

Cortisol secretion in children with symptoms of Reactive

Attachment Disorder

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Abstract

Maltreated children with Reactive Attachment Disorder (RAD) have severe problems with social relationships and affect regulation. An association between early maltreatment and changes in the daily rhythm of cortisol secretion has already been reported for maltreated toddlers. We sought to find out whether such changes were apparent in school-age children with symptoms of RAD, who had experienced early maltreatment but were currently adopted in well functioning families. We recruited 66 children: 34 5-12 year old adopted children with an early history of maltreatment and with social difficulties such as indiscriminate friendliness; and 32 age- and sex-matched comparison children with no history of maltreatment or social difficulties. Daily rhythms of cortisol production were determined from saliva samples collected over two days. The adopted group had significantly lower absolute levels of cortisol compared to the control group, but a typical profile of cortisol secretion. There was no association between cortisol secretion and symptom scores for psychopathology.

1. Introduction

Reactive Attachment Disorder (RAD) is a serious disorder of social functioning associated with abuse and neglect. The Disinhibited subtype is the best understood and is characterised by indiscriminate friendliness which can be persistent and may be associated with personality problems in adult life (Lyons-Ruth 2008). We have previously shown that children indiscriminate friendliness can have complex neurodevelopmental problems and yet are frequently not engaged with therapeutic services (Kocovska et al. 2012). Sufferers can have problems with emotional and behavioural functioning and affect regulation (Gleason et al. 2011; Green 2003; Rutter and Sonuga-Barke 2010; Zeanah et al. 2002), and research with international (mainly post-institutionalised) adoptees has demonstrated an association between indiscriminate friendliness and abnormalities of the Hypothalamo-Pituitary-Adrenal (HPA) axis, which governs the secretion of stress hormones such as cortisol (Johnson et al. 2011).

RAD is one of only two disorders (the other being Post Traumatic Stress Disorder, PTSD) that are directly associated, in the psychiatric classification systems, with aetiology: it is recommended that a diagnosis of RAD should not be made unless there is a history of maltreatment in the first 5 years of life (World Health Organisation 2007; American Psychiatric Association 2000). However, not all children who have experienced maltreatment in early life develop RAD and both genetic and environmental factors contribute to causality (Minnis et al. 2007). Because of the recognised association, in institutionalised children, between indiscriminate friendliness and abnormalities of the HPA axis, we have decided to focus, in this study, on the subgroup of maltreated children who are indiscriminately friendly.

Maltreatment in early life can be associated with long-term changes in regulation of the stress hormone cortisol and we have previously published a systematic review of this literature (Hunter et al. 2011). Our review has demonstrated that studies of adults who have been maltreated show conflicting results regarding the impact of maltreatment on diurnal secretion of cortisol and that there is a gap in the literature as regards cortisol production in maltreated school-age children (Hunter, Minnis, & Wilson 2011). Altered function of the HPA axis has been described in depression (Holsboer 2001), post-traumatic stress disorder (Yehuda 2009), conduct disorder and antisocial personality disorder (Vanyukov et al. 1993). Studies of children reared in institutions have shown that lack of caregiver sensitivity and positive regard is associated with a general suppression of the hypothalamic-pituitary axis (Johnson and Gunnar 2011) and that this can recover if the environment improves. For example, in 2006 Dozier and colleagues (Dozier et al. 2006) reported alterations in the production of salivary cortisol in maltreated toddlers in foster care and substantial recovery has been demonstrated with environmental improvement (Dozier, Manni, Gordon, Peloso, Gunnar, Stovall-McClough, Eldreth, & Levine 2006; Fisher et al. 2006; Tarullo and Gunnar 2006). There is, however, no available research indicating the extent to which these changes can persist into middle childhood and the issue has not been explored in non-institutionalised school-age children.

During development, cortisol production is modulated in response to the social environment of the child (Dozier et al. 2008; Hunter, Minnis, & Wilson 2011; Tarullo & Gunnar 2006). By school-age, under optimal conditions, cortisol levels peak in the morning about 30 minutes after waking, followed by a gradual decrease towards evening (Gunnar and Donzella 2002). In an environment of persistent deprivation, neglect or abuse, the development of an infant's daily

cortisol rhythm and/or stress reactivity may differ from that of other children in various ways (Brand et al. 2010). When production is persistently elevated or suppressed, or inadequately regulated in response to stress, there may be long-term consequences including effects on brain functioning (Caldji et al. 2000; Hunter, Minnis, & Wilson 2011). These may cause difficulties in handling stressful situations and predispose individuals towards developing mental health problems later in life (Teicher et al. 2003).

In this study, we examined the daytime pattern of cortisol production in previously maltreated children aged 5-12 years with symptoms of Disinhibited RAD who were currently adopted in well functioning families and comparison children without such difficulties. Our hypothesis was that, in these children, maltreatment in early life may have resulted in differences in cortisol secretion which persisted into school-age.

2. Methods

The study protocol was approved by the West of Scotland 2 NHS ethics committee.

2.1 Statistical power An a priori power calculation based on Dozier 2006 (Dozier, Manni, Gordon, Peloso, Gunnar, Stovall-McClough, Eldreth, & Levine 2006) indicated that a sample size of 10 in each group would have a 90% power to detect a difference in means of -0.2 assuming that the common standard deviation is 0.13 using a two group t-test with a 5% two sided significance level. In order to ensure this computation was not too conservative and to allow for the suspected non-parametric nature of the data, we recruited a larger sample.

2.2 Participants

Because we were interested in potentially persistent effects of *early life* maltreatment in children with RAD, we needed to recruit a group of children with RAD symptoms who had experienced abuse and neglect within the early years, but who had not continued to live in these adverse circumstances. In the UK, the mean age of adoption is 4 years (<http://www.gro-scotland.gov.uk/press/news2004/03adopt-press.html>; <http://www.baaf.org.uk/info/stats/england.shtml>) and the overwhelming majority of adopted children have experienced severe abuse and/or neglect in the early years prior to coming into care. In general, they then reside in well-functioning families (Rushton et al. 2006). We therefore considered adopted school-age children with RAD symptoms to be the ideal group within which to test our hypothesis.

Adopted children were recruited via the charity ‘Adoption UK’: eligibility criteria were discussed with the Scottish Director who contacted all eligible families known to the charity living within travelling distance of the University. Children were eligible for inclusion if they were aged 5-12 years, had the core symptom of the Disinhibited form of RAD - indiscriminately friendly behaviour - plus a history of maltreatment. RAD symptoms were verified using the Relationships Problems Questionnaire (RPQ) (see below). Potentially participating children were excluded if they had moderate or severe intellectual disability (which can itself cause disinhibition), current family instability or ongoing maltreatment. Forty-three children were referred and 40 met inclusion criteria but one female child was subsequently excluded as she had signs of having reached puberty. Two families (five children) withdrew. Thirty-four children (18

boys and 16 girls; mean (SD) age 9.4 (1.8) years were clinically assessed. All adopted children were white British except for one child who was African American by birth.

Comparison children were included if they were aged 5 – 12 years and excluded if they had any known child psychiatric diagnosis, moderate or severe intellectual disability, any history (even suspected) of child maltreatment, known contact with social work, child protection registration or any trauma within the last year. We ensured that no comparison children had high scores suggestive of RAD (i.e. over 6 on Relationship Problems Questionnaire – see later). Children were selected through two general medical practices in Glasgow. The practices had 750 children within the age range 5-12 years and 615 were eligible according to the inclusion criteria. The general practitioners sent 461 invitation letters: 58 responded, 9 withdrew and, because of gender and age mismatches, not all remaining eligible children were invited to participate. In order to address imbalances in age and gender, a further 62 invitation letters were re-sent to non-responders from the original 461, this time only to families with boys aged 6-10 years. Of these, four had moved away, six responded and were assessed. The comparison group eventually comprised 32 children (17 boys and 15 girls; mean (SD) age 8.7 (2.4) years who were clinically assessed. All comparison children were white British.

Children in both the adopted and comparison group were offered a neuropsychiatric assessment using standardised tools for RAD, other diagnoses and measures of cognition and language functioning. These assessments have been described elsewhere (Kocovska et al 2012).

2.3 Procedure

For adopted children, after obtaining consent forms from parents and children, an initial home visit was arranged during which demographic data were collected and parents were interviewed regarding the child's mental health and social functioning. For the comparison group, interviews were carried out either in the child's general practice or at home. Test tubes were delivered and instructions given regarding how to collect saliva samples three times a day over two days. A written instruction leaflet was left for each child (Patel et al. 2004).

2.4 Measures

Emotional and behavioural symptoms were measured using the Strengths and Difficulties Questionnaire (SDQ), a 25 item scale validated in large population research that covers conduct problems, emotional problems (depression/anxiety), hyperactivity, problems with peer relations and prosocial (caring, helpful) behaviour. The first four subscales are totalled to produce a Total Difficulties Score (Goodman et al. 2003).

The Relationship Problems Questionnaire (RPQ) is a 10-item questionnaire, validated in large population research, assessing symptoms of Reactive Attachment Disorder including indiscriminate friendliness. A cut-off score of 7 or above is suggestive of "caseness" (Minnis, Reekie, Young, O'Connor, Ronald, Gray, & Plomin 2007).

2.5 Saliva Sampling

In a normal population the pattern of cortisol levels shows a peak in the morning, followed by gradual descent towards evening (norm: 5 -25 nmol/l for morning and afternoon values; ≤ 1 for

the night value)(22). Saliva samples were therefore collected three times a day: morning: between 6 – 8 am, 30 min after waking, before breakfast and before brushing teeth; mid-day: between 12 – 2pm before meal; evening: between 6 -9 pm, just before going to bed and before brushing teeth. Children were asked to rinse their mouth with clear water 10 minutes before collection and then not to eat, chew or drink anything else prior to spitting directly into the collection tube (minimal volume of 1ml requested). Samples were stored in a freezer for up to 48 hours and sent to our department by post. The samples were then stored in the freezer at -20°C and batches of around 120 delivered to the biochemistry laboratory for an analysis. Mucins were precipitated from saliva by a freeze thaw cycle followed by centrifugation. Cortisol was measured in an aliquot of the clear supernatant by a radioimmunoassay using ¹²⁵I-cortisol as tracer (Patel, Shaw, McIntyre, McGarry, & Wallace 2004).

Cortisol measures were averaged over the two daily readings for each of the subjects. Values were highly skewed and a logarithmic transformation came closest to normalising the data, resulting in a fairly symmetric distribution with descriptive means and medians being almost identical. A repeated measures analysis of variance was performed on the log transformed data and the model included a time by group interaction.

3. Results

3.1 Sample description

As can be seen in Table 1, the adopted children were a typically “late placed” sample, had all experienced maltreatment and had significantly higher symptom scores for both RAD and other forms of psychopathology.

Insert Table 1 about here

3.2 Cortisol Secretion

A repeated measures analysis of variances was performed on the log transformed data. There was strong evidence of a difference between the time points ($p < 0.001$) and also between the groups ($p = 0.047$) although all cortisol results were within physiologically normal limits (see Figure 1). The time by group interaction was not significant ($p = 0.868$) demonstrating that, despite overall differences in secretion, there was a similar diurnal pattern of secretion over time in adopted children compared to controls.

Insert Figure 1 about here

3.3 Association between cortisol secretion and behaviour

As expected, both SDQ and RPQ scores were significantly higher in the adopted group compared to the comparison group (see Table 1). There was no correlation between cortisol

secretion in the morning, afternoon or evening and symptom scores for general psychopathology (SDQ) or Reactive Attachment Disorder (RPQ): Spearman's Rank Correlations ranged from $-.008$ ($p = .96$) to $-.193$; ($p = .17$).

4. Discussion

4.1 Overview

Primary-school aged children with RAD symptoms and a history of early maltreatment have a similar cortisol profile compared to controls, but with slightly lower levels of secretion. We did not detect any association between these small differences in cortisol secretion and social or behavioural difficulties. These small differences in secretion suggest the possibility that other aspects of the stress response system are implicated in these children's social/emotional difficulties and this warrants further investigation. Various genetic and environmental factors affect the stress response system during development (Gunnar 2007; Hunter, Minnis, & Wilson 2011) and it may be that, by middle childhood, cortisol secretion has become better regulated in the group that experienced early childhood maltreatment as a result of nurturing care by adoptive parents. It is also possible that there is a sensitive period for cortisol action in altering behaviour, and this period ends before primary school age, so HPA function normalises but with persistent effects on mental health.

4.2 Limitations and directions for future research

Our sample size was modest ($n = 66$) although adequate according to a priori power calculations (Dozier, Manni, Gordon, Peloso, Gunnar, Stovall-McClough, Eldreth, & Levine 2006). Only a modest proportion of our target population of typically developing children took part in the

study, but we do not regard this as a major limitation as we set out to recruit a group of typically developing children, age and gender matched with our maltreated sample, and did not intend to recruit a sample representative of the general population. It would have been interesting to compare our sample of children with RAD symptoms with a sample of similarly maltreated children who did not have such symptoms, but as we did not have an estimate of the magnitude of differences in cortisol secretion in school-age children it would have been premature to design such a study. This would be an important next step and would demonstrate whether the reduced cortisol secretion is associated with the diagnosis of RAD, or is simply a broader index of maltreatment. We do not know whether and how the stress response system was altered during the severe maltreatment period in the early infancy/childhoods of these adopted children as their cortisol levels were not measured at that time and we did not have the opportunity to follow these children from infancy. Longitudinal studies following maltreated children from infancy will be required to fully understand the developmental trajectory of the stress response system in the context of abuse and neglect. We were only able to test the basal activity of the HPA axis and not HPA reactivity to stressors: future research should encompass longitudinal study of the HPA axis in maltreated children from infancy as well as studies of cortisol reactivity to stress.

4.3 Conclusion

Cortisol secretion, in this sample of maltreated adopted children, was significantly lower than in comparison children but had a similar profile and was not associated with psychopathology.

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Table 1 – comparison of demographics, maltreatment history and symptom scores between adopted children and comparison children

Variable	Adopted children (n = 34)	Comparison children (n = 32)		
Gender (%males)	51.5%	43.1%		
	Mean (SD)	Mean (SD)		
Age (years)	9.4(1.8)	8.7(2.4)		
Age of adoption (in months)	62.9 (25.3)	N/A		
Months with adoptive family	51.3 (26.8)	N/A		
Birth parent alcohol misuse	74%	N/A		
Birth parent drug misuse	62%	N/A		
Physical and/or emotional neglect by birth parent	100%	N/A		
History of physical abuse in birth family	49%	N/A		
History of sexual abuse in birth family	20%	N/A		
			Statistical Test	
Total Difficulties Score on parent SDQ	20.1 (7.8)	7.59 (6.03)	6.83	<.0001
Parent total RPQ score	9.2 (7.1)	.7 (1.8)	5.84	<.0001

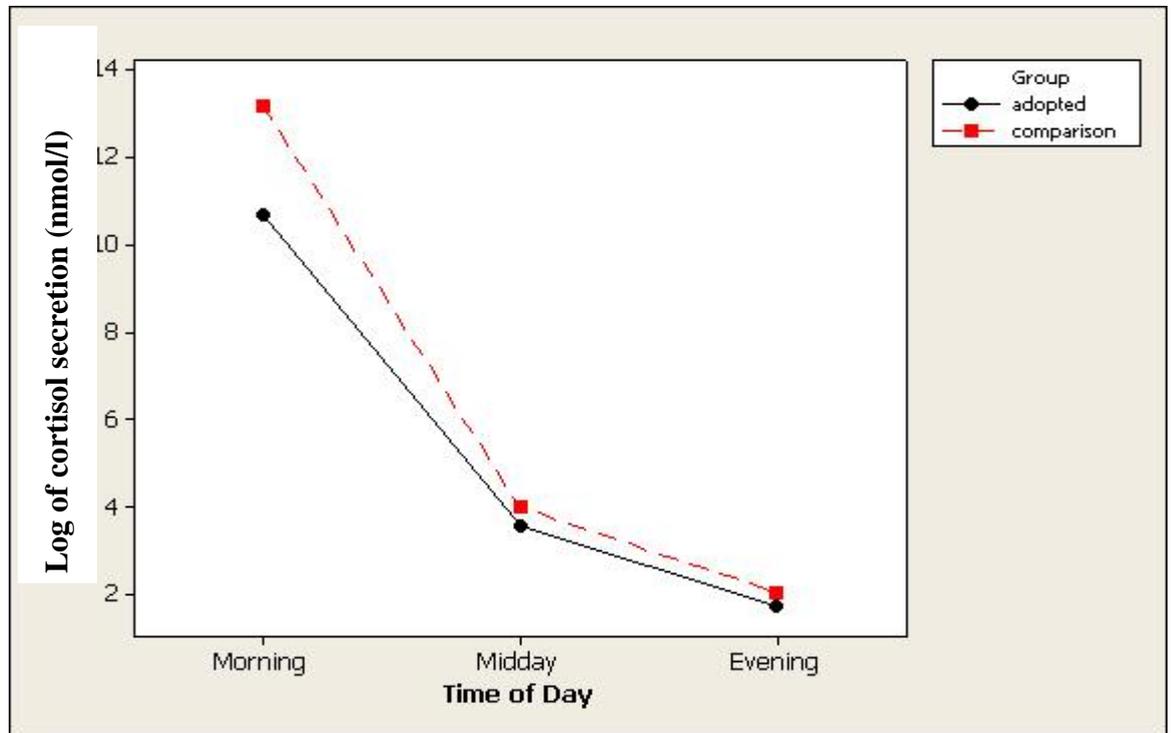


Figure 1- diurnal secretion of cortisol in adopted children and comparisons