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ORIGINAL CONTRIBUTION

Differences in hypothalamic–pituitary–adrenal axis functioning among children with ADHD predominantly inattentive and combined types

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Abstract Some evidence suggests that the HPA axis may be dysfunctional in children with attention-deficit/hyperactivity disorder (ADHD). The aim of this study was to investigate whether a different pattern of HPA axis activity is found between the inattentive (I) and combined (C) subtypes of ADHD, in comparison with healthy control children. A total of 100 prepubertal subjects [52 children with ADHD combined type (ADHD-C), 23 children with ADHD predominantly inattentive type (ADHD-I), and 25 healthy control subjects] were studied. The effects of stress were studied by comparing cortisol responses to a psychosocial stressor, consisting of a public speaking task. Children with ADHD-I showed an elevated cortisol response to the psychosocial stressor, in contrast to children with ADHD-C who showed a blunted cortisol response to the psychosocial stressor. When a distinction was made between responders and non-responders (a subject was classified as a responder when there was an increase in cortisol reactivity), hyperactivity symptoms were clearly related to a lower cortisol reactivity to stress. The results indicate that a low-cortisol responsivity to stress may be a neurobiological marker for children with ADHD-C, but not for those with ADHD-I. Directions for future research and clinical implications are discussed.

Keywords ADHD · Children · Cortisol · HPA axis · Stress

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that begins early in childhood and is characterized by three main symptoms: inattention, hyperactivity, and impulsivity. The prevalence of ADHD in school-aged children is approximately 3–7% [4]. Although the rate of ADHD declines with age, at least half the children with the disorder will exhibit symptoms in adulthood [8]. ADHD is accompanied by academic underachievement, substance abuse, conduct problems, anxiety, depression, marital problems, and occupational adjustment [9, 10].

According to Gray's motivational theory [23–26] three interdependent brain systems govern behavior: the fight/flight system, the reward or behavioral activation system (BAS) and the behavioral inhibition system (BIS). The BAS and BIS have opposite effects relative to each other; an imbalance in BIS/BAS levels can result in the emergence of psychopathology. When BAS functioning has the upper hand, either approach or active avoidance results. When BIS functioning predominates, passive avoidance is likely. Some theorists have argued that dysfunction of the BIS has major roles in the mechanism of ADHD [6, 51, 56, 60]. Dysfunction of the BIS results in secondary deficits of working memory, self regulation of affect, internalization of speech and reconstitution like goal-directed behavior [6]. Activation of the BIS results in endocrinological

responses, including elevation of the level of cortisol [59]. If one of the core deficits of ADHD is the dysfunctional BIS, abnormality in hypothalamic–pituitary–adrenal (HPA) axis activity should be observed in patients with ADHD. An inference is also drawn from the clinical features that the HPA axis, which is involved in emotion, learning, and attention, may be impaired in children with ADHD.

Most studies in children with disruptive behavior disorders (DBD) have focused on oppositional defiant disorder (ODD) and conduct disorder (CD). However, both in clinical [21, 39, 41] and in general population studies [20, 31, 64, 70], there is sufficient evidence to assume that ADHD and ODD/CD are independent disorders with different pathophysiology. It is therefore important to distinguish between disruptive children (i.e., those with ODD or CD), and children with ADHD alone when investigating HPA axis reactivity in children with externalizing behavior problems.

Up to now only a few researchers investigated the role of the HPA axis in clinical samples of children with ADHD. Kaneko et al. [32] examined HPA axis functioning in 30 children with ADHD by measuring the diurnal variation and response to the dexamethasone suppression test (DST). They found a normal diurnal salivary cortisol rhythm in only 43% of the ADHD children and DST suppression in 47% of the ADHD children. Moreover, a positive association was reported between hyperactivity and abnormal diurnal rhythm and nonsuppression to the DST [32]. Schulz et al. [63] found no inverse relationship between cortisol secretion and aggressive behavior in boys with ADHD. In a study of King et al. [35], the cortisol levels of patients with ADHD, who retained their diagnosis over the first year of the study, showed a blunted response to stress compared to those that no longer retained the disorder. They suggested that an impaired response to stress might be a marker for the more developmentally persistent form of the disorder. Kariyawasam et al. [33] found lower cortisol levels in 32 children with comorbid ADHD and ODD; this reduction was restricted to the subgroup of patients not prescribed stimulant medication. Hong et al. [29] investigated HPA axis functioning in children with ADHD after a computerized continuous performance test. They suggested that the blunted HPA axis response to stress was related to the impulsivity in children with ADHD.

Although previous studies reported that some patients with ADHD have dysfunctional HPA axis reactivity, no studies investigated the stress response after a psychosocial stress test. Moreover, small sample sizes and other methodological difficulties (e.g., no classification in subtypes) are a profound limitation in the previous studies which examined HPA axis functioning in ADHD children. Furthermore, these studies assumed that ADHD is neurobiologically homogeneous, not taking into account the various subtypes.

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [4] ADHD can be divided into three subtypes: ADHD predominantly inattentive subtype (ADHD-I), ADHD predominantly hyperactive/impulsive subtype (ADHD-H), and ADHD combined subtype (ADHD-C). The emphasis has shifted from a one-dimensional conceptualization to a model consisting of two factors: hyperactivity/impulsiveness and inattention. In the current categorical clinical view, these three subtypes belong to the same diagnostic entity. However, some researchers claim that the inattentive subtype is a distinct disorder and not a subtype of ADHD [5, 7, 16, 48]. More specifically, the three subtypes are different from each other in inattention symptoms, associated features, demographics, and responsiveness to stimulant medication [13, 18, 22, 54]. Nonetheless, the distinctiveness of the ADHD subtypes on neurobiological measures is not clear-cut. Therefore, the aim of the current study is to investigate HPA axis reactivity to a psychosocial stress test in prepubertal children with ADHD subtypes and in healthy control children. Our primary hypothesis was that children with ADHD-C would show cortisol hyporeactivity during psychosocial stress, relative to ADHD-I subjects and healthy control individuals.

Methods

Subjects

Seventy-five children, of age between 6 and 12 years, with ADHD, recruited from the psychiatric outpatient's clinic at the University Center of Child and Adolescent Psychiatry in Antwerp, were the subjects of this study. Parent ratings of behavior were ascertained using the Child Behavior Checklist (CBCL) [2]. Teacher ratings of behavior were obtained using the Teacher Report Form (TRF) [3]. In addition, the Kiddie-SADS-Present and Lifetime Version 1.0 with supplement (K-SADS-PL), a semistructured DSM-IV based psychiatric interview, was administered to children and parents [34, 58]. This semistructured interview has been used extensively to make diagnostic decisions based on DSM criteria and has been validated with children aged 6–17. The interview was first administered to the parent alone, who rates the child's symptoms (current and most severe past). The same clinician then administers the identical interview to the child alone, adjusted to the developmental level of the child. After the child interview, a third pair of ratings is made which represents the clinician's consensus of summary severity scores for each symptom on the basis of all available information (parent, child, school).

When there were little discrepancies, the rater used his/her best clinical judgement. When there were major discrepancies in the child and parent reports, they were interviewed together to clarify their views. All subjects met DSM-IV criteria for ADHD based on psychological assessment and psychiatric interviews with the child, interviews with the parents including discussion of the child's developmental history, and the administration of parent and child responses to the K-SADS. Interviews and diagnoses were performed by trained child and adolescent psychiatrists. When consensus was reached between two child psychiatrists (DvW, DD) on the basis of information of the different informants, the individuals were assigned to one of the diagnostic groups. Severity of symptoms was assessed with the ADHD rating scale (AVL) [62]. AVL is a questionnaire consisting of 18 items and three subscales: inattention, hyperactivity, and impulsivity. Behavioral symptoms were evaluated using a five-point Likert-type scale: 0 = not; 1 = occasionally (or incidentally); 2 = regularly (or monthly); 3 = often (or weekly); 4 = very often (or daily) and was scored by the clinician. The total score is computed as the sum of the scores on each of the 18 items. In addition to the total score, the scores from the inattention, hyperactivity, and impulsivity subscales were computed. All subscales have good internal consistency (Cronbach's alpha = 0.89–0.93), inter-rater reliability (Kappa statistic = 0.83–0.92), test–retest reliability (Intra-class correlation coefficient = 0.92–0.95), and construct and discriminant validity. Fifty-two children met criteria for the ADHD-C subtype and 23 children met criteria for the ADHD-I subtype. No child met diagnostic criteria for the ADHD-H subtype. Although there is a high rate of comorbid disorders among patients with ADHD, all patients with a comorbid diagnosis in addition to ADHD were excluded to achieve a more homogenous sample. Comorbid symptomatology was described from a dimensional point of view using CBCL and TRF scores. However, ten (19%) children with the ADHD-C subtype had a learning disability (10% reading and 15% math disability) compared to 7 (26%) children with the ADHD-I subtype (13% reading and 22% math disability). None of the ADHD subjects or healthy controls was on medication.

Twenty-five control subjects 6–12 years old were recruited from grades 1 to 6 of regular local elementary schools and screened for psychiatric problems, using the CBCL filled out by the parents. None of the children had any symptom cluster score above the 98th percentile and none had a CBCL attention problem score above the 84th percentile.

All children with a Full-Scale IQ, as measured by the Wechsler Intelligence Scale for Children-Revised (WISC-R) [72] of less than 85 and children with a history of any neurologic or endocrinologic disorder were excluded from this study. All children were physically well on the day of testing, and none of them had signs of current infection. None of the children had recent tooth loss and children were asked to refrain from eating and drinking for at least 1 h before the beginning of the test session (since blood or food in saliva are known to alter cortisol values).

Stage of pubertal development was assessed in the parent interview using schematic drawings of secondary sex characteristics associated with the five standard Tanner stages of pubertal development (score range: 1–5) [43]. Subjects with a score higher than 2 were excluded from the study. As a second measure of physical development, the body mass index (BMI) was computed. Socioeconomic status (SES) was measured using the Hollingshead Four-Factor Index of Social Status [28]. This measure generates an SES score for each family based upon maternal and paternal education and occupation. Pubertal development [27, 47], SES [42] and body composition [71] are all associated with various kinds of psychopathology, which makes them candidate confounders provided they are also related to individual differences in the cortisol measures.

The study was approved by the Medical Ethical Committee of the University of Antwerp, and parents gave written informed consent after investigators explained the purpose and course of the study.

Study design

The psychosocial stress test consisted of a public speaking task (PST); it is well demonstrated that this stressor is effective in both children and adults [17, 38]. The PST was imbedded in a 135-min test session, consisting of an initial resting period (60 min), the PST (15 min) and a post-test resting period (60 min) (Fig. 1). For this population, we used an adapted version of the Trier Social Stress Test (TSTT) [36], mainly by shortening its duration and increasing its relevance to participants. This procedure has been described in detail elsewhere [69]. For each subject, seven saliva samples were collected for measurement of the cortisol concentration. The first saliva sample was taken during the initial resting period, 30 min after the start of the test session ($t = -30$). The second sample was taken after 60 min, at the end of the initial rest period just before the public speaking task ($t = 0$). Saliva was also collected right after the 10-min preparation period ($t = 10$) and after the 5-min talk ($t = 15$). During the second rest period of an hour, a further three saliva samples were collected at 20-min intervals ($t = 35, 55, 75$) (Fig. 1).

Saliva assay

All stress tests were carried out in the afternoon, when the HPA-activity is low and stable and therefore more

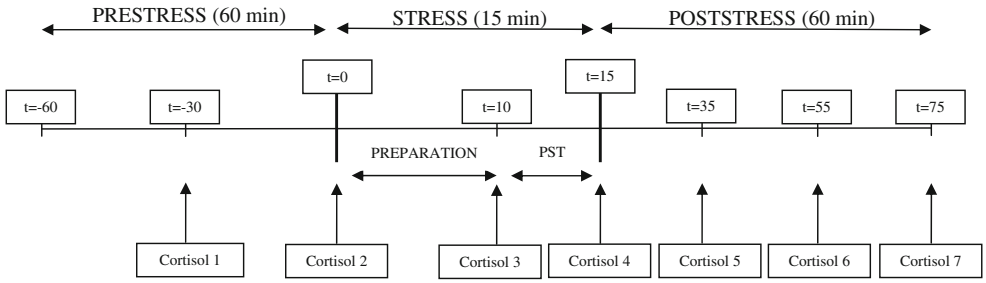

Fig. 1 Study design

susceptible to stimulation [37]. Cortisol can be measured from saliva in a reliable and stress-free way [37], and reflects the biologically active (unbound) fraction of serum cortisol [1]. After the start of an effective stressor, salivary cortisol increases can be observed 15–20 min later [37]. Subjects collected saliva by holding a dental roll in the mouth and chewing on for 30–90 s until they felt that the swab was soaked with saliva. The saturated roll was placed in Salivette (Sarstedt, Nümbrecht, Germany) collection devices and stored at room temperature until completion of the session. Samples were then stored at −20°C until biochemical analysis. Salivettes were centrifuged at 3,000 rpm for 5 min, which resulted in a clear supernatant of low viscosity. Cortisol analyses were performed in duplicate by direct radio-immunoassay on 100 µl of salivary free cortisol samples in competition, with a HPLC preparation of cortisol-3CMO coupled with 2-[125I]odohistamine as tracer, for specific antibodies raised against cortisol-3-CMO-BSA [66]. The lower detection limit of the assay was 12 ng/dl, with a mean intra-assay coefficient of variation of 4.3% ($n = 10$). The coefficients of variation for between-run assays are 12.26 and 9.38% (at concentrations of 34.39 ± 4.22 and 410.59 ± 38.53 ng/dl, respectively) ($n = 30$). Each sample was processed in duplicate.

Statistics

Because cortisol values were positively skewed, they were transformed to the natural logarithm scale to render the distributions more symmetrical and normally distributed as tested with a Kolmogorov–Smirnov analysis. All other variables were normally distributed. Differences in gender ratio between groups were tested by using chi-square analysis. One-factor analyses of variance (ANOVAs) were used to assess the effect of diagnostic group on age, Tanner stage, BMI, SES, IQ, clinical symptom cluster scores (AVL, CBCL, TRF), and cortisol variables. Repeated-measures ANOVA with "group" (ADHD-I vs. ADHD-C vs. NC) as between-subjects factor and "time" as within-subjects factor were used to assess changes in levels of log (cortisol). Huynh–Feldt corrections were used where the assumption of sphericity was violated. Main effects of "time" and interactions between "time" and "group" were further analyzed by conducting difference contrast tests, i.e., comparing the values of a sample at a certain time point to all previous ones. All post hoc analyses were corrected with the Bonferroni method for multiple comparisons. As a specific measure of responsivity to the stressor, four additional cortisol variables were computed: basal, AUCtot, AUCnet, and Deltapeak. Basal represents the mean free cortisol concentration over the two time points before the PST. Deltapeak is the maximum free cortisol concentration after the PST corrected for basal. The area under the curve (AUC) was calculated to incorporate the cortisol concentrations at five time points after the initial resting period according to the trapezoid method described by Pruessner et al. [55]. AUCtot is the total area under the curve and represents the total cortisol output. AUCnet is identical to AUCtot, except for the removal of the area between the ground and Basal. When a negative value was the result for this measure, this would typically be set to zero to avoid a negative area measure and to denote the lack of an increase for this subject [55]. Because this results in a potential loss of information about the strength of the decrease, we continued the statistical analysis including negative values. The results were therefore "indices of decrease" rather than an area [55]. Relationships between psychometric scores and stress reactivity (AUC_net) were examined by using Pearson correlation coefficients. Finally, a logistic regression model was applied to the data to study the possible explanatory variables for change in cortisol. All tests were two-tailed and statistical significance was set at $P \leq 0.05$. Following Cohen's guidelines [15], r values of 0.10, 0.30, and 0.50 (correlation), f values of 0.10, 0.25, and 0.40 (ANOVA), and f^2 values of 0.02, 0.15, and 0.35 (Repeated-measures ANOVA) are generally used as thresholds to define small, medium, and large effects, respectively. For statistical analysis, we used SPSS for Windows, version 15.0.

Results

Performance

All children in the study managed to give a talk during the PST. The number of interruptions was not significant different between diagnostic groups: mean number of interruptions were 3.5 ± 3.1 for the ADHD-C subtype, 4.0 ± 2.8 for the ADHD-I subtype, and 2.7 ± 2.0 for the group of control children. Performance on the PST was not correlated with the patient's IQ.

Demographic and psychometric characteristics

Demographic characteristics of ADHD children and healthy controls are shown in Table 1. There was no significant difference between ADHD-C subtype versus ADHD-I subtype versus NC group status in any of the demographic variables. Table 2 shows ADHD symptom scores and *T* scores of CBCL, and TRF. The ADHD-C subtype differed significantly from the ADHD-I subtype and normal controls in their mean AVL Total, hyperactivity, and impulsivity scores. Inattention scores were not different between the ADHD-C subtype and the ADHD-I subtype. Both groups of ADHD children (combined and predominantly inattentive type) differed significantly from the normal controls in all their mean CBCL and TRF scores (except TRF scores for somatic complaints and delinquency). The ADHD-C subtype had significantly higher scores compared to the ADHD-I subtype and the normal controls in their mean CBCL scores for social problems, delinquency, aggressive behavior, externalizing and total problem behavior and TRF scores for delinquency, aggressive behavior, and externalizing problem behavior. The ADHD-I subtype had significantly higher scores compared to the ADHD-C subtype and the normal controls in their mean CBCL scores for withdrawn and somatic complaints, and TRF scores for withdrawn and internalizing problem behavior. The ADHD and NC group could not be differentiated on the basis of their scores on the TRF somatic problems scale.

Cortisol

A graphic representation of mean salivary log (cortisol) levels by subgroup is shown in Fig. 2. Repeated-measures ANOVA revealed a significant main effect of time for salivary cortisol levels [$F = 82.68$, $P < 0.001$; effect size $f^2 = 0.46$]. Difference contrasts revealed that this was mainly attributable to significant effects for samples 10 min after preparation period (sample 3) [$F = 32.20$, $P < 0.001$], immediately (sample 4) [$F = 84.59$, $P < 0.001$], 20 min (sample 5) [$F = 57.43$, $P < 0.001$] and 60 min (sample 7) [$F = 223.36$, $P < 0.001$] after the talk. Furthermore, a significant main effect of group [$F = 14.54$, $P < 0.001$; effect size $f^2 = 0.23$] and a significant group by time interaction was found [$F = 21.91$, $P < 0.001$; effect size $f^2 = 0.31$]. Difference contrast tests, comparing each sample with all previous ones, revealed that this was because of significant differences for samples 10 min after preparation period (sample 3) [$F = 9.43$, $P < 0.001$], 20 min (sample 5) [$F = 32.82$, $P < 0.001$], 40 min (sample 6) [$F = 46.09$, $P < 0.001$] and 60 min (sample 7) [$F = 17.78$, $P < 0.001$] after the talk.

Table 3 lists the four cortisol variables (basal, Deltapeak, AUCtot and AUCnet) with the standard deviations in all three samples. An ANOVA on HPA reactivity to the stressor, by subgroup (ADHD-I vs. ADHD-C vs. NC), revealed a significant difference between groups for basal [$F = 3.28$, $P = 0.04$; $f = 0.06$], deltapeak [$F = 13.98$,

Table 1 Demographic characteristics of patients with ADHD, predominantly inattentive subtype (ADHD-I), combined subtype (ADHD-C) and healthy controls. Mean values and standard deviations

Measure	ADHD-C ($n = 52$)		ADHD-I ($n = 23$)		Control ($n = 25$)		F (2, 97)
	Mean	SD	Mean	SD	Mean	SD	
Age	8.52	1.84	8.65	1.47	8.88	1.54	0.39
Gender (M/F)	45/7		18/5		20/5		$\chi^2_{2,0.95} = 0.99$
Tanner stage	1.02	0.14	1.04	0.21	1.08	0.28	0.81
BMI	16.29	2.05	16.57	2.00	16.48	1.77	0.18
SES	39.92	7.14	43.30	7.59	42.40	5.66	2.31
TIQ	99.67	8.14	101.24	10.97	103.86	10.80	0.86
VIQ	100.40	9.72	101.04	9.87	103.62	13.69	0.53
PIQ	98.93	7.65	101.78	9.42	102.81	10.00	1.05

All test results were not significant

BMI body mass index, *SES* socioeconomic status, *TIQ* total intelligence quotient, *VIQ* verbal intelligence quotient, *PIQ* performance intelligence quotient

Table 2 Psychometric characteristics in patients with ADHD, predominantly inattentive subtype (ADHD-I), combined subtype (ADHD-C) and healthy controls

		ADHD-C ($n = 52$)	ADHD-I ($n = 23$)	Control ($n = 25$)	F (2, 97)	Contrasts[a]
AVL	Total	46.2 (12.4)	23.7 (7.2)	9.7 (5.4)	121.8**	ADHD-C > ADHD-I > NC
	Inattention	16.9 (4.3)	15.7 (4.1)	3.3 (2.2)	110.4**	ADHD-C, ADHD-I > NC
	Hyperactivity	14.4 (6.7)	4.3 (4.5)	3.9 (4.4)	40.8**	ADHD-C > ADHD-I, NC
	Impulsivity	14.9 (6.4)	3.7 (3.3)	2.5 (2.3)	69.5**	ADHD-C > ADHD, NC
CBCL	Withdrawn withdrawal	61.3 (6.6)	65.5 (4.3)	50.9 (2.3)	50.8**	ADHD-I > ADHD-C > NC
	Somatic complaints	57.4 (6.5)	61.4 (6.8)	52.3 (4.2)	13.5**	ADHD-I > ADHD-C > NC
	Anxious/depressed	63.3 (5.2)	64.1 (5.3)	51.6 (4.1)	53.7**	ADHD-C, ADHD-I > NC
	Social problems	62.1 (5.9)	57.1 (3.0)	50.7 (2.1)	51.3**	ADHD-C > ADHD-I > NC
	Thought problems	60.8 (8.5)	59.9 (7.3)	50.4 (2.0)	18.9**	ADHD-C, ADHD-I > NC
	Attention problems	71.0 (4.2)	70.0 (5.0)	52.8 (6.4)	119.8**	ADHD-C, ADHD-I > NC
	Delinquency	63.4 (1.8)	56.1 (6.4)	51.4 (3.7)	91.5**	ADHD-C > ADHD-I > NC
	Aggression	64.0 (2.8)	55.6 (5.6)	51.5 (4.5)	91.3**	ADHD-C > ADHD-I > NC
	Externalizing score	64.2 (2.0)	53.9 (6.0)	45.0 (8.7)	113.2**	ADHD-C > ADHD-I > NC
	Internalizing score	61.9 (4.0)	63.5 (2.2)	47.6 (7.3)	92.5**	ADHD-C, ADHD-I > NC
	Total problem score	64.2 (3.4)	59.0 (3.0)	45.6 (9.2)	100.0**	ADHD-C > ADHD-I > NC
TRF	Withdrawn	56.8 (8.4)	61.8 (6.2)	51.2 (2.9)	14.1**	ADHD-I > ADHD-C > NC
	Somatic complaints	54.3 (6.3)	52.3 (4.4)	51.6 (4.0)	2.5	–
	Anxious/depressed	57.6 (5.9)	59.8 (4.3)	50.7 (2.1)	24.2**	ADHD-C, ADHD-I > NC
	Social problems	61.4 (7.1)	59.5 (5.5)	50.5 (1.5)	30.0**	ADHD-C, ADHD-I > NC
	Thought problems	56.2 (8.1)	55.5 (7.9)	50.3 (1.2)	6.4*	ADHD-C, ADHD-I > NC
	Attention problems	65.0 (3.7)	64.0 (4.0)	50.6 (1.8)	160.4**	ADHD-C, ADHD-I > NC
	Delinquency	60.3 (4.0)	55.0 (2.3)	52.4 (4.7)	40.2**	ADHD-C > ADHD-I, NC
	Aggression	62.3 (3.4)	55.9 (2.1)	52.2 (3.5)	92.4**	ADHD-C > ADHD-I > NC
	Externalizing score	61.1 (2.8)	52.4 (7.7)	47.1 (6.1)	67.2**	ADHD-C > ADHD-I > NC
	Internalizing score	55.1 (4.2)	58.3 (5.2) (5.28.3)	42.6 (6.1)	72.2**	ADHD-I > ADHD-C > NC
	Total problem score	60.9 (4.4)	59.3 (3.0)	42.5 (7.1)	122.4**	ADHD-C, ADHD-I > NC

Mean values and standard deviations

[a] Bonferroni, $P < 0.05$; * $P < 0.01$; ** $P < 0.001$

$P < 0.001$; $f = 0.22$], AUCtot [$F = 24.52$, $P < 0.001$, $f = 0.34$], and AUCnet [$F = 36.40$, $P < 0.001$, $f = 0.44$]. Post hoc analysis showed significant differences between both the ADHD-I and control groups and the ADHD-C group on deltapeak ($P < 0.001$ and $P < 0.01$, respectively) and AUCtot (both $P < 0.001$). Furthermore, the ADHD-I group had significantly higher AUCnet levels compared with the ADHD-C group ($P < 0.001$) and the control group ($P < 0.01$); the control group had significantly higher basal levels of cortisol compared with the ADHD-C group ($P = 0.03$).

CBCL scores for delinquency ($r = -0.48$, $P < 0.001$), aggressive behavior ($r = -0.43$, $P < 0.001$), externalization problems ($r = -0.24$, $P = 0.02$), and total problems ($r = -0.26$, $P = 0.008$) were significantly and negatively correlated with AUC_net. CBCL, and TRF scores for social withdrawal ($r = 0.31$, $P = 0.002$ and $r = 0.26$, $P = 0.009$, respectively) were significantly and positively correlated with AUC_net. A trend for a negative correlation between TRF scores for Aggressive Behavior ($r = -0.18$, $P = 0.07$) and externalization problems ($r = -0.19$, $P = 0.06$), and AUC_net was also found. Moreover, hyperactivity ($r = -0.82$, $P < 0.001$) and impulsivity ($r = -0.82$, $P < 0.001$) scores were significantly and negatively correlated with AUC_net.

Finally, all subjects were divided into responders and non-responders in terms of the cortisol response to the psychosocial stress test in order to evaluate factors that may be responsible for response or non-response to the stressor. A subject was classified as a responder when there was an increase in cortisol reactivity (positive AUC_net value). By this criterion, 18 (35%) of 52 ADHD-C patients, 22 (96%) of 23 ADHD-I patients and 22 (88%) of 25 control subjects, were qualified as cortisol responders. There was no significant difference between responders versus non-responders in any of the demographic variables.

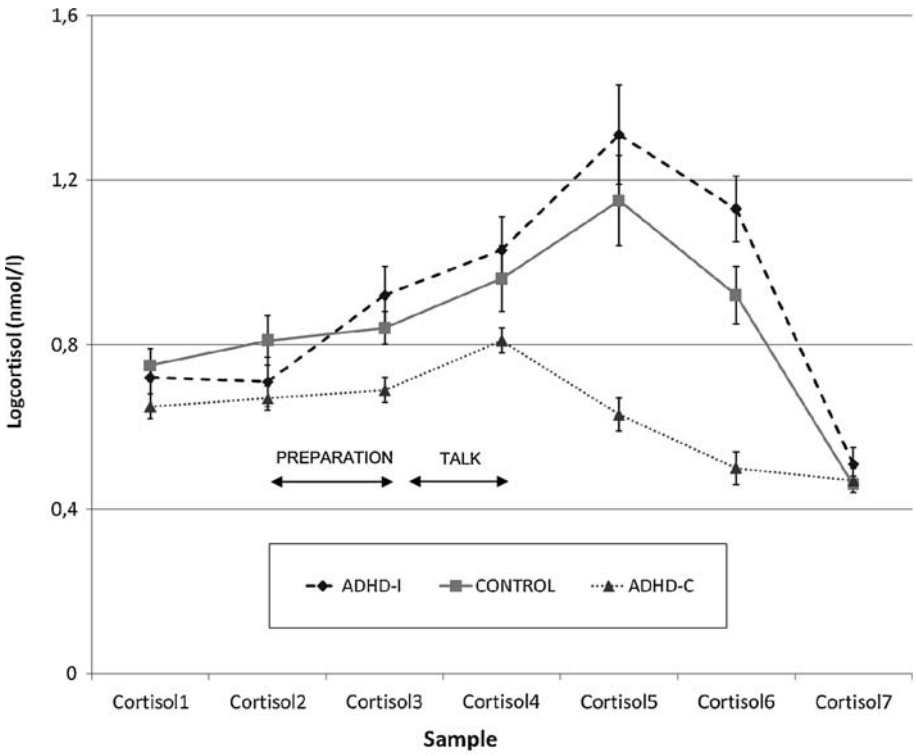

Fig. 2 Salivary cortisol responses to the psychosocial stress test in patients with ADHD, predominantly inattentive subtype (ADHD-I), combined subtype (ADHD-C) and healthy controls. Mean values and standard error scores are indicated

Table 3 Mean values of the four computed cortisol variables in patients with ADHD, predominantly inattentive subtype (ADHD-I), combined subtype (ADHD-C) and healthy controls

Measure	ADHD-C ($n = 52$)		ADHD-I ($n = 23$)		Control ($n = 25$)		F (2, 97)	Contrasts[a]
	Mean	SD	Mean	SD	Mean	SD		
Basal	0.66	0.13	0.72	0.24	0.78	0.26	3.28*	NC > ADHD-C
Deltapeak	0.26	0.15	0.54	0.28	0.41	0.26	13.98**	ADHD-I, NC > ADHD-C
AUCtot	28.78	8.60	50.93	19.21	44.25	16.31	24.52**	ADHD-I, NC > ADHD-C
AUCnet	−4.71	9.56	11.77	5.69	4.25	5.71	36.40**	ADHD-I > NC > ADHD-C

[a] Bonferroni, $P < 0.05$; * $P < 0.05$ ** $P < 0.001$

Psychometric characteristics for responders and non-responders are given in Table 4. To analyze the dichotomous variable 'responder, we studied a forward stepwise multiple logistic regression model. The hyperactivity scores on the ADHD rating scale in block 1 turned out to be the best predictor (Wald = 23.42, $P < 0.001$) and this variable alone resulted in 88% of the children being correctly classified and has a sensitivity of 87% and a specificity of 91%.

Discussion

To the best of our knowledge, this is the first report on HPA axis reactivity in prepubertal children with ADHD subtypes as compared with healthy controls.

The reactivity of the HPA axis to stress may have prognostic significance [35]. These findings assist in the speculation that not all patients with ADHD have an underreactivity of the HPA axis, and those that do may have more deficits than the patients with an appropriate reactivity. The present results suggest that hyperactivity and impulsivity in children with ADHD might be associated with dysfunction of the HPA axis. Consistent with our findings, Kaneko et al. [32] demonstrated that abnormal variations in diurnal salivary cortisol were found to be more frequent in severely and moderately hyperactive children with ADHD. More recently, in a population-based study of reactions to a dental examination of children with and without ADHD, indications of a blunted HPA axis response in children with ADHD with high hyperactivity/impulsivity scores were found [11].

Table 4 Psychometric characteristics in responders versus non-responders

	Measure	Responders ($n = 62$)		Non-responders ($n = 38$)		t (1, 98)
		Mean	SD	Mean	SD	
AVL	Total	21.65	12.40	48.61	14.34	9.94***
	Inattention	12.08	7.21	15.05	6.04	2.22*
	Hyperactivity	4.89	3.98	16.95	6.21	10.70***
	Impulsivity	4.68	4.08	16.61	6.48	10.19***
CBCL	Withdrawn	60.75	8.32	57.89	5.59	−2.05*
	Somatic complaints	56.48	6.77	57.97	6.91	1.07
	Anxious/depressed	60.64	8.29	60.43	4.98	−0.16
	Social problems	57.78	7.46	58.64	4.96	0.70
	Thought problems	56.23	7.46	60.87	8.99	2.79**
	Attention problems	64.08	9.77	69.71	7.14	3.32**
	Delinquency	56.23	6.63	62.76	5.53	5.31***
	Aggression	56.79	7.13	62.44	4.36	4.92***
	Externalizing score	54.12	10.09	61.77	6.84	4.51***
	Internalizing score	58.07	9.26	59.71	5.25	1.13
	Total problem score	56.35	10.47	61.55	6.09	3.14**
TRF	Withdrawn	57.47	7.52	55.05	8.09	−1.52
	Somatic complaints	52.38	4.86	54.44	6.20	1.85
	Anxious/depressed	57.25	6.25	54.96	5.09	−1.91
	Social problems	56.87	6.94	60.47	7.59	2.43*
	Thought problems	53.78	6.98	55.81	7.88	1.34
	Attention problems	59.65	7.53	63.66	5.28	3.13**
	Delinquency	56.38	5.63	58.29	4.00	1.98*
	Aggression	57.10	5.66	60.29	4.31	3.18**
	Externalizing score	53.14	8.68	59.61	4.16	5.01***
	Internalizing score	51.56	8.37	54.59	6.33	2.05*
	Total problem score	54.13	10.26	58.88	6.36	2.86**

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Several studies suggest an overall relationship between hyperactivity and DBD, which suggests that hyperactivity may be a risk factor for the further development of DBD [19, 30, 49, 67, 73]. Although none of our patients met the diagnostic criteria for a comorbid disorder, from a dimensional point of view we found negative correlations between HPA axis reactivity and externalizing problem scores; furthermore, we found positive correlations between HPA axis reactivity and scores for social withdrawal. These findings are consistent with previous studies which suggest that a reduced responsiveness to stress lacks the ability to exhibit age-appropriate inhibition of impulsive and/or aggressive behavior [35, 45, 50, 52, 53, 68, 75]. On the contrary, elevated salivary cortisol levels have been detected in shy and behaviorally inhibited children [61].

In this study, two distinct patient groups with ADHD were identified according to the reactivity of the HPA axis to stress. ADHD-C patients showed a decrease in cortisol reactivity, whereas ADHD-I patients showed an increased cortisol reactivity. As stated by several authors, the ADHD-I subtype appears to be a somewhat heterogeneous group [14, 46, 48]. Evidence suggests two distinct dimensions of inattention. The first dimension is the set of inattentive symptoms that can be thought of as primarily reflecting distractibility. The second dimension reflects a quality that is more sluggish, passive, hypoactive, daydreamy, slow-moving, staring, confused, and lethargic in form, and that has been described as sluggish cognitive tempo (SCT). In a study of Carlson and Mann [14] the inattentive-sluggish group received significantly higher teacher ratings on anxiety and depression symptoms than both the inattentive-low sluggish tempo group and the ADHD-C group. Symptoms of SCT are not included in the DSM-IV-TR symptoms of inattention and may be useful in assembling more homogenous groups. An important direction for research is to distinguish subtypes of children with ADHD-C, ADHD-I high in SCT, and ADHD-I low in SCT, and to compare these groups on measures of HPA axis reactivity.

In a recent study by Randazzo et al. [57], the stress response in adolescents with inattentive type ADHD symptoms in both a threshold group with six symptoms and a moderately inattentive group with three symptoms was investigated. Although the sample size was small, they demonstrated that the group at the diagnostic threshold displayed a blunted cortisol response whereas the moderate and comparison groups displayed a normal cortisol stress response.

Some methodological limitations of the present study need to be noted. First, we did not systematically collect information on the occurrence of significant early life events in our children. We can therefore only speculate about the possible mechanisms underlying our findings. Early adverse experiences, including neglect or abuse, can have permanent effects on the developing neurobiological systems in the brain, including the HPA axis [12]. Second, the study cannot clarify whether a pattern of underreactivity in ADHD-C children is the cause or the consequence of the problem behavior. Only longitudinal studies can resolve the issue of the direction of causality. Third, there is a possibility that the subtypes may change during development; some children shifted to another subtype, whereas others desisted from ADHD in later years [40]. We tried to compensate for this by a narrow limitation of the age range. Fourth, no subjects with ADHD-H could be included in this study, so that one can only speculate on HPA axis reactivity in this subtype. The inclusion of ADHD-H subtypes is a desideratum for future research. Fifth, the absence of comorbid mood disorders has implications for generalizability of our findings.

In conclusion, the present findings suggest that patients with ADHD-C are characterized by low-cortisol responsivity to psychosocial stress. Our findings could contribute to the ongoing debate on the possibility that ADHD-C and ADHD-I could be qualitatively distinct and unrelated disorders. The emphasis on ADHD-I as an independent entity could lead to the formulation of new theories concerning this disorder. The currently leading psychological theories on ADHD focus on response inhibition deficit [74], a deviant motivational attitude [44], or an energetical state dysregulation [65], thereby emphasizing the construct of impulsiveness which is only accounted for by ADHD-C and ADHD-H.

The current findings warrant further research on the biological mechanisms that regulate the reaction to psychosocial stress and activation of the HPA axis in ADHD subtypes. Future research should aim to investigate HPA (re)activity at different levels of the axis (hypothalamus, pituitary and adrenals) and at higher levels (e.g., the amygdala and limbic system) simultaneously to elucidate the neuroendocrinological mechanisms underlying the observed HPA axis dysfunction in ADHD populations. Moreover, new strategies for investigating psychoneuroendocrinological systems should be developed, in combination with both structural and functional imaging techniques, as well as molecular genetic studies to provide a better understanding of both the (neuro) biological and psychosocial mechanisms involved in the development of ADHD.

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