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Symptoms of attention deficit hyperactivity disorder in children are associated with cortisol responses to psychosocial stress but not with daily cortisol levels

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A R T I C L E I N F O

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We tested associations of diurnal hypothalamic-pituitary adrenal axis (HPAA) activity and its response to stress with behavioral symptoms of Attention Deficit Hyperactivity Disorder (ADHD) among 272 eight-year-old children. We measured their diurnal salivary cortisol and salivary cortisol responses to the Trier Social Stress Test for Children (TSST-C). Mothers rated their child's behavior with the ADHD-IV Rating Scale and the Child Behavior Checklist (CBCL). There were no significant associations between ADHD symptoms and diurnal cortisol concentrations. The boys with predominantly inattentive symptoms of ADHD (ADHD-I; scores at or above the 90th percentile) had 26% lower mean salivary cortisol levels during the TSST-C than the boys with scores below this cutoff. In the girls with symptoms of ADHD-I, initial salivary cortisol levels prior to the TSST-C were higher and fell more rapidly during and after the TSST-C, which was not seen in the remaining girls ($P = 0.007$ for interaction 'ADHD-I $\times$ sampling time'). Controlling for Oppositional Defiant Disorder/Conduct Disorder and Anxiety Disorder or excluding children with these comorbid problems did not substantially affect these findings. We conclude that the boys and the girls with behavioral symptoms of ADHD-I had reduced HPAA responsiveness to stress, which is also seen in people after traumatic events or with chronic stress. Their diurnal cortisol rhythm was not affected. Thus, ADHD-I may be associated with dysregulation of the HPAA or reduced engagement with stressful stimuli.

1. Introduction

It has been argued that poor response inhibition, tied to hypoactive function of the hypothalamic-pituitary-adrenocortical axis (HPAA), is a central feature in attention deficit hyperactivity disorder (ADHD). Yet, studies testing the HPAA function in children with sub-clinical symptoms or clinical diagnosis of ADHD, have produced inconsistent results.

With regard to diurnal salivary cortisol, a study (Sondeijker et al., 2007) in over 1700 children found no associations between self- and parent-rated ADHD symptoms and salivary cortisol levels measured upon awakening, and a modest positive association between self-rated (but not parent-rated) ADHD symptoms and salivary cortisol levels in the evening. A small-scale kindergarten study (Hatzinger et al., 2007) found that boys, but not girls, who were rated high on hyperactivity and impulsivity by their parents, exhibited higher levels of salivary cortisol upon awakening ($N = 102$). Salivary cortisol in the evening was not measured. In contrast, salivary cortisol levels upon awakening were lower in 40 clinic-referred children aged from 7 to 14 years who were rated high in in attention/overactivity by their parents, teachers, and at

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the clinic (Scerbo and Kolko, 1994). In addition to the above studies, there exist studies that have found no significant differences of diurnal HPAA function in children with ADHD compared to controls (Freitag et al., 2009; Hastings et al., 2009).

With regard to salivary cortisol responses to stress, Randazzo et al. (Randazzo et al., 2008) showed in a community-based sample ($N = 39$) of 9–13 year-olds that children with higher inattentive ADHD (ADHD-I) scores had lower salivary cortisol responses to the Trier Social Stress Test for Children (TSST-C). However, this effect was restricted to children with the most severe symptoms. Van West (van West et al., 2009) showed that in comparison with 6-12-year-old healthy controls, children with ADHD combined type (ADHD-C) had lower, and children with ADHD-I had higher cortisol responses to stress induced by a public speaking task ($N = 100$). Finally, King et al. (King et al., 1998) reported that in comparison with 6–8 year-old children with transient ADHD symptoms, children with persistent ADHD over a one year period had lower salivary cortisol responses to stress induced by psychological tests assessing academic performance ($N = 20$). One study ($N = 95$) did not find significant differences in HPA function between children with ADHD and controls in response to stress induced by a video game (Snoek et al., 2004).

Interpretation of this evidence is complicated by the facts that (a) there is considerable variation in the circumstances during which cortisol was measured, (b) results vary according to whether predominantly inattentive and hyperactive children were tested separately, (c) most studies have been small with insufficient power to detect small to moderate effects and, most importantly, (d) disparate stressors have been used that have been shown to vary markedly in their capacity to stimulate the HPAA (Dickerson and Kemeny, 2004). Only one (Randazzo et al., 2008) previous study used the TSST-C (Kudielka et al., 2004), a standardized stress protocol with the best published record for consistent stimulation of HPAA responses (Dickerson and Kemeny, 2004).

Because existing evidence is conflicting, we tested the associations between parent-rated symptoms of ADHD, diurnal salivary cortisol pattern and salivary cortisol responses to the TSST-C in 272 eight-year-old children. Furthermore, following studies that have reported that HPAA activity in ADHD children may be confounded by psychiatric problems (Hastings et al., 2009; Snoek et al., 2004), we controlled the analyses for symptoms of Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), and Anxiety Disorder. We also repeated our analyses, excluding subjects with these symptoms, to test their impact on our findings.

2. Methods

2.1. Participants

Children were recruited from an urban cohort of 1049 infants born in a level two maternity hospital between March and November 1998 in Helsinki, Finland (Räikkönen et al., 2010a; Strandberg et al., 2001). In 2006, 413 children and their parents still living close to or in Helsinki were invited to participate in a follow-up study (Pesonen et al., 2009; Räikkönen et al., 2010a, 2009, 2010b; Strandberg et al., 2001) and 321 (77.7%) did so ($M = 8.1$, $SD = 0.3$ years). Non-participation did not relate to child's gender, birth date, weight, length, head circumference or body mass index (BMI, kg/m^2) at birth, birth order, mode of delivery, mother's gestational diabetes, gestational hypertension, preeclampsia, age, height, weight, BMI, occupational status or blood pressures at delivery, maternal licorice use (Räikkönen et al., 2010a, 2009) or alcohol consumption or stress during pregnancy (P values > 0.10). Non-participation was related to more frequent maternal smoking during pregnancy ($P = 0.02$). Of the 321 participants in the follow-up study, 289 underwent diurnal cortisol sampling and 290 completed the TSST-C. Of these, 274 children had valid data with no more than one cortisol value missing and all ADHD data available. Two of these children were excluded due to diagnosed developmental delay. Altogether, we obtained complete data on mother-rated ADHD symptoms and diurnal cortisol for 272 (48.6% male), and ADHD symptoms and TSST-C cortisol for 271 (48.6% male) children.

2.2. ADHD symptoms

Symptoms of ADHD were rated by mothers on the DuPaul ADHD Rating Scale IV (DuPaul et al., 1998). The scale consists of 18 items directly adapted from the ADHD symptoms list in the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition [DSM-IV]). Mothers selected a response for each item that best described the frequency of the specific behavior over the past 6 months. The four-point scale ranged from 'never or rarely' (scored as 0) to very often' (scored as 3). A higher mean score indicated greater ADHD-related behavior. Previous studies using exploratory factor analysis have revealed two factors in the scale, ADHD-I and ADHD-H (DuPaul et al., 1998) which correspond to the DSM-IV categorization into inattentive and hyperactive subtypes of ADHD (APA, 1994). Therefore, in addition to the combined ADHD-C, two subscale scores representing these two factors were calculated. Previous studies have demonstrated adequate levels of test–retest reliability, internal consistency, and criterion validity for the two subscales as well as for the total rating score (DuPaul, 1991; DuPaul et al., 1998). In the current study the reliabilities (Cronbach's α) for the ADHD-C, ADHD-I and ADHD-H were 0.91, 0.86, and 0.85. As Table 1 shows, the boys scored significantly higher in all ADHD scales. Therefore, the $\geq$90th percentiles of ADHD symptoms in each scale were computed separately for the girls and boys; the 90th percentile cutoff scores were 7.9 and 13.5 for ADHD-I, and 12.0 and 16.0 for ADHD-H, for the girls and boys respectively. Children scoring above the $\geq$90th percentile for both ADHD-I and ADHD-H scales were categorized as having ADHD-C. Since there were only 7 (5.4%) boys

Table 1
Descriptive statistics of the study variables.

	Boys	Girls	*P*-value
	$N = 143$	$N = 129$	
	Mean (SD)	Mean (SD)	
Child			
Age (years)	8.2 (0.3)	8.1 (0.3)	0.07
Weight (kg)	29.0 (5.6)	28.5 (5.2)	0.42
Height (cm)	131.9 (6.0)	130.4 (5.2)	0.03
BMI (kg/cm^2)	16.5 (2.2)	16.6 (2.3)	0.69
ADHD scores			
Inattentive	7.8 (4.4)	5.3 (3.3)	<0.001
Hyperactive	9.0 (5.1)	7.0 (3.7)	<0.001
Total	16.8 (8.7)	12.3 (6.5)	<0.001
Diurnal cortisol (nmol/liter)			
Upon awakening	7.7 (1.6)	8.9 (1.6)	0.02
Peak after awakening	10.0 (1.6)	11.5 (1.7)	0.01
Awakening response	1.3 (1.6)	1.3 (1.7)	0.90
Awakening AUCg	7.8 (1.6)	8.9 (1.6)	0.02
Awakening AUCg increment	1.1 (1.4)	1.1 (1.5)	0.93
Nadir	0.8 (2.5)	0.8 (2.4)	0.48
TSST-C (nmol/liter)			
Arrival	3.7 (1.8)	3.0 (1.8)	0.13
Baseline	2.3 (2.0)	2.5 (2.0)	0.14
Peak after stress	3.5 (2.0)	4.6 (2.4)	0.005
Increment	1.6 (1.7)	1.8 (2.3)	0.07
AUCg	2.4 (1.8)	3.0 (2.0)	0.005
AUCg increment	1.0 (1.5)	1.2 (1.9)	0.15