisol levels may manifest itself during childhood itself rather than being a delayed effect in adulthood (Gunnar & Vazquez, 2001). However, as outlined above, hypercortisolism may precede adult neuroendocrine dysfunction. Only longitudinal studies of sufficient longevity could reveal any such neuroendocrine transition. Differences detected in the direction of cortisol appear to reflect the nature of the maltreatment, psychological diagnosis and timing of both maltreatment and assessments following the experience. A compelling study from the adult literature (Resnick et al, 1995) illustrates what may be happening across the child-adult neuroendocrine transition. In this study of the effect of rape on cortisol levels, women who had not experienced an assault previously, revealed raised plasma cortisol levels but those with a history of assault had lower cortisol levels (Resnick et al., 1995).

Another focus within this research area has encompassed the notion of intergenerational stress transmission, for example by investigating adult children of Holocaust survivors with post traumatic stress disorder (PTSD) (Yehuda et al, 2001). Results revealed a lower mean 24-hour cortisol level in those who had experienced emotional abuse as a child, compared to controls (Yehuda et al., 2001). Other studies have reported have reported subsequently altered cortisol levels in adult survivors of child sexual abuse (Newport et al, 2004). The notion of an intergenerational cycle of abuse is further developed by the psychobiological model of developmental traumatology put forward by De Bellis (2001). Such findings are similar to those found in animal models of maltreatment (Mar Sanchez, 2001). Furthermore, it is worth pointing to the literature on heritability of cortisol, both genetic, estimated at 60% for cortisol measured at 45 minutes post awakening in a sample of 162 twin pairs at 12 years of age (Bartels et al, 2003) and social via socioeconomic status (SES) (Lupien et al, 2001). Data supporting this latter relationship comes from a later study which examined a group of 6-16 year olds and found morning cortisol levels to be significantly higher in children with low SES status but only for those children aged up to 10 years, a finding which appears linked to mothers' level of depressive symptoms (Lupien et al, 2000). Hence there are known psychosocial factors which can influence disease progression and outcome and traumatic experiences early in life have been linked to physiological alteration in childhood and in adulthood.

Children of clinically depressed mothers have also revealed altered patterns of cortisol production. Using an experimental paradigm, Ashman et al (Ashman et al, 2002) reported an indirect relationship between maternal depression during the first two years of childhood and elevated cortisol responses to a laboratory stressor (fear-potentiated startle procedure) in seven year old children. Elevated levels of cortisol were observed only with children who had scored at a clinically significant level for internalizing symptoms (Ashman et al., 2002). A recent study compliments this finding, reporting significantly higher morning cortisol levels and greater variability compared to those not exposed to post natal depression, in a sample of 13-year–old adolescents (Halligan et al, 2004). One of the main issues obscuring this area is that of disentangling the impact of duration of exposure to maternal depression versus sensitization at an early and crucial age.

Cortisol Disruption in the Social Context of Preschool

Thus the influence of early social experience on development was examined in the literature initially from a parenting perspective and focused mainly on specific groups of children deprived of healthy contact or healthy children under experimental conditions. This begs the question of what is known about HPA-axis activation in healthy children under naturalistic conditions. Later research focusing on the role of social interaction beyond the family, to encompass social relationships of peers and group interaction in naturalistic day care settings has yielded some notable findings. In keeping with increasing exposure of preschool age children to various forms of childcare outside of the home, due to changes in maternal occupational patterns, more recent research has examined the nature of the childcare experience and differential outcomes of varying levels of care quality. Both naturalistic and experimental research has studied the interplay between social experience and temperament within this context. The influence of social experience on physiological stress hormones involved in the stress response systems has enabled this research to offer substantial insights into the effects of changing social and family environments on health related responses. Evidence is accumulating which suggests that children certain emotional temperaments are more likely to show elevations in cortisol in poorer quality childcare setting (Crockenberg, 2003; Dettling et al, 2000; Gunnar & Donzella, 2002). Preschool classroom observation studies have revealed a significant association between social isolation and cortisol levels in four-year old preschool children (Sanchez-Martin et al., 2001). The directional relationship with cortisol was dependent on the meaning of the isolation behaviour for the child. Those retreating to social isolation due to anxiety and inadequate social interaction skills revealed high cortisol levels whereas those engaging in social isolation as a result of avoidance of the stressful social behaviour revealed lower cortisol responses (Sanchez-Martin et al., 2001). The exact nature of these temperamental responses in conjunction with environmental conditions both at school and at home remains to be addressed. Furthermore, it is necessary to consider the relative importance of multifactorial effects and whether these effects may be bi-directional rather than simply causal. In other words, can the experience of childcare received shape the stress response system itself and if this is so can a normalisaton of the stress response system be engineered through appropriate in interventions

The stress hormone cortisol has also been the hormone of preference in examining altered patterns of activation in children. As stated earlier, under normal conditions cortisol reveals a decline from awakening to evening levels by approximately three months of age (Gunnar & Donzella, 2002). Before exploring the diurnal cortisol literature in relation to children, it seems pertinent to highlight an important development within the adult literature on cortisol, that of the awakening response (ie peak in cortisol approximately 30 mintes after awakening). Particularly in studies of healthy individuals, the effects of a number of factors including awakening time, health status and psychosocial factors have been examined in relation to the awakening cortisol response (Edwards et al, 2001; Evans et al, 2004; Frederenko et al., 2003; Kudielka & Kirschbaum, 2003). As Evans et al (2004) point out, whilst an important role for the awakening response as a diurnal regulator of cortisol and related immune functions, the specific direction of effects, particularly in terms of psychosocial sequalae are not yet known. Interestingly, however, there are some initial findings implicating larger cortisol awakening responses to more symptoms of upper respiratory infection (Edwards et al, 2003). There appears to be an absence of research, however, on this awakening cortisol response in children. Whilst the author can find no published research studies examining the awakening response exclusively in children, some researchers have included a subgroup of children within their population sample but findings have been at best inconclusive in this respect (e.g. (Feder et al., 2004).

Returning to diurnal, cortisol responses, disruption of the normal pattern and an elevation in afternoon cortisol levels have been observed in children attending full day preschool, particularly for those whose social skills are less developed (Dettling et al, 1999; Watamura et al, 2003). In an assessment of cortisol reactivity in response to starting preschool, Gunnar and colleagues (1997) argue that it is not the reactivity per se but its flexibility that is important when viewed as a dynamic process with the interaction of ‘individual’ and ‘contextual’ differences. Thus although they report that children with an outgoing temperament and a high level of social competence exhibited high cortisol reactivity to the initial preschool experience, these children revealed a low reactivity one term later at follow-up (Gunnar et al., 1997). Hence it is the adaptability rather than initial reactivity that appears to be the important defining factor for longer-term outcome. A contrary pattern of initial lower cortisol in shy/anxious children and higher cortisol observed in children exhibiting assertive/externalising behaviour at the beginning preschool has also been linked to the school environment with opposite effects been found on ‘at home’ days (de Haan et al, 1998). However, studies with such contrary findings have taken mid morning measures of cortisol. Use of diurnal or awakening measures of cortisol may have reflected a more accurate and stable measure of overall physiological stress reactivity (Pruessner, 1997; Wust et al., 2000). Evidence for both direct and indirect pathways between temperament and cortisol activity, the indirect relationship involving aggression and peer rejection, has most recently been provided (Gunnar, 2003). Furthermore, a study by Zimmerman and Stansbury (2004) using an experimental stranger-approach scenario in three-year old children report a rise in cortisol in both shy and bold children although the level of response was predicted by degree of shyness, and that this response attenuated in the majority of children after the stressor had terminated. They argue that it is not neuroendocrine activation per se that may present a problem in shy children by the repeated triggering of the stress response given that shy children are more likely to perceive threat to a greater number of everyday events in their environment (Zimmermann & Stansbury, 2004). This supports the notion of context-specific HPA-axis activation during early life experiences (Watamura et al., 2003).

Although beyond the scope of this review, the health issues raised by preschool/nursery care are not likely to diminish but rather to become increasingly urgent, given changes in family structure and women's occupational roles which necessitate an increased need for alternative forms of childcare. Indeed, research from my own laboratory has found maternal occupational factors such as maternal satisfaction with work and level of emotional exhaustion to have interactive effects with the daycare experience in influencing cortisol levels in children (Turner-Cobb et al (unpublished), as well as having effects on cortisol in the mothers themselves (Chryssanthopoulou et al, unpublished). Factors relating to maternal stress including home/work balance and the possible neuroendocrine effects of maternal stress exposure during the first year of life in subsequently sensitizing children to increased stress exposure at age 4.5 years old have also been reported (e.g. Adam & Gunnar, 2001; Essex, 2002). The implications of this developing field of research are enormous, with applications extending to include the effect of social experience on learning and on health outcomes. This is particularly so for the study of social transitions experienced by children, exemplified by compulsory movement through the school system. The structure of the education system within western countries means that children are placed in social groups in relatively competitive environments. There are natural transition stages which require significant adaptation, both at a social level and the accompanying physiological level. As Gunnar and colleagues pointed out over a decade ago (Gunnar et al., 1992), neuroendocrine responses in older children are likely to follow similar patterns to those found in infants to maternal separation but for different age related stressors such as academic examinations. A neuroendocrine perspective on coping provides a potentially fruitful line of research therefore, highly relevant to educational systems such as the UK where academic assessment has substantially increased over recent years. An interesting and thought provoking study by Schreier & Evans (Schreier & Evans, 2003) presents an argument for a differentiation between modern stressors (e.g.'a close family member has had a serious medical problem … and was in hospital' or 'our family has had serious financial problems') and ancient stressors (e.g. 'a parent, brother or sister died' or 'sometimes our family had little food to eat ') in terms of their perceived stressfulness at a physiological level. Using overnight urinary cortisol as a measure of stress reactivity, they report that greater exposure to modern stressors to be related to greater HPA-axis activity in a group of eight to ten year old healthy children (Schreier & Evans, 2003). From this perspective, school transition related stress could be viewed as a collection of modern stressors which require significant adaptation.

Allostasis as the Underlying Concept Linking Stress and Health

One underlying concept which provides a unifying theoretical explanation linking psychosocial stress responses to outcome across the lifespan is that of “allostasis” and associated “allostatic load,” the collective somatic burden or accumulated lifetime stress associated with repeated stress responses (McEwen, 1998; McEwen & Stellar, 1993; McEwen & Wingfield, 2003; Sterling & Eyer, 1988). Whilst this perspective has been increasingly applied to adult research (Seeman et al, 2002) there is a comparative lack of research investigating developmental aspects in physiological stress response systems. The importance of such research is demonstrated by the adverse health consequences that can subsequently ensue from chronic overactivity of stress response systems (McEwen, 1997). In reference to cumulative stress experience, a recent study highlights the importance of positive social experiences in lowering allostatic load in various ages within the adult population (Seeman et al., 2002). Indeed the positive influence of supportive relationships is well documented across all age groups, including children (for example, (Dubow, 1989, 1991; House et al, 1988; Uchino et al, 1996). Other examples of allostatic factors include noise and crowding, both of which have been linked to higher cortisol levels in children (Haines et al, 2001; Johnston-Brookes et al, 1998).

Physiological Responsivity in School Transition

The process of transitioning into school can be viewed as a novel and potentially stressful social experience for children, to the degree of increasing stress hormone levels and suppressing immunity (Boyce et al., 1995). Life transitions such as those experienced in relation to schooling, therefore, provide a unique window on the HPA-axis under naturalistic stress conditions in healthy children, particularly given that ability to adapt appears to be a central component for health outcomes as evidenced by the work of Gunnar and colleagues (1997; 2002; & 2003). Such stress is generated predominantly by the necessity for social engagement with peers and social competence within the school environment. Adjustment in response to this life transition is clearly dependent on a number of factors including child temperament and social competence, as well as prior experience of social interaction gained through preschool facilities.

These school transition conditions provide a unique opportunity to examine the effects of a potentially stressful naturalistic situation on stress reactivity responses and associated outcomes relating to learning and to health. Furthermore, high levels of cortisol secreted over a prolonged period of time have also been associated with damage to the hippocampal area of the brain, resulting in further excessive cortisol secretion (Sapolsky et al, 1986). Reduced cognitive capacities such as impairments in memory and spatial thinking have been reported in response to elevated cortisol levels in adults (McEwen, 1997). Yet in acute stress under experimental conditions, rather than long term cumulative stress, the effects are less clear for healthy individuals. Experimental studies in the elderly and in young adults reveal a modulatory rather than a 'unidirectional' effect of hormones such as cortisol on learning and memory (Lupien et al., 1999; Lupien et al., 2002). Using pharmacological manipulation in young adults (mean age 23.1 years), Lupien et al (2002) reduced morning cortisol levels by the addition of metyrapone, resulting in impairments in delayed memory, reduction in cortisol preventing recall of learning information. In contrast, a second study run in conjunction (Lupien et al., 2002) revealed that hydrocortisone given during the trough in afternoon cortsiol resulted in a positive effect on cognitive ability, by improving response times on word recognition tasks. A recent study by Quas and colleagues (2004) reports that at two-week follow-up, physiological reactivity in children aged approximately 4-7 years old (mean age 5.25 years) induced via a standardized laboratory protocol had differential effects between cortisol and autonomic reactivity. Whilst cortisol reactivity was associated with poorer memory, autonomic reactivity conferred risk only under non-supportive environmental situations, which in this scenario, was that of a nonsupportive interviewer. Thus the psychophysiological effects of school transition needs further exploration to reveal possible links with learning and memory.

However, despite this, only a comparatively small amount of research has been conducted on the developmental physiological alterations brought about by the potential social challenge of transitioning into school and the impact of the adaptation required. One study by Smider et al (2002) assessed late afternoon/early evening salivary cortisol levels in a group of 4.5 year olds prior to starting Kindergarten, as a predictive tool of subsequent socioemotional adjustment. The strength of the reactivity argument is provided by the finding that cortisol levels predicted behavioural adjustment, in the form of internalizing/externalizing behaviors, to the experience of Kindergarten measured 18 months later (Smider et al, 2002). In a recent study of cortisol response across the day during the first five days of a new school year, 6-7 year old children exhibited a greater rate of change in cortisol (higher morning levels and lower evening levels) on the day of school when compared with weekend days (Bruce, Davis, & Gunnar, 2002). Interestingly, for those children who scored high on Surgency, this greater rate of change was still evident on the fifth day of school (Bruce et al., 2002). As the authors point out, there are inconsistencies in the direction of the relationships linking cortisol and temperament between this study and some previous research (Davis et al, 1999) in which midday and evening cortisol measures were obtained. Yet both studies found that more exuberant, surgent children exhibited the larger cortisol responses to the new school year on the fifth day of the first week, albeit in different directions for the evening cortisol measure (Bruce et al, 2002). A more detailed examination of temperament effects with tighter methodological sampling of cortisol with respect to diurnal variation, including details of potential confounding factors would yield more consistent findings. Results from experimental studies with children of school age also provide evidence for individual differences in cortisol responses between seven year olds who perceive themselves as socially competent compared to those with rate lower on self competence (Schmidt et al., 1999). The authors argue that self competence in novel/social situations reflects both ability to regulate emotion and elicits less fear of approaching such situations, further increasing levels of self competency (Schmidt et al., 1999). It is worth noting that parental expectations of the transition experience, as related to the parents assessment of their child's ability to cope with the transition from preschool to kindergarten, also appear to have an influence on morning cortisol levels (Quas, 2002). As noted, the majority of this preschool and school transition research to date has been conducted in the United States (US). One important difference in educational practice between the UK and the US is that progression to the entry class of mainstream school (i.e. reception, the UK kindergarten equivalent) is on average one and half years earlier. This means that children in the UK experience this transition 18 months prior to US children and as such may have less prior social experience to bring to the school situation. These cultural differences may yield insight into the psychophysiological stress process through which children are required to experience, the effects of which may be highlighted by variation in age. There is a paucity of research, however, assessing the link between the potential stressor of school entry and subsequent health outcome in children. Such a longitudinal study is currently being conducted in our laboratory, investigating both health and learning outcomes in children starting school at four years of age. Similarly, transition to senior school at age 11 is an important stage at which to examine psychophysiological responses and their consequences for health and learning. Whilst these transitions have been explored by educationalists and developmental psychologists resulting in numerous intervention programs to facilitate the transition process, associated psychobiological adaptations required have largely been ignored. At the transition to senior school stage, this offers a particular challenge and opportunity to psychoneuroimmunological research, given the paralleled transition to puberty occurring at this time. Such pubertal changes appear to be particularly relevant to levels of cortisol and dehydroepiandrosterone (DHEA), at different pubertal stages, in relation to health outcomes (Goodyer et al, 2001; Netherton et al, 2004; Tornhage, 2002).

This review began with a brief summary of the influence of psychological factors in chronic illnesses such as cancer and HIV/AIDS, pointing out that despite the wealth of research generated in this area, influences on the setting of the HPA-axis responsivity during childhood and subsequent health effects into adulthood are poorly understood. A separate body of research exists examining the influence of psychosocial factors on less serious illnesses, namely on acute infection, examining the incidence of the common cold or upper respiratory infections (URI's). Such studies, of both an experimental (for example, Cohen et al, 1991; 1995) and naturalistic nature (for example, (Boyce et al., 1995; Cohen et al., 2002; Evans & Edgerton, 1991; Graham et al, 1986; Meyer & Haggerty, 1962; Turner Cobb & Steptoe, 1996; Turner Cobb & Steptoe, 1998) have linked higher levels of stress with increased susceptibility to the common cold in adults and in children. These findings also implicate various psychosocial mediating resources, such as coping responses and moderating effects such as social support and health related behaviours. As mentioned above, there is very little research to date that has incorporated acute physical health outcomes as measures of ability to deal with naturalistic psychophysiological challenge such as that encapsulated by school transition. One recent study is notable in this respect (Ball et al, 2002). This study evaluated susceptibility to the common cold across a longitudinal time period of the first 13 years of life. They report that children who attended large scale day care centers, although observed to have a higher incidence of the common cold at age two years, revealed a subsequent protection from the common cold, reporting fewer incidences at ages 6, 8, and 11 years (Ball et al., 2002). However, this study assessed URI's at specific ages rather than URI incidence from the perspective of the novel stressor of transitioning to school. Furthermore, it did not assess in conjunction with the social experience and temperament of the children or with mediating hormonal responses to such a situation. Measurement of the occurrence of the common cold is a simple and non-intrusive way of assessing immune impact of stressful events compared to direct measurement of immune responsiveness as has been conducted in other studies (Boyce et al., 1995).

Current Status and Relative Importance of Cortisol Research

One important consideration in the research outlined so far is the assessment of physiological activation. In the studies detailed above, the overarching assessment of choice is that of cortisol, in saliva, as the end product of the HPA-axis and a measure of HPA-axis alteration, as already detailed. Whilst not all the studies cited here sampled saliva for cortisol detection, some assessing cortisol in urine or plasma, the overwhelming majority chose salivary assessment, either through use of a cotton swab or ‘dribble’ samples collected in sterile pots. There have been many excellent reviews written on this subject and only a brief summary of the most relevant points in relation to longitudinal effects of cortisol and health is afforded here. For more detailed reviews on this specific topic, readers are encouraged to refer to (Biondi & Picardi, 1999; Granger & Kivlighan, 2003; Kirschbaum & Hellhammer, 1989). Of particular note is the ease of sampling using salivary assessments in children, the ability for home assessments under parental supervision and the potential for repeated sampling protocols. The use of research using salivary cortisol sampling has advanced at an exponential rate over the last decade and a half, an effect mirroring that of growth in the previous decade (Kirschbaum & Hellhammer, 1989). Yet what is the state of art for cortisol assessment in children as empirical findings move the literature forwards in the early years of the new millennium? Secondly, what do the alterations in cortisol levels, diurnal change and laboratory reactivity mean in terms of health outcomes? As Granger & Kivlighan (2003) point out, the state of current psychosocial research examining cortisol in children has focused on linear relationships, often ignoring potential non-linear comparisions. The authors call for a focus of attention towards the use of non-linear analytical techniques which more accurately explore the pattern of hormone secretion in response to multiple interacting influences.

With these caveats in mind, the use of cortisol as a physiological marker of reactivity to psychosocial stress has proved a valuable tool indeed. This is not only so for studies of children experiencing extremely stressful events such as trauma and abuse but also in studies of healthy children in the naturalistic environment undergoing normal life experiences such as daycare and during periods of school transition. A recent study by Bugental and colleagues (Bugental et al, 2003) specifically examined the effects of subtle differences in maternal parenting. They found that children whose mothers used frequent spanking/slapping as a form of punishment exhibited greater cortisol reactivity to the stress of experimental separation and those whose mothers used various forms of emotional unavailability, whether intentionally or not, had higher baseline cortisol measures. The authors conclude that such early experiences may contribute to the child's allostatic load and be linked to subsequent negative health outcomes. That HPA-axis normalization can also be enabled from interventions to address parenting is also referred to by these authors (Bugental et al., 2003). It is the subtle types of behaviour that are being studied in healthy children experiencing normal events, which are not expected to create abnormally large reactions as may be seen in clinical populations of children suffering PTSD. The responses under investigation are those within the normal published reference values for cortisol (Tornhage, 2002). This begs the question of whether empirical investigations can reliably detect significant differences given such subtle changes. Indeed, is this really necessary and worthy of research investment? The answer to this question seems to be unequivocally positive, indeed vital for both theoretical and clinical understanding of the effects of stress response activation and prediction of health outcomes in the normal population. Whilst early research in the area produced some interesting but often inconsistent results, for example, reports of cortisol levels increases during afternoon for children in childcare, subsequent research has revealed explanatory subgroups with in these findings, for example, as with the use of alternative non-linear modeling (Adam & Gunnar, 2001) as referred to above.

The awakening cortisol response highlighted earlier in this review is clearly an area that requires a systematic evaluation from early infancy to adolescents and indeed could be a tool in itself to evaluate, for example, the effect of early childhood experience on development of the cortisol awakening response in puberty. Other recent advances in assessment which have applications for the developmental psychoendocrine literature include that of DHEA pointed to earlier, in relation to puberty. Authors have also called for other measures of HPA-axis activation available through salivary assessment, such as DHEA, depending on the age appropriateness of the sample (Granger & Kivlighan, 2003). A further additional method of assessment is the evaluation of immune antibodies (IgA) in saliva. So far, salivary IgA assessment in field studies has yielded promising but inconclusive findings in adults, particularly in relation to acute infection (Deinzer et al, 2000; Hucklebridge, 1998) and studies on sIgA levels in children have been scarce (Sanchez-Martin et al., 2001). Although this scarcity may in part be due to the methodological difficulties involved (e.g. controlling flow rate) and such difficulties are not to be underestimated, accurate sampling for sIgA in children is is possible and may yield important findings in regard to understanding the developmental psychobiology of stress experience in children and its health outcomes.

In Summary

Research across these critical gaps and a greater coherence between the multiple disciplines which contribute to the overall sum of knowledge in this area, may bring us closer to a more refined assessment of the influence of early life stress on HPA-axis development and functioning across the lifespan, certainly into adulthood, and link to acute and chronic diseases in later life. Furthermore, such studies may provide insight into important psychosocial factors and the necessary critical stages for intervention. Given that significant differences in HPA-axis activation are detectable in both experimental studies and under naturalistic conditions for normal healthy populations of children, one critical question remains. That is, of what clinical importance are these subtle changes within what is considered a normal range? Are we doing more harm that good in singling them out and running the risk of over interpretation of psychosocial effects on physiological responses, accompanied by over inflation of the implications? Caution is always merited in interpretation of data, specifically when crossing boundaries between disciplines. However, consistent significant findings within the smaller boundaries of the normal cortisol range, offers substantial potential for early detection of subtle alterations prior to subsequent longitudinal symptomotology.

This review has examined activation of the stress response system in children, considering in particular the findings and potential of studies investigating salivary cortisol reponses in healthy children undergoing a naturalistic life transition (school entry and progression) the adaptations to which are frequently within the normal range. The importance of these alterations, it is argued, may be early subtle indicators of and contribute to physical health outcomes in adulthood. Through further examination of such alterations it may be possible to help bridge the gap between infant research findings and those of chronic illness in adulthood, where retrospective examinations of alllostatic load all too often evade current research. Longitudinal studies incorporating measures of acute physical health outcome and of learning and memory as transitory markers are clearly needed, in addition to more long term measures of health symptomatology. It is suggested that assessment of acute illness such as URI’s may provide a suitable model of acute illness in crossing this gap and enabling continued prediction, intervention and prevention in psychobiological research.

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