

Altered stress responses in children exposed to early adversity: A systematic review of salivary cortisol studies

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Abstract

Pathological stress responses are implicated in numerous disorders. Hypothalamic–pituitary–adrenal axis function is influenced by gene–environment interaction, with early-life environmental adversity having long-lasting effects. We examine the evidence that, in humans, these effects are apparent from infancy. We systematically reviewed published findings on cortisol response to a stressor, in 0–5-year-olds already exposed to adversity. Adversity was defined as a negative environmental influence present post-conception. We searched Ovid MEDLINE (1950–May 2010), EMBASE (1980–May 2010) and PsychINFO (1806–May 2010). We included peer-reviewed, English language studies that analysed salivary cortisol before and after a standardised stressor. We identified 30 studies, of which 27 reported a significant effect of adversity on the cortisol response to stress. Six of these demonstrated an effect of prenatal substance exposure. Thirteen studies found that psychosocial adversity increased cortisol reactivity. Three studies reported that cortisol reactivity could be normalised by intervention programmes. The studies were heterogeneous, both in nature of adversity studied and in stressor used, precluding meta-analysis and assessment of publication bias. Our review presents evidence that adversity disrupts the stress response from an early age. Longitudinal studies are required to determine whether effects persist, alter with time, or are reversible with intervention.

Keywords: *Adversity, early life, HPA axis, human, programming, stress*

Introduction

We aimed to examine the evidence that adversity, defined as a negative environmental influence present during pregnancy or after birth, has measurable effects on the human stress response early in life.

The ability to respond appropriately to a stressor is a valuable attribute. A normal response to an acute stressor comprises rapid sympathetic nervous system arousal, followed by the activation of the hypothalamic–pituitary–adrenal (HPA) axis. The end products of the HPA axis are the glucocorticoid hormones—cortisol in humans and corticosterone in most rodents. These bring about long-lasting effects such as mobilisation of energy stores, heightened vigilance and changes in learning and memory. Importantly, they also exert negative feedback control on the axis to terminate the stress response when

appropriate. The timely activation and deactivation of stress response systems thus allow an organism to successfully manage a threat and return to normal function. An abnormal, or pathological, stress response may represent an inability to activate or deactivate the HPA axis, resulting in failure to manage a potentially life-threatening stressor, or prolonged exposure to glucocorticoids. This in turn may have long-term consequences for behaviour, memory and vulnerability to mental illness (de Kloet et al. 2005).

In normal adults, stress-induced cortisol secretion reaches a peak level at 20–40 min and falls back to baseline levels once the stressful situation is resolved. In addition to the stress response, cortisol is secreted throughout the day in a pulsatile ultradian pattern superimposed upon a circadian rhythm of high levels on morning awakening, gradually decreasing to a nadir at midnight. Studies suggest that the child's

stress response is apparent early (*in vivo* work demonstrates an independent cortisol rise from mid-gestation (20 weeks) onwards (Gitau et al. 2001)), but that stability of HPA axis function is not achieved until several months, or possibly years, of age (Jessop and Turner-Cobb 2008). Week-to-week stability of cortisol baseline secretion and peak percentage increases, but not temporal patterning, after a stressor is found in 12–18-month-olds; peak levels nevertheless occurred within 20–40 min after a stressor (Goldberg et al. 2003).

A normal range for cortisol responses in infancy and childhood is not well established due to great variation between studies (Jessop and Turner-Cobb 2008). However, by calculating effect sizes, Jansen et al. (2010) reported decreasing cortisol responses with age in their systematic review of acute stress responses in healthy 0–2-year-olds. This was most marked over the first 6 months and particularly evident for physical stressors such as examination. Thereafter, few studies using laboratory stressors report significant cortisol responses in normal children before the age of 6 years, although this may reflect the paucity of studies in this age group (Gunnar et al. 2009). A period of hyporesponsivity has similarly been observed in animal models (Sapolsky and Meaney 1986). In adolescence, significant cortisol responses are noted once more (Gunnar et al. 2009). Thus, a cortisol rise in response to stress is observed *in utero* it, may diminish in degree during early childhood but increases again in adolescence.

In adolescence, psychosocial stressors appear to be of greater potency than physical stressors (Gunnar et al. 2009). It should, however, be pointed out that ethical considerations define the range of acceptable stressors, and the relative magnitude of available physical and psychological stressors may vary at different ages.

A pathological response to stress is implicated in numerous psychiatric disorders; depression and post-traumatic stress disorder (PTSD) being two well-known examples (Heim et al. 1997; Yehuda 2009). There is evidence from both animal and human studies that pathological stress responses in adulthood are programmed by adversity earlier in life. That is, some environmental influence leads to long-lasting or permanent change in the functioning of the HPA axis. Adolescent and adult female victims of childhood sexual abuse have abnormal levels of corticotropin-releasing factor and adrenocorticotrophic hormone (De Bellis et al. 1994; Heim 2000), maternal stress during pregnancy alters offspring HPA axis function (reviewed in Meaney et al. (2007)) and war veterans with PTSD report higher rates of childhood abuse than veterans without (Bremner et al. 1993). Our understanding of the mechanisms of such programming is growing. One of the key remaining questions concerns the age at which an abnormal stress response

becomes apparent. In this paper, we review aspects of the stress response in young children exposed to adversity.

We do not attempt to review all of the extensive work in this field. Rather, we have performed a systematic literature review asking what is the cortisol response to a stressor in children aged 0–5 years who, either *in utero* or in postnatal life, have already experienced some form of adversity? We thus aimed to address the question: Are variations from normal HPA function already apparent in this age group? If so, by comparison with what is known about normal HPA axis function in children (Gunnar et al. 2009; Jansen et al. 2010), we then consider what changes are apparent, and whether these are consistent with the changes found in older age groups, or whether the influence of adversity changes with time.

The stressors employed in experimental studies may be based in either a laboratory or natural environment, and may be physical or psychological. As discussed above, the response to a stressor may depend on its nature. However, to keep our search broad, we decided to look at studies that employed any situation considered to present a challenge. Given that HPA axis activity in young humans is most often assessed experimentally by measuring cortisol levels in saliva, this being minimally invasive, we focused our review on those studies that measured salivary cortisol.

Method

Our study was designed as per the PRISMA guidelines for systematic reviews and meta-analyses (Moher et al. 2009; see Additional Materials).

We searched the databases MEDLINE (1950–May 2010), EMBASE (1980–May 2010) and PsychINFO (1806–May 2010) using the Ovid gateway. The following common search strategy was used:

Search 1: Cortisol.ti OR cortisol.ab

Limited to human, English language, infant (birth to 23 months) OR preschool child (2–5 years). Limits not available in PsychINFO.

Search 2: Stress.ti OR stress.ab

Search 3: Saliva*

Search 4: 1 AND 2 AND 3

The search engine was then asked to remove the duplicate results. We deliberately used a broad search strategy: narrowing the search with terms for adversity would have risked excluding useful studies.

Search results were then filtered by first reading the titles, then abstracts and then full texts of papers found. At each stage, studies were excluded if they were not in the English language, not peer reviewed, were review articles or case reports, did not study human subjects, studied the wrong age group, or an age group that was too broad, if subjects had not

experienced any adversity, if salivary cortisol in response to a stressor was not measured, or if subjects had a pre-existing psychiatric disorder.

Adversity was defined as an environmental influence, present during pregnancy or after birth, which could influence the development of an otherwise normal HPA axis. Examples include maternal psychiatric illness, substance exposure or low socio-economic status. We did not include obstetric complications or childhood illness as forms of adversity in this study.

We reviewed the remaining papers and extracted the following data: authors, year of publication, location of study, nature of study, nature of adversity, age range of subjects (months), mean age of subjects (months), number of subjects, nature of stressor, study conclusions, times of cortisol sampling, cortisol measurements and units of measurement. The bibliographies were searched to identify further eligible papers.

Results

Thirty studies were identified

The study selection process is illustrated in Figure 1. Thirty studies were identified (Magnano et al. 1992;

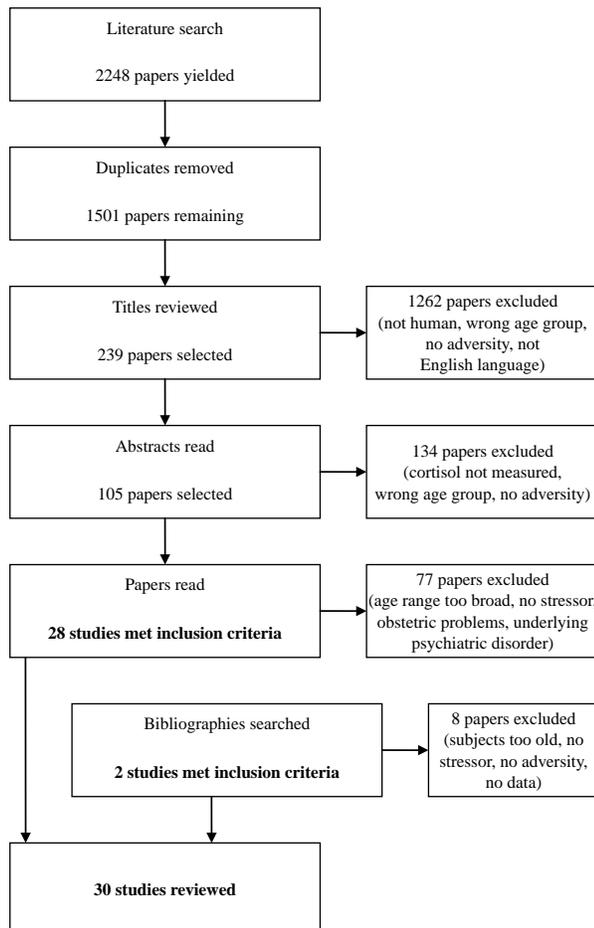


Figure 1. Flowchart showing the study selection process.

Hertsgaard et al. 1995; Gunnar et al. 1996; Nachmias et al. 1996; Ramsay et al. 1996; Jacobson et al. 1999; Gutteling et al. 2004, 2005; Huot et al. 2004; van Bakel and Riksen-Walraven 2004; Blair et al. 2006, 2008; Haley et al. 2006; Azar et al. 2007; Brotman et al. 2007; Granger et al. 2007; Mörelius et al. 2007; Smeekens et al. 2007; Dozier et al. 2008; Fernald et al. 2008; Oberlander et al. 2008a,b, 2010; Ouellet-Morin et al. 2008; Schuetze et al. 2008; Fernald and Gunnar 2009; Frigerio et al. 2009; Grant et al. 2009; Brand et al. 2010; Leung et al. 2010).

Studies were heterogeneous in nature

Studies were published between 1992 and 2010. Total sample sizes ranged from 11 to 1292. Twenty studies originated from North America, six from Europe, two from Mexico and one each from Australia and South Africa. The average age of subjects ranged from 2 days to 64 months. The studies were heterogeneous both in the nature of adversity experienced by subjects and in the method used to induce a stress response. Adversity experienced included maternal substance abuse (alcohol, cocaine and tobacco), maternal anxiety and depression, maternal history of childhood abuse, low income and high psychosocial risk, low maternal sensitivity and negative parent-child interaction, insecure maternal attachment and maternal separation (children in foster care). Stressors used to elicit a cortisol response included physical stressors (heel prick, inoculation or venepuncture, arm restraint and physical examination) and psychosocial stressors (strange situation, still face paradigm, encountering strangers and novelty, unfamiliar peer groups and first day at school). A summary of each study is presented in Table I.

Cortisol reporting was inconsistent

Sixteen studies reported actual cortisol values (Magnano et al. 1992; Hertsgaard et al. 1995; Nachmias et al. 1996; Ramsay et al. 1996; Blair et al. 2006, 2008; Haley et al. 2006; Azar et al. 2007; Brotman et al. 2007; Granger et al. 2007; Mörelius et al. 2007; Dozier et al. 2008; Fernald and Gunnar 2009; Grant et al. 2009; Brand et al. 2010; Oberlander et al. 2010). The means of reporting varied as did the times of cortisol sampling. Given this, and the heterogeneity of the study methodologies, we decided that the meta-analysis was not appropriate.

Twenty-seven studies reported an effect of adversity

Of the 30 studies, 27 (Magnano et al. 1992; Hertsgaard et al. 1995; Gunnar et al. 1996; Nachmias et al. 1996; Ramsay et al. 1996; Jacobson et al. 1999; Gutteling et al. 2004, 2005; van Bakel and Riksen-Walraven 2004; Blair et al. 2006, 2008, 2010;

Table I. Characteristics and findings of studies identified, listed by ascending subject age.

Reference	Nature of adversity	Study description	Stressor	Subject age in months (range or mean)			Adversity group (n)	Control group cortisol response to stress	Adversity group cortisol response to stress	Limitations/study bias
				Neonates	Control group (n)	Adversity group (n)				
Magnano et al. (1992)	Prenatal cocaine exposure	Healthy pre-term population. Cocaine exposure determined by maternal urine toxicology or maternal reports of use	Newborn exam; heel stick	Neonates	38	11	Significant rise	Significant rise	No data on duration or degree of cocaine exposure, subjects pre-term	
Leung et al. (2010)	Maternal stress during pregnancy	Mother-infant dyads recruited at birth. Perceived maternal stress during pregnancy and infant stress response assessed at post-natal day 2 and 10 months	Heel stick	Neonates		33	Greater perceived maternal stress during pregnancy predicted greater neonatal and postnatal cortisol reactivity	Pre- and post-stressor levels significantly lower than control group	Measure of perceived rather than actual stress during pregnancy	
Oberlander et al. (2010)	Prenatal alcohol exposure	Mothers recruited during third trimester of pregnancy at obstetric clinic	Heel stick	Neonates	14	14	No change	Significant decrease in cortisol over time	Relied on honest reporting of alcohol consumption	
Ramsay et al. (1996)	Prenatal alcohol and tobacco exposure	Tobacco exposure determined by a postnatal questionnaire (and analysis of meconium)	Inoculation	2 6	9 5	5 6	Significant rise No change	No change No change	Small sample size	
Oberlander et al. (2008a)	Maternal depression during pregnancy	Mothers recruited during second trimester of pregnancy. Infant stress reactivity studied at 3 months of age	Infant-controlled habituation task	3	45	31	In SSRI-exposed infants, cortisol rose in both breastfed and non-breastfed infants	In non-SSRI-exposed infants, cortisol rose in breastfed infants but fell in non-breastfed infants	Study did not initially intend to study the effect of feeding method	
Oberlander et al. (2008b)	Maternal depression during pregnancy	Mothers with and without depression recruited prospectively. Infant methylation status of glucocorticoid receptor gene (NR3C1) promoter and cortisol response were assessed	Infant-controlled habituation task	3	33	49	Maternal depression in the third trimester was associated with greater cortisol response to stress and greater methylation of the NR3C1 promoter			
Mörelis et al. (2007)	High psychosocial risk	Mother-infant dyads at high psychosocial risk (history of alcohol use, psychiatric illness, teenage mom and forensic history)	Nappy change	1-6		22	Infants younger than 3 months showed a significant cortisol rise in response to the stressor. This was not so for infants older than 3 months		Internal controls only. Nappy change not usually associated with cortisol rise	
Azar et al. (2007)	Maternal history of lifetime depression	Subjects recruited from a large cohort study of teen pregnancy. Depression assessed by questionnaire	Arm restraint	4.38	126	62	No change	Increased cortisol reactivity	No main effect of depression during pregnancy	

TABLE I – continued

Reference	Nature of adversity	Study description	Stressor	Subject age in months (range or mean)	Control group (n)	Adversity group (n)	Control group cortisol response to stress	Adversity group cortisol response to stress	Limitations/study bias
Huot et al. (2004)	Maternal depression during pregnancy	Subjects recruited from cohort studying monitoring depression pre- and post-partum using Beck Depression Inventory	Series of mild stressors (noises, seat belt/arm restraint)	6		123	Maternal depression during pregnancy but not post-partum, associated with negative affect in infant. Cortisol response in infant also associated with negative affect	Maternal depression during pregnancy but not post-partum, associated with negative affect in infant. Cortisol response in infant also associated with negative affect	No correlation between maternal depression and infant cortisol assessed
Blair et al. (2006)	Maternal sensitivity	Subjects from large longitudinal study of rural poverty. Mother-child interaction scored	Mixed—mask presentation, barrier, toy reach, arm restraint	6		1292	High maternal sensitivity was associated with lower baseline cortisol, an increase in response to stress, then a decrease in recovery. Low maternal sensitivity was associated with higher baseline cortisol and decreasing levels after stress and in recovery	High maternal sensitivity was associated with lower baseline cortisol, an increase in response to stress, then a decrease in recovery. Low maternal sensitivity was associated with higher baseline cortisol and decreasing levels after stress and in recovery	Reliance upon maternal reports of alcohol consumption
Haley et al. (2006)	Prenatal alcohol exposure	Study of women identified as showing risky alcohol consumption in pre-pregnancy recognition period	Still face procedure	5–7		55	Higher alcohol consumption in pregnancy was associated with greater increase in cortisol response. Association different for boys and girls	No change	Reliance on maternal reports of childhood abuse
Brand et al. (2010)	Maternal childhood abuse	History of maternal childhood abuse derived from completion of childhood trauma questionnaire	Maternal separation, then noise/arm restraint	6.23	88	38	No change	No change. But significantly lower baseline cortisol	Reliance on maternal reports of childhood abuse
Schuetz et al. (2008)	Prenatal tobacco exposure	Interview-based questionnaire used to quantify maternal cigarette smoking during pregnancy	Mixed—arm restraint, puppet show, mask presentation	7	40	51	Positive association between maternal smoking during pregnancy and cortisol reactivity. No correlation between cigarette exposure and baseline cortisol	Positive association between maternal smoking during pregnancy and cortisol reactivity. No correlation between cigarette exposure and baseline cortisol	
Granger et al. (2007)	Postnatal tobacco smoke exposure	Smoking and non-smoking mothers were recruited from a large longitudinal study of rural poverty	Mixed—mask presentation, barrier, toy reach, arm restraint	7.16	115	82	No association was found between maternal smoking and infant stress reactivity	No association was found between maternal smoking and infant stress reactivity	
Blair et al. (2008)	Poverty, low maternal engagement	Subjects were from a large longitudinal study of rural poverty. Maternal engagement in infancy was assessed from video recordings and questionnaire responses	Mixed—mask presentation, barrier, toy removal, arm restraint	5–13.4		1292	Greater maternal engagement was associated with greater cortisol reactivity in infancy and lower cortisol levels in toddlerhood	Greater maternal engagement was associated with greater cortisol reactivity in infancy and lower cortisol levels in toddlerhood	
				13.5–22.3					

TABLE I – continued

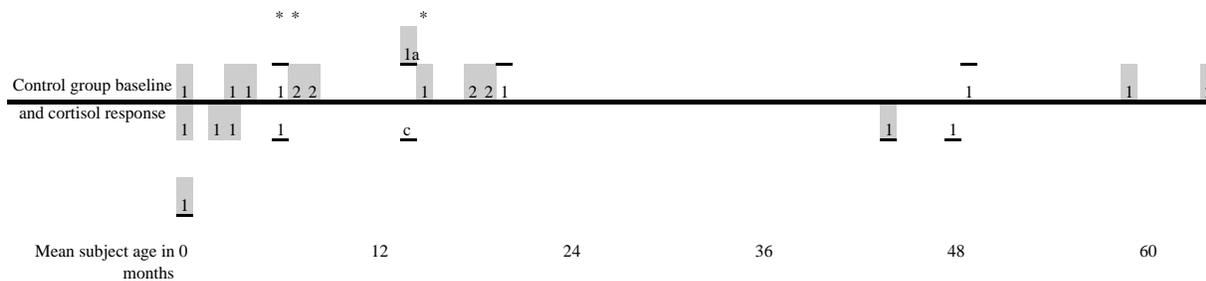
Reference	Nature of adversity	Study description	Stressor	Subject age in months (range or mean)	Control group (n)	Adversity group (n)	Control group cortisol response to stress	Adversity group cortisol response to stress	Limitations/study bias
Grant et al. (2009)	Maternal prenatal anxiety disorder	Mothers recruited prenatally as part of larger longitudinal study. Maternal anxiety derived from questionnaire responses and neuropsychiatric interview	Still face procedure	7.89	71	17	Significant decrease in cortisol levels	Significantly higher post-test cortisol	Efficacy of stressor questioned
Jacobson et al. (1999)	Prenatal alcohol and cocaine exposure	Alcohol and cocaine consumption was determined from interviews during pregnancy	Venepuncture/finger prick	11.5–18.4	83	83	Alcohol exposure was associated with higher pre- and post-test cortisol levels. Cocaine exposure was associated with lower baseline levels	Alcohol exposure was associated with higher pre- and post-test cortisol levels. Cocaine exposure was associated with lower baseline levels	Reliance upon maternal reports of alcohol and cocaine consumption
Frigerio et al. (2009)	Insecure attachment	Study of interaction between attachment, genetic polymorphisms (5-HTTLPR, COMT and GABRA6) and infant stress response in middle-class mother–infant dyads	Strange situation	12–18	100	100	Significant interaction between serotonin transporter and GABA receptor polymorphisms and attachment in determining infant alpha-amylase, but not cortisol response	Significant interaction between serotonin transporter and GABA receptor polymorphisms and attachment in determining infant alpha-amylase, but not cortisol response	
van Bakel and Riksen-Walraven (2004)	Insecure attachment	Subjects were recruited from a project exploring parent–child interaction. Quality of attachment was determined from video recordings. Childrens’ cognitive function was also assessed	Stranger, frightening robot, strange situation	15.1	85	85	Greater cognitive competence predicted greater cortisol response in insecurely, but not securely attached children	Greater cognitive competence predicted greater cortisol response in insecurely, but not securely attached children	
Gunnar et al. (1996)	Insecure attachment	Attachment assessed during a well-baby exam. Child fearfulness assessed by a maternal questionnaire	Strange situation	18	73	73	Insecure attachment and greater levels of fearfulness in the child were associated with greater cortisol responses	Insecure attachment and greater levels of fearfulness in the child were associated with greater cortisol responses	Child fearfulness determined by mother’s answers rather than assessment of child
Nachmias et al. (1996)	Insecure attachment	Subjects were recruited from university databases. Attachment was assessed during strange situation. Behavioural inhibition was assessed during a series of tasks involving novelty	Strange situation	18	78	78	Insecure attachment and greater levels of behavioural inhibition were associated with greater cortisol responses	Insecure attachment and greater levels of behavioural inhibition were associated with greater cortisol responses	

TABLE I – continued

Reference	Nature of adversity	Study description	Stressor	Subject age in months (range or mean)	Control group (n)	Adversity group (n)	Control group cortisol response to stress	Adversity group cortisol response to stress	Limitations/study bias
Hertsgaard et al. (1995)	Disorganised/avoidant/secure/resistant attachment	Subjects were recruited from a larger longitudinal intervention programme. Attachment was assessed during strange situation	Strange situation	18.5–20.2		11	Toddlers with disorganised attachment showed higher cortisol levels than other attachment types	Adversity group cortisol response to stress	No pre-test cortisol levels
Ouellet-Morin et al. (2008)	Familial adversity	Subjects were recruited from the Québec Newborn Twin Study. Familial adversity was a product of maternal education, behaviour, age, smoking and household income	Novelty	19		5 17 1 346	Greater familial adversity was associated with greater cortisol response. In low adversity, genetic and environmental factors contributed to individual differences. In high adversity, only environmental factors did	Adversity group cortisol response to stress	
Dozier et al. (2008)	Maternal separation (in foster care)	Randomised controlled-trial of attachment-based intervention (ABC) in fostered children. Compared with control intervention (DEF) and non-fostered children	Strange situation	15–24		46	None of the groups demonstrated a significant cortisol response to the stressor. Control intervention group had significantly higher baseline cortisol	Adversity group cortisol response to stress	Duration of foster care unclear
Brotman et al. (2007)	High-risk for antisocial behaviour	Randomised control trial of psychosocial family-based intervention in children at risk for antisocial behaviour (siblings prosecuted for delinquency)	Entry into unfamiliar peer group	33–63		92	Control group subjects (n = 45) had lower pre-stressor cortisol levels than those in the intervention group (n = 47). There was no difference in post-stressor cortisol levels; neither group showed a significant increase in cortisol levels in response to the stressor	Adversity group cortisol response to stress	Sibling delinquency interpreted as a marker of exposure to adversity
Fernald and Gunnar (2009)	Very low income	Study of families involved in <i>Oportunidades</i> , a poverty-alleviation programme in rural Mexico, compared with control group	Encounter with strangers	24–72	706	491	Control subjects had significantly higher baseline cortisol. There was no difference in cortisol response. In <i>Oportunidades</i> , the greatest impact on baseline cortisol was in children of depressed mothers	Adversity group cortisol response to stress	No control intervention, no randomisation
Fernald et al. (2008)	Maternal depression, low income	Sample from larger population study in urban Mexico. Maternal depressive symptomatology gauged from questionnaire responses	Encounter with strangers, cognitive testing	30–72		639	Greater maternal depression was associated with lower baseline cortisol levels and reduced cortisol reactivity	Adversity group cortisol response to stress	

TABLE I – continued

Reference	Nature of adversity	Study description	Stressor	Subject age in months (range or mean)	Control group (n)	Adversity group (n)	Control group cortisol response to stress	Adversity group cortisol response to stress	Limitations/study bias
Gurteling et al. (2004)	Maternal stress during pregnancy	Mothers were recruited during pregnancy. Maternal stress during pregnancy was derived from questionnaire responses	Inoculation	37–71		24	Children of mothers reporting greater stress and anxiety in pregnancy showed higher cortisol levels	Adversity group cortisol response to stress	
Smeekens et al. (2007)	Negative parent–child interaction	Subjects recruited from an earlier study. Parent and child behaviour and interaction scored from video recordings	Vocabulary test	63.6		101	The more negative parent–child interaction, the greater the child’s cortisol response		
Gurteling et al. (2005)	Maternal stress during pregnancy	Subjects were recruited from a prospective longitudinal study of postnatal development. Maternal stress during pregnancy was derived from questionnaire responses	First day at school	64		29	Children of mothers reporting greater stress and anxiety in pregnancy showed higher cortisol levels	Adversity group cortisol response to stress	Unclear when mothers completed the questionnaires



Mörelus et al. 2007 excluded (subjects divided by age).

At 14 months: Jacobsen et al. 1999. a = maternal alcohol consumption in pregnancy, c = maternal cocaine consumption in pregnancy

Figure 2. Diagram illustrating findings of studies identified. Timeline in bold represents baseline salivary cortisol concentration and cortisol response to a stressor of the control group. Smaller bold lines represent baseline cortisol level of adversity groups, if this differed. Shading represents cortisol response to a stressor for the adversity groups, if this differed from control. Numbers represent number of studies reporting that result. Asterisks represent studies reporting no significant differences between controls and adversity groups. For example, at 7 months, one study found no significant differences and two studies reported a greater cortisol responses in adversity groups.

Haley et al. 2006; Azar et al. 2007; Brotman et al. 2007; Mörelus et al. 2007; Smeekens et al. 2007; Dozier et al. 2008; Fernald et al. 2008; Ouellet-Morin et al. 2008; Schuetze et al. 2008; Fernald and Gunnar 2009; Grant et al. 2009; Leung et al. 2010; Oberlander et al. 2008a,b, 2010) reported a significant difference in either pre-stressor (baseline) cortisol levels or change in cortisol level in response to stress (cortisol reactivity) between adversity groups and controls. The findings of all the studies identified are illustrated diagrammatically in Figure 2.

Thirteen studies reported increased cortisol reactivity with adversity

Thirteen studies, investigating maternal stress, anxiety and depression during pregnancy (Gutteling et al. 2004, 2005; Oberlander et al. 2008b; Grant et al. 2009; Leung et al. 2010), maternal lifetime history of depression (Azar et al. 2007), insecure mother-child attachment (Hertsgaard et al. 1995; Gunnar et al. 1996; Nachmias et al. 1996; van Bakel and Riksen-Walraven 2004; Smeekens et al. 2007) and increased psychosocial risk (Mörelus et al. 2007; Ouellet-Morin et al. 2008) found that the cortisol response to a stressor was greater with adversity.

Three studies reported a decrease in cortisol reactivity with adversity

One study of 3-month-old infants of depressed mothers reported that in infants of depressed mothers not treated with selective serotonin reuptake inhibitors (SSRIs) who were not breastfed, cortisol levels fell in response to stress (Oberlander et al. 2008a). Breastfed infants showed an increase in cortisol levels, as did infants of mothers who were SSRI treated, independent of feeding method. A study of 7-month-old infants from rural, low-income families in North America reported that lower maternal sensitivity was associated with lower cortisol reactivity (Blair et al.

2008). In older children from low-income families in urban Mexico, an inverse correlation was found between maternal depressive symptomatology and cortisol reactivity (Fernald et al. 2008).

Three studies reported an increase in baseline cortisol with adversity

A study of the population of North American infants from rural, low-income families found that at age of 6 months, lower maternal sensitivity was associated with higher baseline cortisol levels (pre-stressor) (Blair et al. 2006). Older children (15–24 months) in foster care who underwent a control intervention were found to have significantly higher baseline cortisol levels compared to foster children who underwent an attachment-based intervention (Dozier et al. 2008). Similarly, in children of very low-income families in Mexico (24–72 months), those in a control group had significantly higher baseline cortisol level than those in a poverty alleviation programme (Fernald and Gunnar 2009).

Two studies reported a decrease in baseline cortisol with adversity

Six-month-old infants of mothers who were themselves abused in childhood had significantly lower baseline cortisol levels than control infants (Brand et al. 2010). Children aged 33–63 months old who were considered to be at high risk for antisocial behaviour (siblings prosecuted for delinquency) were also found to have lower baseline cortisol level (Brotman et al. 2007).

Six studies reported an effect of prenatal substance exposure

Six studies examined the effect of prenatal exposure to alcohol, tobacco or cocaine (Magnano et al. 1992; Ramsay et al. 1996; Jacobson et al. 1999; Haley et al. 2006; Schuetze et al. 2008; Oberlander et al. 2010).

All reported an effect. In 6-month-old infants, and 11–18-month-old children, maternal alcohol use was reported to increase cortisol reactivity (Jacobson et al. 1999; Haley et al. 2006). In 7-month-old infants, maternal cigarette smoking during pregnancy was positively correlated with cortisol reactivity (Schuetze et al. 2008). In younger children (neonates, 2-month-olds), subjects exposed to alcohol, tobacco or cocaine had lower cortisol levels compared to controls (Magnano et al. 1992; Ramsay et al. 1996; Oberlander et al. 2010).

Three studies found no effect of adversity

In 7-month-old infants, Granger et al. (2007) did not find a significant association between postnatal exposure to tobacco smoke and cortisol response to mixed stressors. In 6-month-old offspring of mothers with depression during pregnancy, Huot et al. (2004) found an association between maternal depression and negative infant affect, and an association between negative infant affect and greater cortisol reactivity, but not directly between maternal depression and infant cortisol reactivity. Again, mixed stressors were employed. Frigerio et al. (2009) did not find an interaction between insecure attachment and genetic polymorphisms in determining cortisol response to the strange situation in 12–18-month-old children.

Three studies report that psychosocial intervention altered cortisol values

In a randomised controlled trial, foster children aged 15–24 months who participated in an attachment-based intervention programme had cortisol levels comparable to non-foster children, whereas foster children in a control intervention had significantly higher baseline levels (Dozier et al. 2008). In a study of 2–6-year-old children from very low-income families, the children participating in a control intervention had significantly higher baseline levels compared to children whose families participated in a poverty alleviation programme (Fernald and Gunnar 2009). Children aged 33–63 months at high risk for antisocial behaviour who underwent a control intervention had lower pre-stressor cortisol levels than a family-based psychosocial intervention group (Brotman et al. 2007).

Discussion

Study findings

Twenty-seven of the 30 studies identified by our systematic review report a significant effect of adversity on the HPA axis response to stress in young children. There are reports of differences in pre-stressor (baseline) cortisol levels and/or in cortisol

response to stress between control and adversity groups from the neonatal period onwards. The studies examine the effects of different forms of environmental adversity using different stressors, both physical and psychological.

Our findings therefore support the idea that adversity early in life, or even prior to conception (Brand et al. 2010), has effects on the young human stress response, with variation from normal HPA axis function apparent in infancy. However, due to the heterogeneity of subjects, adversity and experimental paradigms, it is difficult to draw conclusions about the nature of these effects or how adversity might alter the function of individual components of the HPA axis.

As study numbers are small, formal comparisons between studies cannot in general be performed. Nonetheless, where studies do share common features, it is interesting to consider the effect of subject age and nature and timing of adversity. For example, Ramsay et al. (1996), Jacobson et al. (1999) and Oberlander et al. (2010) studied children exposed to alcohol *in utero* at ages 0, 2 and 11–18 months, respectively. All employed a painful stressor such as vaccination or heel prick. As neonates, exposed infants showed a decrease in cortisol level, as 2-month-olds, a failure to respond, and an increase in pre- and post-test cortisol levels as 11–18-month-olds. In contrast, Gutteling et al. (2004) and Leung et al. (2010) both looked at maternal anxiety during pregnancy, and both used painful stressors, but found similar results, namely increased cortisol reactivity, at 0 months and at 37–71 months. Granger et al. (2007) and Schuetze et al. (2008) both used mixed stressors in 7-month-old infants but found that those exposed to smoking prenatally had greater cortisol reactivity than controls, whereas those exposed postnatally did not. Such observations support an effect of age at testing and nature of adversity, but this may not always be the case.

Study findings in context

Important adult psychiatric disorders are characterised by altered HPA axis function: hypercortisolism of depression (Holsboer 2001) and hypocortisolism of PTSD (Yehuda 2009) being key examples. Such disorders are multifactorial, but as discussed above, there is increasing evidence that experiences early in life shape the adult stress response.

It is unclear whether a disturbance of normal HPA function might be latent, until a second “hit” later in life, or whether, as our study suggests, HPA dysregulation occurs early. These early changes might then persist unaltered or evolve with age (De Bellis et al. 1994). Thirteen of our studies reported that subjects who had experienced adversity, aged 0–5 years, showed increased cortisol reactivity compared

to controls. Interestingly, an increase in cortisol reactivity is also observed in adults reporting early life adversity (Heim et al. 2001). Similarly, lower baseline cortisol levels were reported in children at risk for antisocial behaviour (Brotman et al. 2007), as also found in adults with conduct disorder, antisocial personality disorder and in animal models of abnormal aggression (Haller and Kruk 2006). These observations could support the argument that early changes persist. However, the reports that psychosocial intervention might normalise the stress response in vulnerable groups (Brotman et al. 2007; Dozier et al. 2008; Fernald and Gunnar 2009) suggest that childhood HPA function is far more plastic. The failure of postnatal tobacco smoke exposure, a stressor known to increase cortisol levels in adults, to produce the same effect in infants (Granger et al. 2007) adds weight to the argument that HPA axis function evolves with age.

Limitations

As observed by Gunnar et al. (2009), there is little solid evidence to support the efficacy of any one of the commonly used stressor paradigms in consistently producing a HPA axis response in young children. The considerable heterogeneity in paradigms reported both in their review and in our present study only serves to emphasise the need for reliable, evidence-based stressor paradigms. One must therefore consider the reproducibility of the results reported in identified studies. It is also of note that the use of physical stressors predominates in infancy (Table I), with psychological stressors being used more in older children. Given that the maturation of the stress response appears to differ with respect to physical and psychological stressors (Jansen et al. 2010), one cannot base theories about the stress response as a whole on studies using only one type of stressor.

The difficulty in translating extensive understanding gained from animal studies to the developing human is highlighted by the limited means of measuring HPA axis activity in our study population. Salivary cortisol measurement is widely used but the assay can be affected by foodstuffs and saliva stimulants, and salivary cortisol is of course only an indirect measure of brain levels. It has, however, been shown to correlate with the HPA axis activity (Schwartz et al. 1998) and remains the most widely used, least invasive technique.

Our finding that 27 of 30 studies identified reported a significant effect of adversity must also lead to the consideration of publication bias as an explanation. Studies reporting non-significant findings may have remained unpublished. Few studies provided sample size calculations, raising the possibility that false positive results were obtained due to small sample

sizes (Newcombe 1987). Meta-analysis using techniques such as the funnel-plot is valuable in detecting publication bias (Moreno et al. 2009), but the heterogeneity of the studies that we identified, with only papers published by the same group being comparable, did not allow this.

Strengths and suggestions for further work

This study is the first to review systematically the existing literature on HPA axis function in 0–5-year-olds exposed to adversity. As such, we feel it has raised important points about how work in this field should continue.

The variation in the demonstrated effects of adversity on the young stress response suggests that effort must be made to control for as many confounding factors as possible. Only by isolating each variable in turn can we begin to understand the human HPA axis to the same extent as the animal models. This is difficult in vulnerable populations but should be attempted. Our review suggests that maternal substance use in pregnancy (alcohol and tobacco, as well as illicit drugs), maternal mood and stress levels in pregnancy, maternal psychiatric and medication history (including childhood abuse), means of infant feeding, socio-economic circumstances, family structure and mother–infant attachment must all be taken into account.

We believe that our study highlights the gaps in our understanding of the longitudinal development of the HPA axis in humans, both normal and abnormal, from the prenatal period. To draw reliable conclusions about the importance of the early environment, we consider a large, long-running cohort study similar to the Dunedin Multidisciplinary Health and Development Study (Silva 1990) most suitable, but ideally with recruitment pre-conception and a series of observations before the age of 3 years. Collecting information on the variables discussed above, such a study could make opportunistic use of events such as vaccination to assess stress responses, or employ well-documented paradigms such as the strange situation procedure. Lifestyle, change of circumstances and significant life events could be recorded at regular follow-up. A standardised means of reporting cortisol responses, e.g. percentage change to peak response and area under the curve have both been suggested as showing best stability (Goldberg et al. 2003), would allow for easier comparison of findings.

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