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The response to stress in Brazilian children and adolescents with attention deficit hyperactivity disorder

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ABSTRACT

This study assessed the function of the hypothalamic–pituitary–adrenal (HPA) axis, during response to stress, through the measurement of salivary cortisol in 38 children with attention deficit hyperactivity disorder (ADHD) and its subtypes, who were matched to 38 healthy control subjects. These measures were made at four time intervals: 15 min before exposing the subjects to a stressor — the Continuous Performance Test (CPT) – and 20, 40, and 60 min after such exposure. The baseline cortisol levels were statistically similar in both groups. The mean values of cortisol at the four time intervals were not statistically different between the three subtypes of ADHD (inattentive, hyperactive–impulsive and combined); thus, the ADHD group was treated as a single group. Following the stressor test, the ADHD group had significantly higher levels of salivary cortisol than the control group at time intervals of 20 and 40 min, whereas in this latter group exposure to the CPT did not induce an increase of cortisol. These results suggest that the increased cortisol levels in the ADHD group could be due to the lack of comorbidities. In addition, these patients, when facing a computerized test, might have responded with a motivational pathway with an increase of cortisol.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common of the emotional, cognitive and childhood behavior disorders (Wilens and Dodson, 2004). It is multifactorial and clinically heterogeneous (Biederman, 2005), with a prevalence rate of 5–8% in school–aged children (Freitag et al., 2009). Data are scarce for ADHD prevalence rates in Brazilian children; however, Rohde et al. (1999) found a rate of 5.8% in a sample of Brazilian adolescent students. ADHD affects more boys than girls, with ratios varying from 2:1 to 10:1 (FontanaI et al., 2007). According to the criteria outlined in the DSM IV-TR (2000), the cardinal symptoms of ADHD are poor concentration, hyperactivity and impulsiveness; leading to its division into the following three subtypes: inattentive, hyperactive–impulsive and combined. These symptoms must be accompanied by impairments in social interactions, academics, quality of life, and the cognitive and emotional development of the individual. Often, the behavior of very young children with ADHD goes unnoticed by their parents; however, when they go to school, even mild cases tend to become evident. This is probably because the school environment provides an opportunity to compare children of the same age, and children are required to pay more attention and need to remain in one place for longer periods than they had to do at home (Rohde and Mattos, 2003).

ADHD is associated with a high rate of psychiatric comorbidity, particularly oppositional defiant disorder, conduct disorder, mood and anxiety disorders, smoking and drug abuse (Wilens and Dodson, 2004). The social cost of untreated ADHD is considerable and includes low academic achievement, behavioral problems, underemployment, car accidents, and relationship problems (Barkley et al., 1993; Biederman et al., 2000; Matza et al., 2005).

Several theoretical models have been formulated in an attempt to understand the mechanisms involved in the etiology of ADHD. Barkley (1997) tried to unify the major ethiological theories based on the neuropsychological functions of the pre-frontal lobes and proposed "response inhibition", a function enabling an individual to delay a determined response to an immediate environmental event, would be impaired in individuals with ADHD. It could then result in a series of secondary deficits, such as difficulty in concentration and errors by precipitation (Barkley, 2006).

Subsequently, neuroimaging studies have demonstrated a delay of cerebral maturation, mainly in the frontal lobe (Shaw et al., 2007, 2011). In fact the executive functions include complex mental activities which are needed to plan, organize, guide, review and monitor behavior required to achieve goals. Such functions begin to develop during the first year of life and continue their development until adolescence; however, these functions seem impaired in patients with ADHD (Barkley, 1998). Furthermore, if one core deficit of ADHD is a dysfunctional behavioral inhibition system, an abnormality of the hypothalamic–pituitary–adrenal (HPA) axis might be expected in patients with ADHD. A low reactivity of the HPA axis to stress in patients with ADHD has been associated with their poor performance. Patients

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with ADHD who retained their diagnosis for more than 1 year showed a blunted response to stress when compared with an ADHD group that no longer met diagnostic criterial (Hong et al., 2003; King et al., 1998).

A recent study of prepubertal children with ADHD subtypes and a healthy control group found that children with inattentive ADHD had an elevated cortisol response to a psychosocial stressor, in contrast to children with combined ADHD who had a blunted cortisol response. The authors suggest that a low-cortisol responsivity to stress might be a neurobiological marker for children with ADHD (van West et al., 2009).

Other studies have not found an association between reduced cortisol concentrations and ADHD. Kaneko et al. (1993) reported that only those with severe and moderate hyperactivity had an increase of cortisol after exposure to stress. Kariyawasam et al. (2002) found lower cortisol levels in 32 children with comorbid ADHD and opposition defiant disorder (ODD); a finding that was restricted to the subgroup of unmedicated patients. Hong et al. (2003) found two different cortisol reactivity patterns during a stress test in patients with ADHD: one group had increased cortisol levels whereas the other one had decreased cortisol levels. Snoek et al. (2004) found normal reactivity to stress in individuals with ADHD. Shirtcliff et al. (2005) reviewed the relationship between cortisol levels and internalized and externalized behavioral problems, concluding that only boys with higher levels of externalizing problem behaviors had low cortisol levels.

Although findings concerning cortisol response to stress were inconsistent in early studies, recent research with larger samples or better methodology has not provided convincing evidence of cortisol changes in non-comorbid forms of ADHD. Several of these studies have not examined the differences of cortisol's reactivity in the three sub-types of ADHD as specified by the DSM IV-TR. Therefore, it is not clear whether the cortisol decrease in response to a stressor is a characteristic of the ADHD diagnosis or of one of its subtypes (Randazzo et al., 2008).

It is important to emphasize that until the last decade, knowledge about the function of the HPA axis was limited to research in animals and human adults. The lack of research in children and adolescents was likely because of the invasive techniques needed to obtain cortisol samples. Currently, the high sensitivity of the immunoassay to measure salivary cortisol, given the significant correlation between free salivary and total plasma cortisol levels in both adults and children, facilitated these studies in young samples (Kahn et al., 1988; Klimes-Dougan et al., 2001; Raff et al., 1998).

Furthermore, most previous studies have important differences in their methodological designs, such as sampling, diagnostic assessments, repeated cortisol measures, and stressors (Lackschewitz et al., 2008; Randazzo et al., 2008). Another major limitation has been the lack of assessment of comorbid disorders. Thus, we decided to study a sample of ADHD without psychiatric comorbidities.

These study objectives were: a) to investigate difference of cortisol reactivity to stress in ADHD subtypes; b) to compare the ADHD group with healthy controls.

2. Method

This project was approved by the Research Ethics Committee of UNIFESP-HSP (protocol no 1616/06). The control patients and their families were provided with information about the study procedures. The parents of the children who agreed to participate in the study signed an informed consent form.

2.1. Subjects

The subjects were selected from children consecutively enrolled by their parents at the Center of Neuropsychological Interdisciplinary Child Care, Department of Psychobiology, Universidade Federal de São Paulo (UNIFESP). This Center has expertise in the diagnosis and interdisciplinary research on neurodevelopmental disorders, delivery of care, research and teaching with an emphasis on ADHD.

The inclusion criteria were as follows: 1) children and adolescents between 6 and 17 years of age from both genders, 2) a diagnosis of ADHD, 3) no history of psychostimulant medication use or any other medication that might interfere with cortisol production, 4) no history of a serious medical illness (e.g., diabetes, epilepsy), 5) no comorbid mental disorder, and 6) an IQ score higher than 75 points.

The control group was obtained from schools, either public or private, to keep the pairing also from the same grade, without mental disorders and use of any medication.

2.2. Diagnostic evaluation

A diagnosis of ADHD was made based on psychiatric, neurological and neuropsychological evaluations. The diagnosis of ADHD was based on the application of a Brazilian version of the SNAP-IV and the CBCL (Child Behavior Checklist). The SNAP-IV is a questionnaire consisting of symptoms from the Diagnostic and Statistical Manual - Fourth Edition (DSM–IV) of the American Psychiatric Association which has been validated in Brazil (Mattos et al., 2006). It permits the classification of ADHD subtypes. The CBCL is a questionnaire that assesses social competence and behavior problems at ages 4 to 18 years, from information provided by the parents, and it has been previously validated in Brazil (Duarte and Bordin, 2000). Both were applied to parents or guardians. The children, following their parents' above–mentioned assessment, underwent a battery of neuropsychological tests, including the continuous performance test (Rizzutti et al., 2008). Then, they were evaluated by a child specialist: a neurologist and a psychiatrist. At the end of this evaluation, their cases were discussed by the service team and the diagnoses established.

A social evaluation was run with the Brazil Criteria of Economic Classification, a self-reported questionnaire (ABEP, 2003), which is divided into seven categories based on the values obtained.

The neuropsychological protocol included the following: 1) Intellectual Level Assessment: (Wechsler Intelligence Scale for Children; WISC-III abbreviated) (Wechsler, 2002); 2) Computerized Attention Test: CPT – Conners' Continuous Performance Test (Conners, 2000; Miranda et al., 2008) – assesses sustained attention abilities and mental flexibility. The Conners' CPT is a computerized visual task that requires distinguishing non-target (X letters) and target (non-X letters) stimuli. The child is instructed to press the computer keyboard for any key that appears on the screen, except for the X. The program generates several measures indicating inattention, impulsivity or sustained attention problems and *t*-scores and percentiles were only used as auxiliary to the ADHD diagnoses. The CPT scores above 50% were considered suggestive of a clinical diagnosis of inattention. 3) Working memory assessed with: a) forward and backward Digit Span (Lezak, 1995), which assesses the phonological loop component of working memory; b) forward and backward Corsi blocks (Lezak, 1995), which measure the ability to reproduce a sequence of stimuli (blocks) in a visuo-spatial design. 4) Rey Figure: a task for assessing the visual constructive functions (Rey Copy) as well as visual memory (Rey Memory) through a guided reproduction from memory of a complex figure (Meyers and Meyers, 1995); 5) Attention: Symbols Cancelation (Mesulam, 1985); 6) Mental Flexibility: Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993);

2.3. Experimental procedures

The CPT was used as the stressor test, besides being part of the standard initial assessment. It has been chosen because previous studies have shown absence of learning effects as well as its use as a stressor (Quay, 1997; King et al., 1998; Hong et al., 2003; Yang et al., 2007; Lackschewitz et al., 2008). Furthermore, other stressor tests such as those involving social performance (Klimes-Dougan et al., 2001), competition with videotaped opponent (Snoek et al., 2004), and mathematical tests (Randazzo et al., 2008) have not been validated in Brazil.

The salivary samples were always collected in the children's schools, between 1 pm and 4 pm (Kirschbaum, et al., 1990).The four samples were collected at the following time points: 15 min before exposing the subject to the CPT (pre-test) = Time Zero (T0); post-test 20 min = Time 1 (T1), 40 min = Time 2 (T2); and 60 min = Time 3 (T3).

These samples were collected using the Sarsted Salivette — SALIVETTE ® system. Each sample was collected after mouth washing with filtered water, and after an interval of at least 30 min following ingestion of solid or liquid food. The samples were placed into plastic tubes by the subject directly spitting or by using the Salivette which contains chewable cotton as an aid for the salivary secretion. Citric acid was not used to stimulate saliva production because there have been reports that it causes an artificial elevation in the levels of cortisol (Schwartz et al., 1998) and modern biochemical methods only require a small amount of saliva for analysis (Snoek et al., 2004).

Later, cortisol in the salivary samples was measured twice using the EIA method (DSL — Diagnostic Systems Laboratories, Inc-Texas, USA). The intra- and inter-assay coefficients of variation were $0.1\% \pm 0.01$ intra-assay and $3.70\% \pm 0.03$ inter-assay for low cortisol levels and $8.8\% \pm 0.15$ intra-assay and $6.40\% \pm 0.006$ inter-assay for high cortisol levels. The sensitivity of this method was 0.05 μg/mL. The samples were measured at the Validation and Research Brandi Diagnostic Medicine of the Association Fund of Incentive to Psychopharmacology (AFIP).

2.4. Statistical analysis

The socio-demographic data were expressed as means, standard deviations and percentages. All statistical analyses used SPSS v. 16.0 (SPSS Inc., an IBM Company). An Analysis of Variance for repeated measurements (ANOVA) taking age as a covariate was used to analyze the levels of cortisol at the four different time-points for the