Cortisol and its effects on cognitive function in a sample of Egyptian school-aged children with attention-deficit hyperactivity disorder

Omneya Ibrahim, Wafaa El-lithy, Khaled Abd El-Moez

Department of Neuropsychiatry, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

Correspondence to Khaled Abd El Moez, MD, Assistant Professor of Psychiatry, Faculty of Medicine, Suez Canal University, Ismailia, Egypt
Tel: +00201060677901; fax: 0643398457;
e-mail: naomsal2012@hotmail.com

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Background
Several studies have suggested that cortisol level influences the development and functioning of the brain in children and that it is implicated in a variety of processes including memory and attention.

Objective
This study was conducted to investigate the relation between cortisol level in children with attention-deficit/hyperactivity disorder (ADHD) and their cognitive function profile.

Methods
The participants of the study, held in Suez Canal University Hospital in Ismailia, were recruited from among those attending the childhood and adolescent psychiatry clinic. They were divided into two groups, the ADHD group [diagnosis based on *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (DSM-IV-TR) through a structured clinical interview], composed of 43 children (pure ADHD children with no comorbid conditions), and the control group, composed of 31 typically developing children. All of them participated voluntarily in this study. The participants' ages ranged from 6 to 12 years; both sexes were included. Early morning awakening salivary cortisol levels were collected on two different days 2 months apart. The Stanford–Binet intelligence test 4th edition, the Wisconsin Card Sorting Test, Conner's test, and the child behavioral checklist were administered on all participants.

Results
Early morning salivary cortisol levels in both groups showed a statistically significant difference. Comparison shows that there was a statistically significant difference in the mean total score and the mean subdomain score of Stanford–Binet intelligence test 4th edition and Wisconsin Card Sorting Test (total number of errors, perseverative errors) between ADHD children and the comparison group. These results were positively correlated with decrease in mean cortisol awakening response.

Conclusion
There are significant associations between salivary cortisol levels and cognitive and executive function impairment in children with ADHD.

Keywords:
attention-deficit/hyperactivity disorder, cortisol, executive functions, school-aged children

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Introduction

The definition of executive function was based on the description of two central conceptual themes. The first associates executive function with 'higher' cognitive functions, such as insight, will, abstraction, and judgment, which are mostly dependent on functioning of the frontal lobe. The second emphasizes behavioral regulation of nonexecutive processes by frontal control systems (American Psychiatric Association, 1994, 2000; Royall *et al.*, 2005).

The term executive function seems to incorporate the following: volition, planning, and purposive, goal-directed, or intentional action; inhibition and resistance to distraction; problem-solving and strategy development, selection, and monitoring; flexible shifting of actions to meet task demands; maintenance of persistence toward attaining a goal; and self-awareness across time (Barkley, 2000).

No single etiology has been identified yet for attention-deficit/hyperactivity disorder (ADHD), and findings are much more consistent with a 'multifactorial hypothesis'(Hoza *et al.*, 2001), but ADHD behavioral symptoms have been also explained by deviations from an optimal arousal level (Sonuga-Barke *et al.*, 2010).

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Such deficits in arousal modulation in ADHD have been studied by examining cortisol levels in saliva, which is a reliable peripheral measure for evaluating hypothalamic–pituitary–adrenal (HPA) axis functioning (Kirschbaum and Hellhammer, 1989).

The HPA axis plays an important role in regulating central nervous system neurotransmitters and behavior, such as attention, emotion, learning, memory, and movement (Pariante and Lihtman, 2008; Marques *et al.*, 2010).

Cortisol influences the development and functioning of the brain in children (Goodyer *et al.*, 2001) and is implicated in a variety of mental processes including regulation of attention, behavior, and emotion exerted through affecting processes within the prefrontal cortex and hippocampus (Prudhomme and Mulligan, 2005).

ADHD, among other neurodevelopmental disorders, is implicated in the frontostriatal system (dorsolateral prefrontal cortex, lateral orbitofrontal cortex, anterior cingulate, supplementary motor area, and associated basal-ganglia structures), which is responsible for our adaptive responses (initiation, execution, or withholding) to environmental situations, and the above disorders, involving effectively excessive release or withholding of various types of response, are all a consequence of changes in specific frontostriatal regions (Bradshow and Sheppard, 2007).

Levels of cortisol are often regarded as a better biomarker, as catecholamine is more immediate and transient, more sensitive to exercise, and more expensive to analyze (Vanaelst *et al.*, 2012).

A significant proportion of ADHD children will experience failure in school. As a result, the burden of ADHD on affected individuals, on their families, and on society is considerable (Barkley, 2000). Evidence shows a broad range of negative effects one changes made to the affected individuals and a serious financial burden on families and society; hence, it is considered a major public health problem (Polanczyk *et al.*, 2007; Karama *et al.*, 2008).

The goal of this study was to determine the relationship between cortisol level in ADHD children and their cognitive function. The results might also provide a foundation for future research focused on interventions based on the impact of cortisol level.

Methods

Sample recruitment

This study was a cross-sectional comparative case–control trial held at the Child and Adolescent Psychiatry Clinic, Suez Canal University Hospital, in Ismailia.

Participants

Consecutive attendees to the 'Child and Adolescent Psychiatry clinic' who were diagnosed with ADHD (44 children) with no comorbid conditions were enrolled. The control group (31 children) comprised matched healthy, typically developing children who were recruited from Ismailia primary schools.

The ADHD diagnosis was made before inclusion into the study. The diagnosis of ADHD and of other psychiatric disorders was based on *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (DSM-IV-TR) criteria using a standardized, structured child psychiatric interview.

A physical/neurological assessment was made on all participants in the study before inclusion, and a standardized battery of psychological assessments was applied on all participants.

All children participated voluntarily in the study. Assent from the child and written consent from the parents with regard to the aim, the tools used in the research, benefits, risks, confidentiality, and voluntary participation were prerequisites. The tools for diagnosis carried less than the minimal accepted risk. The research plan was approved by the 'Faculty of Medicine's Scientific Research Ethical Committee'.

Procedures

The ages of the children under study ranged from 6 to 12 years. Both boys and girls with intelligence quotient (IQ) more than or equal to 80 were included. Children with any comorbid psychiatric condition, any neurological condition, serious medical illness that could have affected the HPA axis function or those on hormonal and dental treatments during the trial or girls who experienced menarche or those who have a history of any sensory or motor disability were excluded.

Measures

Saliva was collected two times on two different days (at early morning awakening and before morning breakfast).

The following tools and instruments were applied in this work.

Child behavioral checklist: to aid in the recognition of the comorbid conditions for exclusion.

Conners 3 – Parent version: to assess ADHD symptoms and comorbid conditions.

Wisconsin Card Sorting Test (WCST): to assess the executive functions of the children in both groups.

Stanford–Binet 4th edition: to determine the IQ of the children.

Statistics

Unpaired *t*-test and analysis of variance test was used for comparison between quantitative variables.

Results

There was no statistically significant difference between the two studied groups regarding residence and parental educational level.

The mean age of children in the ADHD group was 7.3 ± 0.7 years, and was 7.0 ± 0.7 years in the typically developing (control) group ($P < 0.05$, no statistically significant difference) (Fig. 1).

There was no statistically significant difference between the two groups regarding sex distribution ($P > 0.05$). Most of the studied participants in the two groups were male (statistically significant difference $P < 0.05$) (Fig. 2).

Comparison between the control group and the ADHD group regarding the mean and SD of the salivary cortisol levels

Early morning awakening cortisol levels were lower in the ADHD group in comparison with controls, with a statistically significant difference ($P < 0.01$) (Fig. 3).

Mean and SD for early morning awakening salivary cortisol levels between the three ADHD subtypes

There was no statistically significant difference between ADHD subtypes regarding early morning awakening salivary cortisol levels on days 1 and 2, nor in the average cortisol level indices ($P > 0.01$).

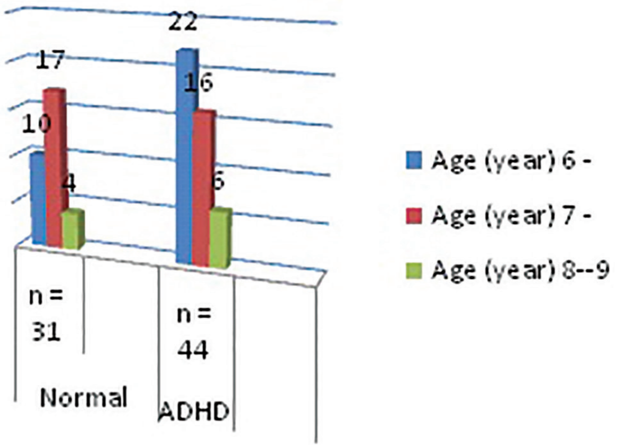
Comparison between the ADHD group and the control group regarding mean and SD of the Stanford–Binet intelligence scale scores

t-Test results were lower in the ADHD group in comparison with the control group, and differences were statistically significant ($P < 0.01$) for all subscales of the Stanford–Binet intelligence Scale.

Comparison between boys and girls of the ADHD group regarding mean and SD of the Wisconsin Card Sorting Test scores

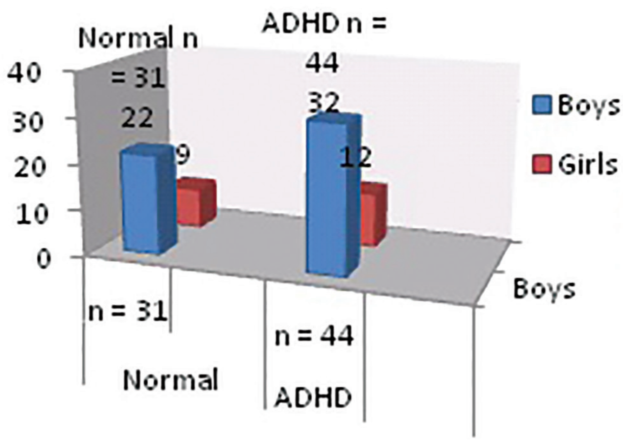
Independent-sample *t*-test results for the mean and SD between ADHD boys and girls showed statistically significant differences in total number of errors, perseverative responses, and perseverative errors in addition to the number of categories completed and responses to the first category, with boys displaying lower performance.

Figure 1



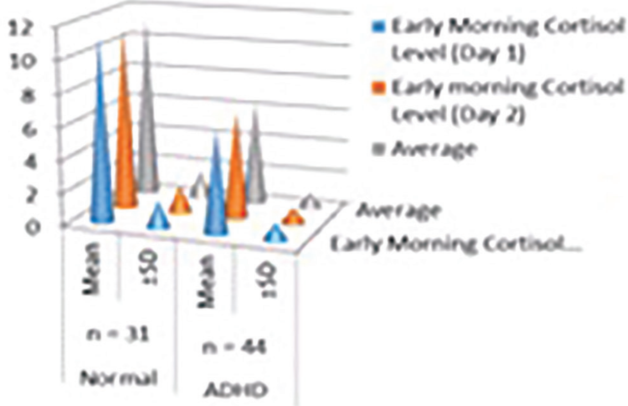
ADHD, attention-deficit hyperactivity disorder.

Figure 2



ADHD, attention-deficit hyperactivity disorder.

Figure 3



ADHD, attention-deficit hyperactivity disorder.

Correlation between salivary cortisol and Wisconsin Card Sorting Test between the two groups

There was significant positive correlation between early morning salivary cortisol level and WCST domains (Table 1).

Discussion

In this study, in the ADHD group, boys outnumbered girls by three-fold, similar to the results of a large body of research (Gozal and Molfese, 2005; Polanczyk *et al.*, 2007; Farah *et al.*, 2009; Roufaele *et al.*, 2012; Abdel-Hamid *et al.*, 2013; El Missiry *et al.*, 2013; Sciberras *et al.*, 2013; Richa *et al.*, 2014).

Here early morning awakening cortisol levels were assessed in noncomorbid ADHD children compared with healthy controls, similar to some other studies.

Bäumler *et al.* (2014) studied 35 preschool children (aged 36 years) in good mental and physical health who were not taking any medication. The children's postawakening cortisol levels were estimated. Results revealed mean and SD of 15.05 and 3.89 nmol/l, respectively, and these results were somehow different from those of the current research (as the mean and SD in our control group were 11.4 and 1.7 nmol/l, respectively).

Ma *et al.* (2011) investigated the relationship between the HPA axis and ADHD in ordinary, nonstressful states, as we did in our research. In that study, they recruited only 128 boys with ADHD with ages ranging between 6 and 14 years and compared them with 30 healthy boys. The diagnosis was also based on DSM-IV, but they did not clarify whether children with comorbid psychiatric conditions were included.

Table 1 Correlation between Salivary cortisol and Wisconsin Card Sorting Test between the two studied groups

Wisconsin card sorting test (WCST)	Average Early Morning Awakening Salivary cortisol Levels		
	Normal *n* = 31	ADHD *n* = 44	Total *n* = 75
	Pearson's Correlation Coefficient		
Number of trials	-0.062	0.165	-0.772**
Total No. of errors	-0.059	0.081	-0.751**
Total No. of perseverative responses	0.141	0.073	-0.764**
Total No. of perseverative errors	0.084	0.170	-0.742**
Total No. of non-perseverative errors	-0.150	-0.020	-0.707**
Number of categories completed	0.300	-0.251	0.822**
Number of responses to complete first category	0.077	0.037	-0.705**
Failure to maintain a set	0.076	0.028	-0.371**
Learning to learn	-0.149	0.547**	0.598**

*Correlation is significant at the 0.05 level (2-tailed); **Correlation is significant at the 0.01 level (2-tailed).

Isaksson (2014) investigated the effect of stress and ADHD in school-aged children (aged 6–12 years) by exploring diurnal levels of saliva cortisol and comparing with age-matched healthy controls. His results were consistent with ours regarding the lower cortisol levels in children with ADHD, especially the morning levels.

Although the IQ scores, estimated by the Stanford–Binet 4th edition , for all ADHD children were above 80 (mean and SD for the total score of intelligence was 105.9 ± 10.4), it was still lower than that of the control group of normal children (128.8 ± 8.7); the scores for Short-term memory, Verbal reasoning, Quantitative reasoning, and Abstract/visual reasoning subscales yielded statistically significant results. These results were consistent with the findings from many other studies (Abdeldayem and Selim, 2005; Yanez-Tellez *et al.*, 2012; Marusiak and Janzen, 2013) reporting significantly lower cognitive abilities in ADHD children as estimated through IQ tests and compared with matched controls. With regard to the results of the WCST, results showed statistically significant differences between the ADHD group and the control group, indicating lower executive performance on WCST in all the test domains, a finding that was concluded by multiple other studies (Oosterlaan *et al.*, 2005; Royall *et al.*, 2005; Barkley *et al.*, 2007; Zorcec and Pop-Jordanova, 2010).

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Conflicts of interest

There are no conflicts of interest.

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