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CLINICAL RESEARCH ARTICLE

Relationship between hair cortisol concentrations and cognitive functioning in adolescents with ADHD

Marta Llorens[a,b], Maria Barba[c], Jordi Torralbas-Ortega[d], Roser Nadal[e,f,g], Antonio Armario[e,f,g,h], Humberto Gagliano[h], Lara Urraca[c], Susana Pujol[c], Itziar Montalvo[b,c,e,g,i], Rebeca Gracia[b,c], Diana Polo[a], Laura González-Riesco[a], Josep Lluís Matalí[a,b,g,j], Diego Palao[b,c,e,g,i], Montserrat Pàmias[b,c,e,g,i] and Javier Labad [b,e,g,i,k]

[a]Department of Child and Adolescent Mental Health, Hospital Sant Joan de Déu, Barcelona, Spain; [b]Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Bellaterra, Spain; [c]Department of Mental Health, Parc Taulí Hospital Universitari, Sabadell, Spain; [d]Nursing Care Research Group, Sant Pau Biomedical Research Institute (IIB SANTPAU). Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [e]Institut de Neurociències, Translational Neuroscience Research Unit I3PT-INc-UAB, Sabadell, Spain; [f]Psicobiology Unit, Faculty of Psychology, Universitat Autònoma de Barcelona, Bellaterra, Spain; [g]Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain; [h]Animal Physiology Unit (Department of Cellular Biology, Physiology and Immunology), Faculty of Biosciences, Universitat Autònoma de Barcelona, Bellaterra, Spain; [i]Institut d'Investigació i Innovació Parc Taulí (I3PT), Sabadell, Spain; [j]Child and Adolescent Mental Health Research Group, Institut de Recerca Sant Joan de Déu, Barcelona, Spain; [k]Department of Mental Health, Consorci Sanitari del Maresme, Mataró, Spain

ABSTRACT

Background: Our study aimed to explore whether the hair cortisol concentration (HCC), a measure of long-term cortisol output, is associated with poorer cognitive functioning in adolescents with attention deficit and hyperactivity disorder (ADHD). We further aimed to test the potential moderating effects of sex and childhood maltreatment.

Methods: In this cross-sectional study, fifty-three adolescents with ADHD were studied. The ADHD Rating Scale (ADHD-RS) and Childhood Trauma Questionnaire (CTQ) were administered. Seven cognitive tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB) were administered, and two cognitive factors (attention and memory and executive functioning) were identified by confirmatory factor analysis. A 3-cm hair sample from the posterior vertex region of the head was obtained. HCCs were determined by a high-sensitivity enzyme immunoassay kit. Multiple linear regression analyses were used to explore the association between HCCs and either cognitive performance or ADHD severity while adjusting for sex, childhood maltreatment and the ADHD-RS total score.

Results: Sex moderated the relationship between HCCs and attention/memory confirmatory factor analysis (CFA) scores, with better performance in boys with higher HCCs. HCCs were not associated with executive functioning or ADHD symptoms. Childhood maltreatment was associated with inattention symptoms in adolescents with ADHD.

Conclusions: Our study suggests that HCCs are positively associated with attention and memory performance in adolescents with ADHD, with a moderating effect of sex (the relationship is strongest in boys).

Relación entre las concentraciones de cortisol capilar y el funcionamiento cognitivo en adolescentes con TDAH

Antecedentes: Nuestro estudio tuvo como objetivo explorar si la concentración de cortisol en el cabello (CCC), una medida de la producción de cortisol a largo plazo, se asocia con un peor funcionamiento cognitivo en adolescentes con trastorno por déficit de atención e hiperactividad (TDAH). Además, nuestro objetivo era probar los posibles efectos moderadores del sexo y el maltrato infantil.

Métodos: En este estudio transversal se estudiaron cincuenta y tres adolescentes con TDAH. Se administraron la Escala de Calificación del TDAH (ADHD-RS) y el Cuestionario de Trauma Infantil (CTQ). Se administraron siete tareas cognitivas de la batería automatizada de pruebas neuropsicológicas de Cambridge (CANTAB) y se identificaron dos factores cognitivos (atención, memoria y funcionamiento ejecutivo) mediante análisis factorial confirmatorio. Se obtuvo una muestra de cabello de 3 cm de la región del vértice posterior de la cabeza. Las CCCs se determinaron mediante un kit de inmunoensayo enzimático de alta sensibilidad. Se utilizaron análisis de regresión lineal múltiple para explorar la asociación entre las CCCs y el rendimiento cognitivo o la

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关键词
ADHD；皮质醇；认知；童年期创伤；性别

HIGHLIGHTS

- We studied the relationship between cortisol and cognition in adolescents with ADHD.
- Hair cortisol concentrations (HCCs) were determined.
- We explored the moderating effects of sex and childhood trauma.
- Sex moderated the relationship between HCCs and attention and memory.
- Childhood trauma did not moderate the relationship between HCCs and cognition.

CONTACT Javier Labad jlabad@csdm.cat; labadj@gmail.com Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Cerdanyola del Vallès, Bellaterra, Spain

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gravedad del TDAH mientras se ajustaba por sexo, maltrato infantil y puntuación total del ADHD-RS.
Resultados: El sexo moderó la relación entre las CCCs y las puntuaciones del análisis factorial confirmatorio (AFC) de atención/memoria, con mejor rendimiento en los niños varones con CCCs más altos. Los CCC no se asociaron con el funcionamiento ejecutivo ni con los síntomas del TDAH. El maltrato infantil se asoció con síntomas de falta de atención en adolescentes con TDAH.
Conclusiones: Nuestro estudio sugiere que las CCCs se asocian positivamente con el rendimiento de atención y memoria en adolescentes con TDAH, con un efecto moderador del sexo (la relación es más fuerte en los niños varones).

ADHD青少年患者头发皮质醇浓度与认知功能之间的关系

背景：我们的研究旨在探讨头发皮质醇浓度（HCC）（衡量长期皮质醇输出量的指标）是否与患有注意力缺陷多动障碍（ADHD）的青少年认知功能较差有关。我们进一步旨在检验性别和童年期虐待的潜在调节作用。
方法：在这项横断面研究中，对 53 名患有ADHD的青少年进行了研究。使用了 ADHD 评定量表 (ADHD-RS) 和儿童创伤问卷 (CTQ)。 使用了剑桥神经心理学测试自动组 (CANTAB) 的七项认知任务，并通过验证性因素分析确定了两个认知因素（注意力与记忆力和执行功能）。从头部后顶点区域获取 3 厘米的头发样本。通过高灵敏酶免疫分析试剂盒测定 HCC。使用多元线性回归分析探讨 HCC 与认知表现或 ADHD 严重程度之间的关联，同时调整性别、童年期虐待和 ADHD-RS 总分。
结果：性别调节了 HCC 与注意力/记忆验证性因素分析 (CFA) 分数之间的关系，患有 HCC 较高的男孩表现更好。HCC与执行功能或ADHD症状无关。童年期虐待与ADHD青少年的注意力不集中症状有关。
结论：我们的研究表明，HCC 与 ADHD 青少年的注意力和记忆力表现呈正相关，性别具有调节作用（这种关系在男孩中最强）。

1. Introduction

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis occurs through specific underlying pathogenic mechanisms and developmental pathways in several psychiatric disorders (Lupien et al., 2009; Strüber et al., 2014). This dysregulation may be related to prolonged exposure to stress, genetic factors and gene-environment interactions (Strüber et al., 2014). HPA axis function has been extensively studied in individuals with attention deficit hyperactivity disorder (ADHD), with meta-analyses reporting a lower basal cortisol level (in both serum and saliva samples) in children and adolescents with ADHD. However, substantial heterogeneity has been found in the effects reported by individual studies (Scassellati et al., 2012). Potential moderating variables need to be considered when exploring the role of the HPA axis in ADHD, such as sex differences, symptom presentation and environmental conditions, which can explain the heterogeneity observed (Pauli-Pott et al., 2023).

In recent years, hair cortisol concentrations (HCCs) have been increasingly established as a measure of long-term cumulative cortisol levels (Gray et al., 2018; Stalder et al., 2016). Hair cortisol may be a promising noninvasive measure of chronic stress in children and adolescents, but a better comprehension of the association of HCCs with stressors and trauma exposure is required before it can be used as a biomarker (Gray et al., 2018). Heterogeneous results have been reported in previous studies regarding the relationship between HCCs and sex (male sex is associated with higher cortisol secretion), age and vulnerable developmental stages, trauma exposure or socioeconomic status (Gray et al., 2018). The complex interaction between neurodevelopmental, social and emotional problems and chronic stress, which negatively affects cognitive performance, behaviour and emotion regulation, must be accounted for (Anand et al., 2020)

ADHD is a prevalent neurodevelopmental disorder (Thomas et al., 2015) with core cognitive alterations, including impairment in sustained attention, executive functioning, working memory and self-regulation (Barkley, 1997). ADHD has been associated with substantially poorer quality of life, especially in the psychosocial domain, and has impacts on the school, emotional and social subdomains (Wanni Arachchige Dona et al., 2023). Despite the high heritability of ADHD, there is also significant heterogeneity in ADHD symptoms (Luo et al., 2019). The phenotypic presentation of ADHD symptoms may differ, with symptoms of inattention, hyperactivity or impulsivity predominating, and could be accompanied by externalizing and internalizing disorders (Luo et al., 2019). Moreover, there are considerable sex differences in this symptomatic presentation and in prevalence rates (Hinshaw et al., 2022). Given that HPA axis function differs between sexes, shows heritability by adjusting to environmental conditions and is related to neurocognitive and emotional functions, a nonuniform pattern of HPA axis dysregulation is likely to be found in children and adolescents with ADHD (Pauli-Pott et al., 2023).

Regarding neuropsychological deficits, ADHD is characterized by deficits in multiple, relatively independent, cognitive domains. It is well known that the executive functions of inhibitory control, working memory, delay aversion, vigilance and planning are impaired in children with ADHD. These deficits, in line with current aetiological models that assume multiple causal pathways in the disorder, are not uniformly present in all patients with ADHD and characterize specific subtypes (Faraone et al., 2015). These primary deficits involve the maturation of hippocampal and prefrontal brain circuitry (Depue et al., 2010). Importantly, it is known that activity in these areas is modulated by glucocorticoid secretion (Schwabe et al., 2012). Several studies including children have reported a negative association between HCCs and cognitive performance (Armstrong-Carter et al., 2020; Kim et al., 2022; Ogawa et al., 2017). In a cross-sectional study, an age-dependent association was found between HCCs and executive functioning in children; a higher HCC predicted worse executive functioning in children younger than 9 years old but not in older children (DePasquale et al., 2021).

Some research groups have explored the association between HCCs and ADHD. Pauli-Pott et al. (Pauli-Pott et al., 2017) found a significant sex-by-ADHD symptom interaction with HCCs, with an association between low hair cortisol concentrations and the severity of ADHD symptoms in boys, particularly those exposed to family adversity. This same group also found that lower HCCs at the age of 4–5 years predicted an ADHD diagnosis at the age of 8 years, with this association being more pronounced in boys and mainly based on inattention symptoms (Pauli-Pott et al., 2019). Focusing on neurocognitive deficits, Mann et al. (Mann et al., 2021) also found sex differences in the association between HCCs and cognitive functioning in a sample of preschool children at risk of developing ADHD, with a sex-by-HCC interaction for working memory performance (low HCCs were correlated with low working memory capacity in boys). Although psychosocial risk was assessed in this previous study, potential interactions between childhood maltreatment and HPA axis measures were not considered. Later studies by the same research group suggested that it would be particularly valuable to consider maltreatment as a potential moderator of this association (Pauli-Pott et al., 2023). In the same way, previous research by our group provided support for childhood maltreatment as a moderator of the relationship between HPA axis measures and cognition in individuals with ADHD (Llorens et al., 2022).

According to the previous literature summarized above, potential moderating factors should be considered in the relationship among HCCs, cognition and ADHD symptoms. First, significant sex differences emerged in the interaction between HCCs and working memory in preschool boys at risk of developing ADHD (a low HCC correlated with a low working memory capacity) (Mann et al., 2021). Second, exposure to environmental adversity, specifically childhood maltreatment, which is especially prevalent in individuals with psychiatric disorders (Teicher et al., 2022), has been related to ADHD (Craig et al., 2020), HCCs (Keresztes et al., 2020; White et al., 2017) and cognitive deficits (Raffington et al., 2018).

Given the limited published work on the determinants of HCCs in adolescents and the potential benefit of better characterizing adolescents with ADHD, the main aim of our study was to test whether HCCs were associated with poorer cognitive functioning in adolescents with ADHD. Second, we characterized the potential moderating effects of sex and childhood maltreatment. Finally, we also wanted to explore the significant links among HCCs, cognitive function, and ADHD symptoms.

2. Methods

2.1. Participants

In this cross-sectional study, we studied 53 (34 boys and 19 girls) 14- to 17-year-old outpatients who were treated at the Children and Adolescents Mental Health Centre of Sabadell (Corporació Sanitària Parc Taulí de Sabadell, Spain). All patients met the criteria for an ADHD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (DSM–5). The diagnosis of ADHD was made by experienced child and adolescent psychiatrists following the gold standard recommendations, which usually require a structured battery of neuropsychological tests, parent and teacher reports, and in-depth clinical interviews (Langevin et al., 2023). All adolescents participated in a previous study (Llorens et al., 2022) that included a sample of 78 patients (56 boys and 22 girls). From this total sample, adolescents exposed to childhood maltreatment (34 adolescents) showed significantly higher scores for inattention symptoms, but there were no differences in age, sex, age at ADHD diagnosis, substance use, estimated intelligence quotient, comorbidities, ADHD severity, pharmacological treatment or hormone levels between the exposed and nonexposed groups. The exclusion criteria were intellectual disability, other neurodevelopmental disorders, having received antipsychotic treatment in the previous 2 months, neurological disease, growth retardation, endocrine disorders or having received glucocorticoid or contraceptive treatments. From the total sample, we included 53 participants who had available hair samples that allowed us to calculate their HCC.

Ethical approval of our study was obtained from the Committee for Ethical Clinical Investigation of the

Hospital Parc Taulí de Sabadell (2018526). Written informed consent was obtained from all the participants and their guardians.

2.2. Clinical variables

A full description of the clinical and psychometric examination of all participants is described elsewhere (Llorens et al., 2022). In brief, sociodemographic and clinical data including race/ethnicity were recorded using semistructured interviews, conducted and recorded by investigators following AMA Manual of Style committee recommendations (Flanagin et al., 2021). Stimulant doses were recoded as methylphenidate equivalents (mg/day) (Llorens et al., 2022).

ADHD severity was assessed with the Attention Deficit Hyperactivity Disorder-Rating Scale (ADHD-RS-IV), which allowed us to obtain two subscores (inattention and hyperactivity) (Vallejo-Valdivielso et al., 2019).

Childhood maltreatment was assessed with the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003). This self-report instrument explores five dimensions (emotional, physical and sexual abuse and emotional and physical neglect) of childhood trauma and gives an overall score by summing all five subscores. This instrument is recommended in childhood maltreatment research for collecting adequate data on exposure to maltreatment in a matter of minutes and is a validated instrument with high test-retest reliability (Teicher et al., 2022).

2.3. Cognitive assessment

To assess intellectual disability, intelligence quotients (IQs) were estimated with two subtests (the Vocabulary and Cubes subtests) of the Weschler Intelligence Scale for Children (WISC-V).

The Cambridge Neuropsychological Testing Automated Battery (CANTAB) (Fray & Robbins, 1996) was used to assess cognitive abilities. The CANTAB is a widely used computerized assessment battery(Fried et al., 2019; Luciana, 2003). All subjects completed the following seven CANTAB cognitive tasks: the reaction time (RTI), rapid visual information processing (RVP), stop signal task (SST), spatial working memory (SWM), verbal recognition memory (VRM), and one touch stockings (OTS) tests and the multitasking test (MTT). These tasks were chosen following the recommended CANTAB test battery for ADHD, considering the core cognitive ADHD impairments. Every task included more than one variable for each domain, so we conducted a confirmatory factor analysis (CFA) to combine all cognitive tests into two dimensions according to previous studies: the attention and memory (composed of the RTI, RVP and VRM tests) and executive functioning (composed of the MTT and SST, SWM, and OTS tests) dimensions (Haring et al., 2015). The two CFA factors were used to assess cognitive performance (higher scores indicated poorer cognition) (Llorens et al., 2022).

All psychometric tests were administered on the same day as the cognitive assessment.

2.4. Cortisol measurement

Several thin hair strands were cut as close as possible to the scalp from the posterior vertex region of the head. The first proximal 3-cm segment was used for the determination of the HCC, which is thought to reflect the cumulative cortisol secretion over the past 3 months (Stalder et al., 2016).

Preparation of the hair samples included weighing 40 mg of hair, washing twice with 4 ml of 2-propanolol (SIGMA, Ref: 335639-2.5 L-M), performing 3 extractions with 1.6 ml of methanol (SIGMA, Ref: 34860-2.5 L-M), and the evaporation of methanol in a Speed-Vac. Reconstituted samples with 0.1 M phosphate buffer were processed with a salivary cortisol, high-sensitivity enzyme immunoassay kit (Salimetrics, Ref: 1-3002-5, UK). The intra-assay coefficient of variation was less than 7%, and the interassay coefficient was 11%. The sensitivity was 0.028 μg/dl.

2.5. Statistical analysis

SPSS version 24.0 software (IBM Corporation, Armonk, NY, USA) was used to perform the statistical analyses. We log-transformed the HCC (ln) to reduce skewness. Of all patients, one had a missing CTQ score, and another had a missing ADHD-RS score. To explore whether there were significant differences by sex or ADHD-RS or CTQ scores in patients without hair samples from the original study (Llorens et al., 2022), we also compared two subsamples (the current sample vs. the sample of patients without hair samples).

As we stated in the Methods section, we used a confirmatory factor analysis (CFA) to reduce the number of cognitive variables obtained with the CANTAB to 2 latent factors, attention and memory and executive functioning, as in similar previous studies (Haring et al., 2015). The results of this analysis, conducted using the lavaan package in R software, are shown in Figure S1. To facilitate the comprehension of the results, the independent variables included in the model are described in Table S1 (used in our previous study: Llorens et al., 2022). The statistical parameters of the CFA were a $\chi 2 = 237.7$ (degrees of freedom = 204, $p = .053$), a comparative fit index (CFI) of .949, and a root mean square error approximation (RMSEA) = .046 (90% confidence interval: .000–.070, $p = .580$). Therefore, the CFA showed a good fit, as the CFI was >.90 and the RMSEA was <.050.

Chi-square tests and T tests were used to compare categorical and continuous data, respectively, between groups based on sex. Significance was defined as a p value <.05 (two-tailed). These two tests were used to explore sex differences in clinical and hormonal variables. The selection of the variables used in the multivariate analyses (multiple linear regression) was not based on the univariate analyses, as they were chosen a priori based on their clinical relevance.

Multiple linear regression analyses were used to explore the association between HCCs and either cognitive performance or ADHD severity. All multiple linear regression analyses were adjusted for female sex, the ADHD-RS total score and the CTQ total score. We tested for two potential interactions: between sex and HCCs and between the CTQ total score and HCCs. For each regression, if an interaction was significant, it was kept in the final model. Nonsignificant interactions were not included in the final equation, as it is not necessary to include nonsignificant interactions in regression analyses (Beck & Bliwise, 2014). Missing values in multiple linear regression were handled with the listwise procedure. This means that patients with missing values were excluded from the analyses.

The main multiple linear regression analyses included the CTQ total score as the main variable of childhood maltreatment. However, as the CTQ has 5 subscales (emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect), we repeated exploratory analyses for each CTQ subscale. Independent multiple linear regression analyses were conducted for each CTQ dimension and for each outcome (the two cognitive factors and two ADHD-RS subscales). We did not include all CTQ subscales in the same regression to avoid problems of collinearity.

3. Results

3.1. Univariate analysis

In terms of race/ethnicity, our entire sample was composed of Hispanic adolescents, 3 of whom were Latino. There were no significant differences in the severity of ADHD symptoms, cognitive variables, pharmacological treatment (including stimulant equivalent doses) or CTQ scores between boys and girls (Table 1).

Regarding hormone levels, we did not find significant sex differences in HCCs (boys: 4.44 ± 1.9; girls: 4.45± 2.33, p = .748). Regarding exposure to childhood maltreatment, the CTQ score was not associated with HCCs (r = .044, p = .754).

When comparing individuals participating in the current study and the subsample of patients without available hair samples, no significant differences were found in the ADHD-RS or CTQ scores. A significantly greater proportion of boys had missing hair samples when compared to girls (38.2% vs. 13.6%, p = .036).

Table 1. Clinical and biological data of the participants.

	Boys (N = 34)		Girls (N = 19)		p
Age	15.5	(.8)	16.1	(1.1)	.024
Substance use					
Tobacco	3	(8.8%)	1	(5.3%)	.547
Alcohol	4	(11.8%)	4	(21.1%)	.301
Cannabis	0	(0.0%)	1	(5.3%)	.358
Age of ADHD diagnosis	9.3	(3.3)	11.1	(3.2)	.074
CTQ total score	31.9	(6.6)	30.9	(5.2)	.580
Treatments					
ADHD stimulant	27	(79.4%)	16	(84.2%)	.484
ADHD nonstimulant	2	(5.9%)	0	(.0%)	.407
Other treatments (no ADHD)	3	(8.8%)	1	(5.3%)	.547
ADHD Rating Scale scores	23.0	(13.2)	20.2	(14.5)	.479
ADHD Rating Scale – Inattention subscale	14.8	(8.2)	12.5	(8.4)	.355
ADHD Rating Scale – Hyperactivity subscale	8.2	(5.9)	7.6	(7.6)	.760
Cognitive scores (CFA factors)					
Attention/memory	.008	(.33)	−.003	(.23)	.893
Executive functioning	.020	(.29)	−.03	(.29)	.594
Estimated intelligence quotient	101.7	(9.6)	98.3	(13.5)	.290
HCC (pg/mg)	4.4	(1.9)	4.5	(2.3)	.983

Note: Data are mean (SD) or N (%).
Abbreviations: CTQ: Childhood trauma questionnaire; ADHD: attention deficit hyperactivity disorder; CFA: confirmatory factor analysis; HCC: hair cortisol concentration.

3.2. Multiple linear regression analysis

The multiple linear regression analysis considering the attention/memory domain as the dependent variable while adjusting for the severity of ADHD symptoms (ADHD-RS total score) and maltreatment (CTQ total score) revealed a significant interaction between cortisol concentrations and female sex (β = .963, p = .045) (Table 2). This interaction is depicted in Figure 1. Sex moderated the relationship between HCCs and attention/memory CFA scores: the slope reflecting the association between these two variables was steeper in boys (higher HCCs were associated with lower scores on the CFA domain, which reflected better cognitive performance) than in girls (the association was less pronounced).

HCCs were not associated with executive functioning or ADHD symptoms. Childhood maltreatment was associated with the severity of inattention symptoms.

Regarding the exploratory analyses considering the five CTQ dimensions, of all dimensions of childhood maltreatment, only that of sexual abuse was associated with both inattention symptoms (B = 3.42, SE = 1.17, standardized β = .395, p = .005, 95% CI for B = 1.07–5.78) and hyperactivity symptoms (B = 2.0, SE = .97, standardized β = .293, p = .044, 95% CI for B = .053–3.94). No interactions between HCCs and the CTQ dimensions were found in any of the multiple linear regression analyses.

4. Discussion

We analysed the association between HCCs and cognitive functioning in adolescents with ADHD, and

Table 2. Multiple linear regression analyses exploring the relationship between hair cortisol concentrations (HCCs) and cognitive performance and ADHD symptoms.

		Unstandardized Coefficients		95% Confidence Interval for B		Standardized Coefficients		
Dependent variable	Independent variables	B	Std. Error	Lower Bound	Upper Bound	β	*t*	Sig.
Attention and memory[†]	(Constant)	.33	.28	−.23	.89		1.17	.246
	HCC[‡]	−.35	.13	−.61	−.08	−.50	−2.63	.012
	Female sex	−.54	.27	−1.10	.01	−.90	−1.99	.053
	CTQ (total score)	.00	.01	−.01	.01	.03	.22	.825
	ADHD-RS (total score)	.01	.00	.00	.01	.25	1.83	.075
	Female sex by HCC interaction	.39	.19	.01	.76	.96	2.06	.045
Executive functioning[†]	(Constant)	.12	.26	−.40	.64		.47	.640
	HCC[‡]	−.07	.10	−.27	.13	−.10	−.71	.479
	Female sex	−.04	.09	−.21	.14	−.07	−.45	.653
	CTQ (total score)	.00	.01	−.02	.01	−.04	−.29	.777
	ADHDRS_TOT	.00	.00	.00	.01	.12	.83	.410
ADHD-RS Inattention	(Constant)	5.86	6.92	−8.06	19.78		.85	.401
	HCC[‡]	−2.87	2.70	−8.30	2.56	−.15	−1.06	.294
	Female sex	−2.11	2.34	−6.82	2.61	−.12	−.90	.373
	CTQ (total score)	.41	.19	.04	.79	.30	2.20	.033
ADHD-RS Hyperactivity	(Constant)	7.86	5.73	−3.67	19.38		1.37	.177
	HCC[‡]	−1.40	2.23	−5.90	3.10	−.09	−.63	.534
	Female sex	−.75	1.94	−4.65	3.15	−.06	−.39	.700
	CTQ (total score)	.08	.15	−.23	.39	.07	.51	.610

Abbreviations: ADHD-RS = HCC = Hair cortisol concentrations; Attention Deficit Hyperactivity Disorder – Rating Scale; CTQ = Childhood Trauma Questionnaire.
[†]Both cognitive variables derived from a confirmatory factor analysis reflect poorer cognitive performance (higher scores indicate lower functioning).
[‡]HCC was used as a log transformed (ln) variable in all regression analyses.

we found that adolescents with lower HCCs had poorer performance on attention and memory tasks, with this effect being strongest in boys. HCCs were not associated with executive functioning or ADHD symptoms.

The main results of our study are in line with previous studies that explored links between HCCs and the development of ADHD symptoms in preschool children, which found significantly stronger positive associations of short-term memory with HCCs in

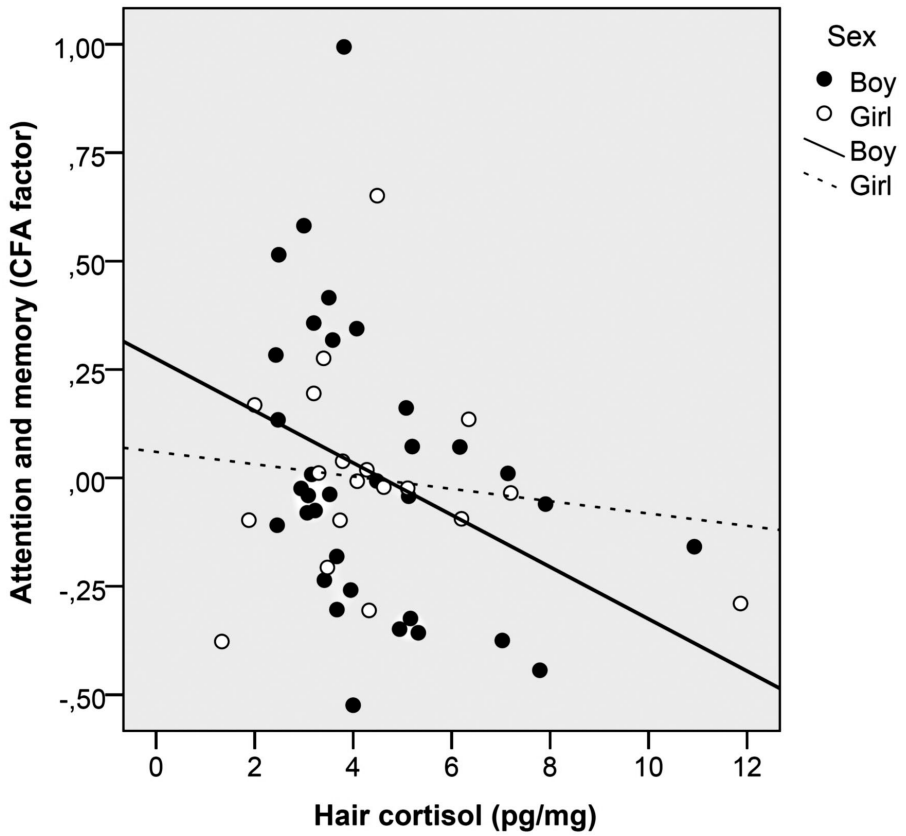

Figure 1. Scatterplot graph of the relationship between hair cortisol concentrations and attention and memory. Analysis stratified by sex. Abbreviation: CFA = confirmatory factor analysis.

preschool boys than girls (Mann et al., 2021) These authors suggested that their results may further circumscribe a specific neurocognitive/endocrine profile in boys at risk of developing ADHD, comprising hypocortisolism combined with memory, attention and performance-intelligence deficits. To our knowledge, our study is the first to analyse the association between HCCs and cognitive functioning in adolescents with an ADHD diagnosis.

Regarding the moderating effect of sex, the association between HCCs and cognitive functioning is consistent with previous studies reporting the same sex-specific pattern in young undergraduate students (McCormick et al., 2007) or in adolescents with ADHD (Llorens et al., 2022). In that last study conducted by our group with the same sample of ADHD patients, we found that sex moderated the relationship between the salivary cortisol level at the clinic and cognitive performance (executive functions) (Llorens et al., 2022). In relation to HCCs, only Mann et al. (2021) previously measured the relationship between HCCs and cognition in individuals with ADHD and found a sex-by-HCC interaction with working memory in children at risk of developing ADHD. Despite growing interest in sex differences in ADHD and many disorders, it is well known that girls are often underdiagnosed because inattention symptoms are more prominent in girls than hyperactivity/impulsivity symptoms. Moreover, girls often develop better coping strategies than boys, which could mask their symptoms, and might show higher comorbidity of anxiety and depression, which can lead to misdiagnosis (Quinn & Madhoo, 2014). These results may encourage further research into the sex-specific presentation of ADHD.

Regarding the moderating effect of environmental adversity, contrary to our expectations, we did not find that childhood maltreatment moderated the association between HCCs and cognition.

In general, maltreated individuals show epigenetic modifications in stress response systems that differ in developmental trajectories, leading to different ecophenotypes (Teicher et al., 2022). The clinical presentation and treatment response change depending on the timing of maltreatment, type of maltreatment and severity of exposure, as well as genetic factors that influence susceptibility and resilience and a set of protective factors that attenuate risk (Teicher et al., 2022). An abnormal HPA axis response to stressors will also reprogram the response to later stressors (Teicher & Samson, 2013). The impact of maltreatment on brain function may not be apparent immediately after exposure. Greater psychopathological repercussions have been associated with more types of reported maltreatment (Teicher et al., 2022) or when the adversity is the product of caregivers or peer groups (Teicher & Samson, 2016).

Childhood maltreatment has an enduring impact on HPA axis function throughout development and is associated with lower morning cortisol levels and a flattening of the diurnal cycle under approximately resting conditions (Gonzalez, 2013). Childhood trauma has been associated with hypoactivation of the HPA axis (Gunnar & Vazquez, 2001; Kumsta et al., 2017; Leneman et al., 2018). Recent reviews examining the association between chronic stress and HCCs reported contradictory results. A systematic review focused on children reported positive associations between chronic stress and HCCs (Li et al., 2023), whereas another review did not find a relationship between chronic stress and HCCs (Schär et al., 2022). Finally, an interesting meta-analysis confirmed that childhood adversity is associated with both higher and lower HCCs (Khoury et al., 2019).

In previous studies by our group (Llorens et al., 2022), we found that childhood maltreatment moderated the relationship between salivary cortisol levels under basal conditions and inattention symptoms in patients with ADHD but did not moderate the relationship between resting salivary cortisol levels and cognitive symptoms assessed with the CANTAB. In our current study, we did not find an association between HCCs and childhood trauma. These results might seem contradictory, as both are measures of cortisol, so it is important to consider the differences between salivary cortisol and HCCs. Dysregulation of the HPA axis as a biological response to stress is one of the main potential mechanisms for understanding the biological integration of social experiences. Cortisol concentrations vary systematically across the day and change in response to acute stress events as well as prolonged exposure to stress. Multivariate twin models suggest that genetic factors that regulate the cortisol response towards laboratory stressors can be separated into those that regulate resting cortisol levels, natural diurnal variation in cortisol, and HCCs (Raffington et al., 2022). In our previous study (Llorens et al., 2022), salivary cortisol was measured the same day as the cognitive assessment, which can be experienced as stressful, especially for adolescents with attention difficulties and a history of childhood trauma. On the other hand, HCCs reflect the cumulative cortisol secretion over the past 3 months, and a lack of association with trauma could be influenced by the temporality and intensity of traumatic events (events experienced more than 3 months before the measurement or events with low intensity). In line with this, Mann et al. (2021) did not find a moderating effect of psychosocial risk when exploring the relationship between HCCs and cognitive functioning in preschool children at risk of ADHD. These differences emphasize the intriguing and complex implications and the directions of connections among ADHD

symptoms, the HPA and trauma and encourage further research on this topic.

Finally, when we explored the significant links among HCCs, cognitive function, and ADHD symptoms, in contrast with the study of Mann et al. (2021), we did not find a relationship between HCCs and inattention symptoms. This difference might be explained by differences between the samples. In their study, preschool children at risk of ADHD were included, whereas in our study, adolescents with an ADHD diagnosis were included. In our sample, most patients had been treated, so the ADHD-RS scores could have decreased, which could have made it difficult to find statistically significant associations between inattention symptoms and HCCs. Future research should assess a broader range of characteristics to more completely identify those that are related to low HCCs in the context of ADHD.

We did find an association between childhood maltreatment and inattention symptoms, in line with evidence presented in previous studies (Kennedy et al., 2016; Lugo-Candelas et al., 2020). In addition, we included all dimensions of childhood maltreatment (emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect) in the exploratory analysis. We found that only sexual abuse was associated with both inattention symptoms and hyperactivity symptoms. An association between child sexual abuse and ADHD has been reported (Langevin et al., 2023). Most studies have conceptualized child sexual abuse as a precursor of ADHD, but the temporal relationship between ADHD and sexual abuse is not clear because of the lack of sufficient longitudinal studies. Due to the cross-sectional design of our study, we cannot address the directionality of these different problems; however, our study highlights the relevance of assessing traumatic experiences, especially sexual abuse, as it is a strong risk factor for psychopathology and ADHD (Langevin et al., 2023).

Some limitations should be mentioned. The relatively small sample size, reduced to only a subsample with available hair samples, could have made it difficult to detect mild effects or interactions due to a lack of statistical power. Therefore, studies with larger sample sizes are recommended for replicating our results before definitive conclusions can be drawn relative to the potential moderating effects of some low prevalent covariates (e.g. female sex). The cross-sectional design did not allow us to infer causality. Childhood trauma was assessed with a self-reported instrument, which could have resulted in recall bias. However, the CTQ is a validated psychometric instrument with good internal consistency and criterion-related validity in clinical and community samples (Majer et al., 2010). Although this study focused on HCCs rather than other endocrine variables, we analysed the concordance of HCCs with salivary cortisol levels taken at the clinic that were assessed in a previous study (Llorens et al., 2022) and showed a statistically significant positive correlation. Finally, a control group of healthy adolescents was not included.

The main strengths of our study are that it is the first study to explore the relationship between HCCs and cognitive abilities in adolescents with ADHD, a full cognitive battery was administered and all analyses controlled for the potential moderating effects of childhood maltreatment.

Despite the lack of a moderating effect of childhood maltreatment on the association between HCCs and cognition in our sample of adolescents with ADHD, we found a relationship between maltreatment and inattention symptoms. In this sense, it is essential that clinicians obtain a maltreatment history when assessing or treating individuals with ADHD, and the CTQ could be an easy instrument for assessment. As maltreatment is such a strong risk factor for mental disorders, there should be an effort to reduce exposure and to develop strategies to prevent the development of psychiatric disorders in exposed youth (Pauli-Pott et al., 2023). This recommendation would also be extrapolated to the importance of obtaining HPA axis measures, and given the plasticity of HCCs in response to targeted interventions, establishing interventions (Blaisdell et al., 2019; Fisher & Stoolmiller, 2008).

In conclusion, our study suggests that HCCs are associated with cognitive performance in adolescents with ADHD. Sex exerts a moderating effect on this relationship, which is clearer in boys, who show better cognitive performance in attention and memory domains when they have higher HCCs. This finding may have translatable clinical implications, as peripheral markers of the HPA axis are easily measured and could be used to screen individuals at high risk of ADHD or to assess the treatment response. Once better defined, they may be useful in differentiating between ADHD subtypes and advancing the characterization of individual differences, a challenge for personalized medicine.

Disclosure statement

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Data availability

The dataset is available at the Zenodo repository: https://zenodo.org/record/7954836.

ORCID

Javier Labad http://orcid.org/0000-0003-2214-1886

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