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Psychiatry Research 141 (2006) 315–320
PSYCHIATRY RESEARCH
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Effect of methylphenidate on Stroop Color–Word task performance in children with attention deficit hyperactivity disorder

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Received 25 March 2005; received in revised form 8 September 2005; accepted 18 September 2005
Dedicated to the memory of Glenn Austin

Abstract

Attention deficit hyperactivity disorder (ADHD) is a neuropsychiatric syndrome common in the pediatric population. It is associated with multiple nonspecific deficits on neuropsychological tests of executive function, and a beneficial response to pharmacotherapy with methylphenidate (MPH) and other psychostimulants. The Stroop Color–Word task is used empirically as an aid in diagnosis and treatment monitoring of ADHD; however, data on the sensitivity of the Stroop interference score to the effects of MPH are limited. To address this issue, we studied Stroop performance in a cohort of 18 MPH-treated prepubescent boys with ADHD and six healthy controls on and off MPH treatment conditions. MPH significantly improved performance in both groups, with the ADHD participants consistently displaying worse scores than those of controls both on and off MPH. These results suggest that though the diagnostic value of the Stroop task in ADHD remains controversial, it has heuristic value for monitoring clinical responses to MPH treatment. More research is needed to ascertain the clinical significance of our findings and to replicate this relatively small effect in a larger cohort, to determine whether MPH effects on Stroop performance are specific to ADHD symptoms or they generalize to other forms of symptomatology.

Keywords: Methylphenidate; Interference; Response inhibition; Attention deficit hyperactivity disorder

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0165-1781/$ - see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.psychres.2005.09.007

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized by locomotor hyperactivity, impulsivity and inattention (American Psychiatric Association, 1994). Due to the lack of established psychometric or biological markers, ADHD diagnosis is dependent upon clinical history, physical examination, and observation. The accuracy of both the diagnosis and the treatment follow-up in ADHD is limited by the lack of pathognomonic psychometric and biological markers and the high incidence of psychiatric co-morbidity. Moreover, symptoms of ADHD are highly context dependent, further complicating treatment follow-up. The primary ADHD symptoms have been attributed to a core deficit in response inhibition (Barkley, 1997a,b), as evidenced by deficits in performance of tasks requiring intermittent withholding of response (Aron and Poldrack, 2005); however, the deficits that children with ADHD exhibit on other neuropsychological tasks suggest broader core psychopathology (Rapport et al., 2001; Nigg, 2005).

In addition to the deficits in behavioral response inhibition, ADHD has been associated with deficits on a variety of neuropsychological tasks broadly described as measures of "executive functioning" (Barkley, 1997a,b; Shallice et al., 2002; Nigg, 2005). One of the classic tasks of this type is the Stroop Color–Word task, and the associated Stroop effect (Stroop, 1935; Rapport et al., 2001; Reeve and Schandler, 2001; van Mourik et al., 2005). The Stroop "interference" effect is the decrease in the speed of reading words that are incongruent with the color of the ink in which they are printed and the word's meaning (e.g. the word "red" written in blue), relatively to the "color-matched" words and shapes (Stroop, 1935; Golden, 1976; van Mourik et al., 2005). The neuropsychological mechanisms underlying this effect are not fully understood (Kipp, 2005). Traditionally, the theoretical justification for Stroop's diagnostic validity in ADHD was based on the association between cognitive "interference" and behavioral response inhibition. The putative basic neural mechanism mediating the Stroop effect both in ADHD and in health was response competition between the relatively automatic word reading and the less habitual color naming; some have been experimentally demonstrated (Peterson et al., 1999; Nigg, 2005; van Veen and Carter, 2005). An influential rationale for the increased Stroop effect in ADHD is a deficit in attentional modulation of the distributed parallel pathways processing word and color stimuli (Cohen et al., 1990; Carter et al., 1995; Peterson et al., 1999). The sensitivity of the Stroop effect to untreated ADHD (Reeve and Schandler, 2001; Shallice et al., 2002; van Mourik et al., 2005) has not been uniform, yet the Stroop task is widely used empirically as an aid in clinical diagnosis (Golden, 1976; Seidman et al., 1997; Katz et al., 1998; Bedard et al., 2002; Nigg et al., 2002; Rucklidge and Tannock, 2002; Schmitz et al., 2002; Shallice et al., 2002).

One of the more consistent features of ADHD is the behavioral response to methylphenidate (MPH) and other psychostimulants (Solanto, 1998; MTA, 2004). The difference in the acute response to MPH between ADHD and health is quantitative rather than qualitative (Rapoport et al., 1978; Weingartner et al., 1980); ethical considerations preclude controlled studies of chronic MPH administration to healthy subjects. Although current hypotheses of ADHD predict that MPH should reduce the Stroop interference effect in ADHD, experimental data of MPH's effect on Stroop performance in children with ADHD are inconclusive, with at least one recent placebo-controlled study reporting improved inhibitory but not interference control in children with ADHD (Scheres et al., 2003). A recent meta-analysis of Stroop performance in ADHD deemed the number of studies on the effect of MPH insufficient for analysis (van Mourik et al., 2005). Thus, though the specificity of the Stroop effect to ADHD has been challenged, it may have clinical value as a treatment follow-up instrument, if shown to be sensitive to stimulant therapy in ADHD, especially in comparison with healthy controls.

The purpose of the present study was to test the effect of MPH on Stroop performance in prepubescent boys with ADHD. We hypothesized that: 1) MPH would reduce the Stroop interference effect in the ADHD cohort and 2) children with ADHD would demonstrate a larger MPH effect than the controls.

2. Methods

The study protocol was approved by the Stanford University Hospital institutional review board. All parents gave written informed consent and the children assented to participate. Eighteen prepubescent boys (mean age = 10.2 years; range = 8.1–12.9, S.D. = 1.3) with ADHD, who demonstrated a favorable clinical response to an average of 12 weeks (range = 8–16) of MPH therapy, were included in the study. All participants were of Caucasian origin. The ADHD diagnosis was confirmed by a multidisciplinary team using clinical history, the Conners Teachers scale, the parents' and teachers' Swanson, Nolan, and Pelham scale (SNAP), and the Wechsler Intelligence Scale for Children, Third Edition (WISC) (Conners, 1989; Wechsler, 1991; Swanson, 1992). Exclusion criteria were a *T*-score < 2 S.D. on the Conners scale above the population mean (mean = 50, S.D. = 10); treatment with medications other than MPH; verbal IQ < 85; history of head trauma, premature birth, or chronic medical or psychiatric disorder other than ADHD. Six demographically matched healthy boys (mean age = 10.8 years; range = 7.4–12.2, S.D. 1.7), participated as controls. Their verbal IQ (WISC III) was slightly higher (125.7 ± 4.1 vs. 114.4 ± 13.8), albeit not significantly ($P < 0.07$, two-tailed *t*-test). The Stroop Color and Word Test© (Stoelting Co., 620 White Lane, Wood Dale, IL 60191, 1994) was performed twice: "on-MPH" and "off-MPH." In the ADHD cohort, the off-MPH condition was achieved by withholding MPH for 36 h and in the controls by testing at least 1 week before or after the single test MPH dose. For the "on-MPH" condition, the morning of the session, ADHD participants received their usual prescribed dose of 10 to 30 mg of MPH, and the controls received a single 10-mg dose of MPH. The on- and off-MPH sessions were conducted 1 to 3 weeks apart, counterbalanced so that approximately half of the participants were tested off-MPH first. The Stroop "interference score" (IntS) was derived by correcting the raw Color–Word (CWS) score by the age-adjusted Word (WS), Color (CS) scores, which reflect the baseline reading and color recognition (Golden, 1976; van Mourik et al., 2005). A higher IntS indicates *less* interference. The investigator performing the Stroop task was blind to the medication state and diagnosis of the participants.

3. Results

One-way ANOVA with group (ADHD and control) as the between-subjects factor and treatment condition (on- and off-MPH) as the within-subject factor revealed that following MPH administration, there was an overall increase (improvement) in the IntS (treatment effect: $F = 8.68$, $df = 1.22$; $P = 0.007$). In addition, we observed a group difference, with ADHD subjects performing worse than controls across both treatment conditions (group effect: $F = 6.27$, $df = 1,22$, $P = 0.019$). There was no significant interaction between group and treatment condition ($F = 0.99$, $df = 1,22$, $P = 0.329$) (Fig. 1).

A post hoc paired *t*-test detected MPH-induced significant increases in the IntS for ADHD participants (48.57 ± 4.07 vs. 50.71 ± 4.84; $t = 2.37$, $df = 1,34$, $P = 0.028$), but not for healthy controls (52.33 ± 5.72 vs. 56.67 ± 6.28; $t = 1.60$, $df = 1.10$, $P = 0.172$). The latter results did not reach statistical significance, perhaps by Type II error resulting from the small sample size.

Secondary analyses were conducted on each of the three subscores used to derive the IntS (i.e. the WS, CS, and CWS). Each of these variables were modeled using repeated measures ANOVA, with group (ADHD and control) as the between-subjects factor and treatment condition (on- and off-MPH) as the within-subject factor. For WS, MPH administration resulted in a significant effect of medication ($F(1,25) = 4.32$, $P = 0.048$) and of group ($F(1,25) = 6.89$, $P = 0.015$). Similarly, For CS, we the medication ($F(1,25) = 9.53$, $P = 0.005$) and the group ($F(1,25) = 8.86$, $P = 0.006$)

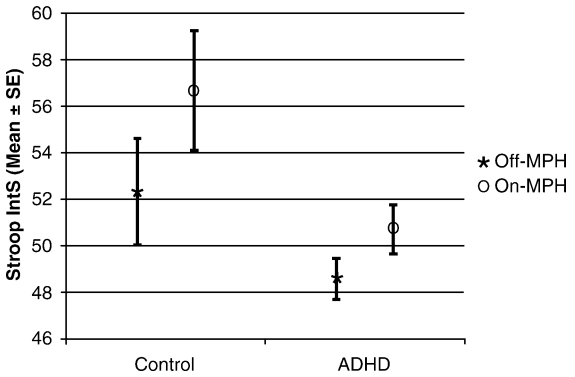

Fig. 1. Stroop interference effect in ADHD ($n = 18$) and controls ($n = 6$) on and off methylphenidate.

effects were similarly significant. Lastly, for CWS, we observed a highly significant effect of medication ($F(1,25)=23.27$, $P<0.001$) and group ($F(1,25)=11.064$, $P=0.003$).

4. Discussion

We found a statistically significant yet modest (approximately 4%) improvement in Stroop response interference scores of children with ADHD after administration of MPH. Inquiry into behavioral correlates of these findings (e.g. classroom performance) will help assess the clinical potential of these findings. Our findings are consistent with prior reports of an increased interference effect and associated neurophysiological abnormalities in ADHD (Bush et al., 1999; Shallice et al., 2002) and with the putative neuropsychological mechanism of action of MPH through enhancement of stimulus salience (Volkow et al., 2005). Our results contrast with two prior studies in children with ADHD (Bedard et al., 2002; Scheres et al., 2003) that did not show an improvement in interference score with MPH, though in Bedard et al. the color and word scores improved significantly. Methodological differences (fixed vs. varied dosing) and the absence of a healthy control group in both prior studies complicate the comparisons between studies and call for further elucidation of the effects of MPH on the Stroop interference effect.

The main effect of group on Stroop data supports the hypothesis that ADHD is associated with a deficiency in resistance to interference that is improved by MPH (van Mourik et al., 2005). This indicates that the Stroop task could be a useful adjunct clinical measure of response to MPH and possibly other stimulant pharmacotherapies. This conclusion is in agreement with previous reports showing that although it may not be specific for ADHD (Katz et al., 1998), performance on the Stroop task is a robust predictor of hyperactive/impulsive ADHD symptoms (Rucklidge and Tannock, 2002) and is sensitive to stimulant effects (Everett et al., 1991; Weingartner et al., 1980). Our findings support the hypothesis that the therapeutic action of MPH is to enhance the salience of the relevant stimuli, essentially increasing the "signal-to-noise" ratio of the distributed parallel systems processing sensory inputs (Volkow et al., 2005). This mechanism could account for the reduced interference we see in the control group after MPH. In our sample, the effect of MPH was more robust in the color than the word score. Although this is not a reliable indication of the effect size, the observation is consistent with prior studies and supports the notion that color naming may be less "automatic" than word reading (Scheres et al., 2004; Nigg, 2005). These data do not add to the debate on the diagnostic specificity of the Stroop task or provide an indication of the expected effect size of MPH on the Stroop performance.

Our study has a number of limitations. A male-only cohort was studied due to the difficulty involved in recruiting girls from a clinic-referred population (Barkley, 1997a,b; Ernst, 1999). Therefore, our results may not apply to females with ADHD. The duration of the drug discontinuation was aimed at exceeding five MPH half-lives to render our subjects free of the clinical effects of MPH, while trying to avoid potential clinical impact of treatment discontinuation (Kimko et al., 1999). Although most clinical data argue against tolerance to the clinical effects of MPH, the existence of sensitization and tolerance with D-amphetamine and cocaine, which share many pharmacological properties with MPH, indicates that this issue requires further investigation (Mendelson et al., 1998; Swanson et al., 1999; Volkow et al., 1999; Scheres et al., 2003). The MPH administration schedule in our study was also constrained by the inability to administer chronic MPH to the normal controls. The off-MPH condition in the ADHD group was 36 h after 8 to 12 weeks of MPH therapy, while in the controls it was 36 h after a single MPH dose. Therefore, the schedules of MPH administration in the two groups are only comparable under the assumption that there is no MPH effect beyond 36 h. An additional potential confound is related to a possibility of performance expectation bias that could have resulted due to the absence of a placebo pill in this study. To offset this issue, the investigators, the participants and their parents were kept blind to the study hypothesis and the investigators were blind to the subjects' MPH status. Although these argue against non-specific anticipatory effects as a basis for decreased performance on this task, future studies employing a true placebo condition may be warranted to fully rectify this issue. Finally, the small sample

size limits the interpretability of the negative findings in the control group. The small number of normal controls was caused by the difficulty to recruit participants for a protocol involving administration of a psychostimulant to healthy children.

In conclusion, we demonstrated that MPH improves performance on one of the common tests of executive function. Although the small number of controls precluded a conclusive test of the potentially discriminating effects of MPH on the Stroop interference effect, our findings suggest that improvements were comparable in the ADHD and control groups and, hence, not specifically related to the diagnosis. However, even in the absence of diagnostic specificity, our results suggest that the Stroop task may be a useful tool for the clinical monitoring of MPH response in children with ADHD.

Acknowledgment

This study was supported by grants from the El Camino District Hospital Board and the National Institute on Drug Abuse.

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