

Effect of Psychostimulants on Distinct Attentional Parameters in Attentional Deficit/Hyperactivity Disorder

JAVIER LÓPEZ¹, VLADIMIR LÓPEZ¹, DANIEL ROJAS¹, XIMENA CARRASCO^{1,2}, PAULA ROTHHAMMER¹, RICARDO GARCÍA³, FRANCISCO ROTHHAMMER³ and FRANCISCO ABOITIZ¹.

¹ Departamento de Psiquiatría y Centro de Investigaciones Médicas, Escuela de Medicina, Pontificia Universidad Católica de Chile.

² Programa de Morfología, Instituto de Ciencias Biomédicas. Facultad de Medicina, Universidad de Chile.

³ Programa de Genética, Instituto de Ciencias Biomédicas. Facultad de Medicina, Universidad de Chile.

ABSTRACT

Although there is extensive literature about the effects of stimulants on sustained attention tasks in attentional deficit/hyperactivity disorder (ADHD), little is known about the effect of these drugs on other attentional tasks involving different neural systems. In this study we measured the effect of stimulants on ADHD children, both in the electroencephalographic (EEG) activity during sustained attentional tasks and in psychometric performance during selective attentional tasks. These tasks are known to rely on different cortical networks. Our results in children medicated with 10 mg of d-amphetamine administered 60 min before the study indicate (i) a significant increase in amplitude but not latency of the P300 component of the event-related potential (ERP) during the sustained attentional task and (ii) a significant improvement in the reaction times and correct responses in the selective attentional task. In addition to supporting the use of stimulants in children with attentional deficit/hyperactivity disorder, these results show a multifocal activity improvement of cortical structures linked to dopamine, and interestingly, to attention. All these analyses are framed in a wider study of diverse attentional functions in this syndrome.

Key terms: Attentional deficit, EEG, event-related potentials, hyperactivity, Stroop, p300.

INTRODUCTION

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), defines attentional deficit/hyperactivity disorder (ADHD) as a complex syndrome involving attentional and hyperactivity impairments to a variable degree, in which there may be emphasis on attentional deficit, on hyperactivity or both. This condition affects between 1 % and 9.5 % of the world's child population, and is more common in boys than in girls (Barkley, 1997, 1998; Sergeant, 2000). ADHD in adults has also been reported, and about 30-60 % of ADHD children are believed to maintain this condition as adults (Barkley, 1997; Sachdev, 1999).

The exact etiology of ADHD is not yet known. Some genetic markers have been described, such as a polymorphism on the exon 3 of the gene coding for the dopaminergic receptor D4 (Cook et al, 1995; Sunohara et al., 2000), in which the allele 7R-DRD4 is associated with the syndrome. Other studies indicate a reduction of dopaminergic and noradrenergic metabolites (Andreasen and Black, 1995), an imbalance between these systems (Tucker and Williamson, 1984; Cocores et al., 1987; Malone et al., 1994) or a dopaminergic/serotonergic imbalance (Oades and Müller, 1997). A current interpretation is that this condition derives from a catecholaminergic (especially dopaminergic) impairment (Lou et al., 1989; Hynd et al., 1993; Castellanos et

Corresponding author: Francisco Aboitiz Ph.D., Departamento de Psiquiatría y Centro de Investigaciones Médicas, Escuela de Medicina, Pontificia Universidad Católica de Chile. Ave. Marcoleta N° 387, 2° piso. Casilla 114-D Santiago 1, Chile. Tel.: (56-2) 354 3808; 354 3028. Fax: (56-2) 665 1951. E-mail: faboitiz@puc.cl; faboitiz@med.puc.cl

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al., 1994; Aylward et al., 1996; Barkley, 1997, 1998; Vaidya et al., 1998; Vaidya and Gabrieli, 1999).

Consistent with this interpretation, it is widely known that ADHD treatment relies on psychostimulants such as amphetamine and derived forms such as dextroamphetamine and methylphenidate, which facilitate dopaminergic transmission in the ventral forebrain and the prefrontal cortex. Some differences have been described between both types of drugs, although there are no clear advantages of one over the other (Elia et al., 1991).

Although the effect of stimulants on daily behavior and sustained attentional tasks on these patients is well known, there are few studies aimed at demonstrating the effect of these drugs on prefrontal-mediated executive functions. In ADHD children in whom stimulants are clinically effective, alterations in the theta and alpha waves of the electroencephalogram tend to disappear with treatment (Chabot et al., 1999). In addition, event-related potential (ERP) studies in sustained attentional tasks reveal a smaller amplitude of the N200 and P300 components, and a longer latency of the P300 component in unmedicated patients versus healthy controls (Satterfield, 1990; Satterfield et al., 1994; Oades et al., 1996; Kilpelainen et al., 1999). The P300 component is partly associated with frontal function, and the most accepted interpretation is that it relates to the involvement of executive and attentional resources (Desmedt, 1981; Mesulam, 1990; Smith et al., 2003; Karayanidis et al., 2000; Barry et al., 2003). There are some studies indicating an increase of the p300 amplitude with stimulant medication in ADHD (Seifert et al., 2003). However, there is still controversy regarding their effect on the P300 latency (Robaey et al., 1992; Satterfield et al., 1994; Strandburg et al., 1996; Taylor et al., 1993).

In this context, the object of this first study is to evaluate the performance of ADHD children with and without stimulants, in attentional tasks that probe frontal cortex function. In this article, we report the results on two tasks; the oddball paradigm which measures sustained

attention, and the Stroop task, measuring selective attention.

In the oddball paradigm, attention must be focused on an infrequent stimulus presented alternately with a frequent stimulus (Squires et al. 1976). The infrequent stimulus produces a P300 response, and the amplitude of this potential is related to the attention devoted to this task (Kutas et al., 1977). The Stroop task, on the other hand, measures selective attention and the inhibition of interfering stimuli, a task dependent on frontal function. The task consists of attending to congruent stimuli (for example, the word 'red' written in red) and to incongruent stimuli (the word 'red' written in green), and having to respond to the color and not the word.

Although both the oddball and the Stroop tasks involve frontal functions, there are differences in the specific frontal areas participating in these tasks. The P300 triggered by the oddball task has a frontoparietal topology and is considered to reflect coactivation of temporal, parietal, and frontal networks (Martin-Loeches 2001; Tarkka and Stokic, 1998). On the other hand, the Stroop paradigm generates specific activation in the cingulate cortex (related to detection of incongruences) and in the dorsolateral prefrontal cortex (related to executive functions and inhibition of irrelevant stimuli) (Pardo et al., 1990; MacDonald et al., 2000; Kerns et al., 2004). Therefore, this first study evaluates the effect of stimulants on SDAH patients on two different frontal functions involving anatomically distinct components. Our findings indicate that stimulants induce an increase in amplitude but not in latency of the P300 during the oddball task and improve performance in the Stroop task.

METHODS

We recruited 11 children (9-14 years old; 10 males 1 female) diagnosed with ADHD who were currently medicated with d-amphetamine. Diagnosis was confirmed according to DSM-IV criteria by a multidisciplinary team consisting of a child

psychiatrist, a child neurologist, and a psychologist. Patients did not present other psychiatric or neurologic conditions and were all right-handed. Patients and their parents agreed to participate in this study, signing an informed consent. The study was conducted while strictly following the ethical requirements of the Human Subject Committees from FONDECYT and the University of Chile.

Children were evaluated with (10mg d-amphetamine 60 minutes before the experiment) and without stimulants. The time between the two measurements was from 1 to 4 months. The conditions with or without medication and first and second measurements were counterbalanced in order to avoid the possible confounding effect of task training over medication outcome. Female-only performance was well within the range of the male subjects.

ERPs were recorded using a digital EEG system (10 bytes, 250 mps). Activity was recorded at three sites on the scalp according to the 10/20 standard, in positions Fz, Cz and Pz, referred to the ear lobules. Visual stimulation was performed with a 250 MHZ PowerPC Macintosh, with a 21" screen at 45 cm from the face. We also used a head restrainer in order to avoid head movements.

The tests were designed with the Macprobe stimulation software. The oddball task consisted of a frequent or standard stimulus (a male face), and an infrequent or target stimulus that had to be attended (a female face). Both stimuli were presented randomly in the center of the screen for 300 msec, had a 4x4cm size and a variable interstimulus interval between 150 and 600 msec. The frequency ratio between the standard and target stimuli was 8:1. The task consisted of mentally counting the times the subjects saw a female face. The EEG recording was filtered between 0.5 and 20 Hz, was segmented in intervals 1000 msec around the stimulus (200 msec before and 800 msec after) and a grand average was obtained for each subject and category. A

window between 250 and 400 msec after stimulus presentation was selected and the average of this time window was calculated. Statistics were performed using a repeated measure ANOVA with a Bonferroni adjustment to correct for errors in multiple univariate comparisons. Statistical significance was set at $P < 0.01$.

The Stroop test consisted of presenting a colored bar (blue, red or white) on the screen beside a color word written in white, both on a black background. The color bar and the word appeared in different visual fields with an eccentricity no less than 8° and the face at 50 cms from the screen. Subjects were instructed to respond only to color and to ignore the word. Response consisted of pressing one of three keys, one for each color. We measured reaction times and percentage of errors in these responses. These parameters were also statistically compared using a Repeated Measures ANOVA design with two factors (Coincidence X Treatment).

RESULTS

Event-related potentials (erps)

In comparison with the non-medicated condition, medication with stimulants produced an increase in P300 amplitude during the oddball task (Figs. 1, 2). There were no significant differences in the latency of this component. All children correctly counted the number of target stimuli that were presented in both situations.

Stroop test

The Stroop test showed a reduction of the response times and a decrease in the percentage of errors in the medicated condition for both coincident and not coincident stimuli (Fig 3). We did not detect asymmetries in the response to lateralized stimuli or group differences among them.

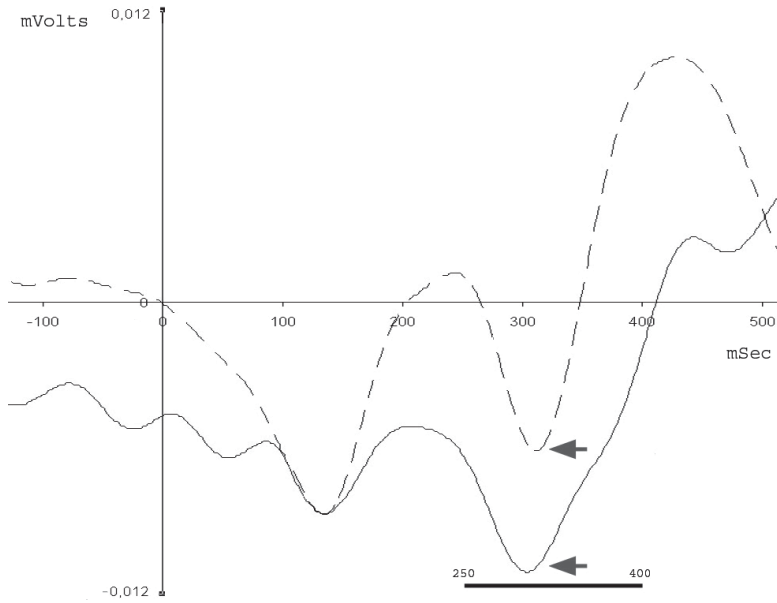


Figure 1. Grand means of ERPs from ADHD children, in conditions of medication with stimulant (continuous line) and no medication (discontinuous line). Arrows indicate the P300 potential, which has more amplitude but the same latency in medicated than in non-medicated conditions (see Fig. 2). This method showed significant effects of medication, of subject and of subject x medication interaction, indicating individual differences in response to treatment, but also a general effect of treatment in all subjects.

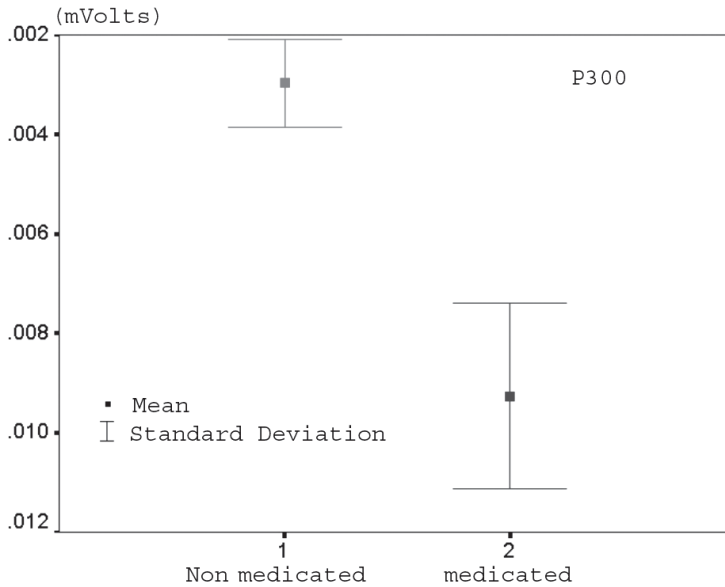


Figure 2. Mean and Standard Deviation of the amplitude of P300 ERP component in ADHD children. Conditions: not medicated and stimulant medication. Voltage Scale is inverted with greater values at the bottom of the chart. Repeated Measures ANOVA yielded a significant effect for the factor medication ($F_{(1,25)}=143.9, p<0.01$) assuring an increase in P300 amplitude after stimulant treatment.

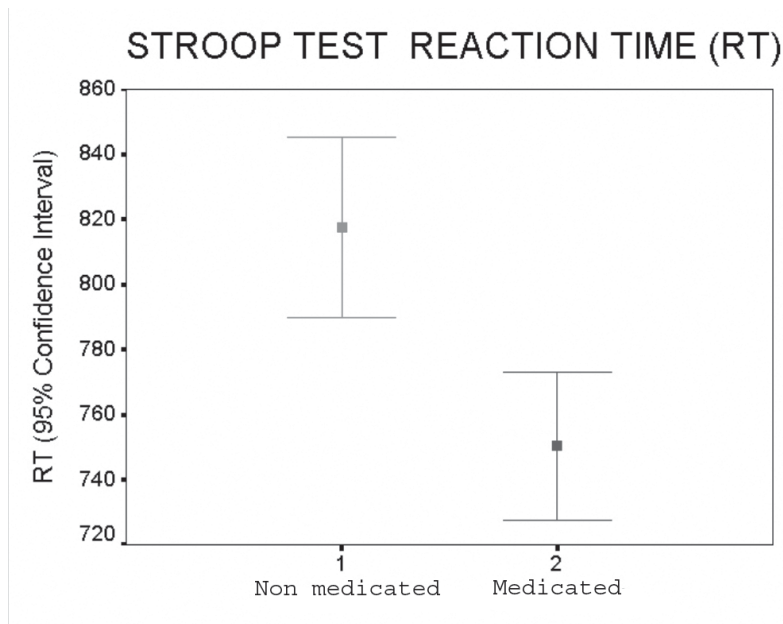


Figure 3. Reaction times in the Stroop task (Mean and 95% confidence intervals). Stimulant Medication produced a significant reduction of reaction times in all subjects, independently of whether it was applied in the first or in the second measurement. ($F_{(1,601)}=7.78$, $p<0.01$) Apart from faster reaction times subjects also showed a significant reduction of errors in the medicated condition.

DISCUSSION

The present study indicates that treatment with stimulants produces an improvement of different estimators of sustained and selective attention. This confirms the validity of the use of these drugs in ADHD treatment and is a first step toward the construction of a database describing the attentional capacities of ADHD children. We suggest that procedures like those reported here may be useful tools in testing the effectiveness of stimulants in single cases. In this way, it is possible to make a more informed choice regarding possibilities of psychopedagogical or pharmacological treatments.

Our results suggest a multifocal activity improvement of cortical structures linked to dopamine, and interestingly, to attention. Performance in the Stroop test has been correlated with the activity of Anterior Cingulate and Dorsolateral Prefrontal cortex (Pardo et al., 1990; MacDonald et al., 2000; Kerns et al., 2004), while the P300 component of the ERP has been extensively used as an index of frontal function

(Martin-Loeches, 2001). It has been hypothesized that cognitive impairment associated with ADHD may result from a hypodopaminergic state in these areas, which normally receive profuse innervation from the mesocortical dopaminergic system of the ventral tegmental region (Durstun, 2003). Stimulants may then act by increasing prefrontal dopaminergic neurotransmission, resulting in improvement in both cognitive functioning and behavioral symptoms.

Pharmacological treatment is an essential part of the global treatment of ADHD, although there has been some recent controversy due to overmedication in children who do not meet their parents' expectations and the possibility that stimulants may later induce substance abuse. However, those instances in which stimulant medication has been correlated with chemical dependence correspond to healthy children or subjects with a history of substance abuse (Kollins, 2003). Furthermore, recent studies show that stimulant medication protects ADHD children from later drug abuse (Faraone and

Wilens, 2003; Kollins, 2003). In fact, there are no consistent reports to indicate that stimulant use for long periods induces drug abuse, manic disorder, psychosis, or other psychopathological signs. This evidence is most relevant when considering that ADHD patients represent a group that is especially vulnerable to developing addictive and other antisocial behaviors (Comings, 1993; Cocores et al., 1987; Lawford et al., 1995).

Interestingly, not all attentional functions are impaired in ADHD. These patients show a consistent deficit in sustained attention and in some selective attention tasks, which are those used in this first report. However, ADHD children respond faster in all externally presented attentional tasks and make fewer mistakes in divided attention tasks (Koschack et al., 2003; see also López et al., 2003). On the basis of this evidence, these authors propose a differential attentional pattern rather than an overall attentional deficit for these children. They found that ADHD may consist of a different distribution of attentional resources with a wider spatial (peripheral) attentional framework and with a narrower time constant (decreased sustained attention).

Within this context, it has been found that the ADHD-associated 7R-DRD4 genetic polymorphism appeared some 40,000 years ago and was subject to intense positive selection, perhaps in an environment that favored risk-taking behavior and peripheral attention (Ding et al., 2002). An ADHD-like wide spatial attentional framework may thus correspond to a more primitive attentional system, while in the course of more recent human evolution the mechanisms involved in sustained attention have undergone significant development in relation to elaborate tool-making, reading and writing, and other human activities. (Aboitz and García, 1997).

Finally, we consider it fundamental to initiate cognitive studies concerning the diversity in attentional strategies in these children and the effects of stimulants on them. The question arises as to whether medication is actually correcting an impairment or restricting the natural

populational variability according to increasing cognitive demands of modern life. This is the first of a series of studies aimed at clearing up this question.

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