BRIEF REPORT

Methylphenidate Improves Response Inhibition in Adults with Attention-Deficit/Hyperactivity Disorder

Adam R. Aron, Jonathon H. Dowson, Barbara J. Sahakian, and Trevor W. Robbins

Background: *Response inhibition is an executive function that requires voluntary control over responses when there is a change of context. The right inferior frontal cortex is necessary for response inhibition, and a deficit in right frontostriatal circuitry might underlie attention-deficit/hyperactivity disorder (ADHD). Many studies of childhood ADHD have demonstrated impaired response inhibition and its amelioration by methylphenidate (MPH). The current study tested response inhibition and the effect of MPH in adult ADHD.*

Methods: *Response inhibition was assessed with the "tracking" stop-signal test in 13 adults with a diagnosis of ADHD, both while taking and while not taking medication, and 13 healthy, unmedicated, age- and intelligence quotient–matched control subjects.*

Results: *Stop-signal reaction time was significantly slower in unmedicated adults with ADHD relative to healthy control subjects, and this deficit was significantly ameliorated by medication.*

Conclusions: *Adult ADHD patients had a response inhibition profile similar to that produced by lesions to the right inferior frontal cortex, which was remedied by stimulant medication.* Biol Psychiatry 2003;54: 1465–1468 © *2003 Society of Biological Psychiatry*

Key Words: Executive function, stimulant drugs, stop-signal, frontal cortex, impulsivity, right hemisphere

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a clinical syndrome with features that include inattention and hyperactivity, and it is often conceptualized as involving executive dysfunction (Barkley 1997; Downey et al 1997; Wender et al 2001). Executive functions are high-level cognitive control processes that optimize low-level subsidiary ones. The stop-signal response inhibition paradigm (Logan and Cowan 1984) has emerged as an important test of executive function by providing a precise measure of cognitive control: the time it takes to stop a prepotent response.

Response inhibition deficits have been demonstrated in children with ADHD compared with healthy volunteers (see Schachar et al 1993 and Oosterlaan et al 1998 for meta-analysis), and functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) indicate brain differences at a specifically right frontal focus (Casey et al 1997; Pliszka et al 2000; Rubia et al 1999). In adult neurologic patients, we have recently demonstrated that right but not left inferior frontal cortex is necessary for response inhibition, because response inhibition speed correlated highly with the amount of damage to that region (Aron et al 2003). Therefore, if adult ADHD subjects have right frontal cortex abnormalities, they should also have response inhibition deficits.

One study found adult ADHD patients to have a response inhibition deficit (Murphy 2002), another did not (Epstein et al 2001), and a third found mixed results depending on the type of ADHD diagnosis (Dinn et al 2001). None of these studies, however, investigated the effect of methylphenidate (MPH)—the main drug in clinical practice (Wilens et al 2002)—a stimulant that acts mainly as an indirect catecholamine agonist, thus increasing extracellular dopamine and norepinephrine levels by blocking transporters (Challman and Lipsky 2000). Showing that a response inhibition deficit in adult ADHD responds to stimulant medication, as has already been adequately documented in childhood ADHD (Tannock et al 1989a, 1989b; see Logan 2000 for review) could have importance for the treatment of the disorder.

Methods and Materials

Thirteen ADHD-diagnosed patients (10 male, mean ± SD age: 26.2 ± 6.9 years, age range: 18–41, estimated verbal intelligence quotient [IQ] from the National Adult Reading Test: 109 ± 7.2, mean Attention-Deficit Scales for Adults [ADSA] score: 205 ± 19.4), recruited from referrals to a psychiatric outpatient clinic for the assessment of adult ADHD, met the following requirements:

1. Self-report from the patient, and from an informant in relation to childhood features, indicating a current diagnosis of one of the types of DSM-IV ADHD (Barkley and Murphy 1998). For the diagnosis of ADHD "in partial remission," three or more self-reported criteria in one or both of the two sets of DSM-IV criteria (inattention or hyperactivity-impulsivity) were required, in addition to a positive informant's rating;

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2. A total score of 172 or above (well exceeding the average) on the ADSA self-report questionnaire for recent symptoms (Triolo and Murphy 1996);

3. A judgment by a consultant psychiatrist that the patient's symptoms did not arise from another disorder;

4. No history of a neurologic disorder, psychotic disorder, or, in the previous 2 months, substance-related disorder;

5. No history suggestive of current major depression; and

6. An estimated IQ of >90.

Consistent with previous reports, however (Pliszka 1998), the patients showed comorbidity (adults with ADHD are particularly likely to have substance-related disorders and mood disorders, as well as "Cluster B" personality disorders; Sachdev 1999), as assessed by the Brief Symptom Inventory (Derogatis 1993): mean Global Severity Index 1.7 ± .9 (i.e., within the range of clinically symptomatic ratings). Three patients received a diagnosis of ADHD "predominantly inattentive" type (ADHD/I), eight "combined" type (ADHD/C), and two patients ADHD "in partial remission." Three patients were asked to omit a regular regime of MPH medication for a minimum of 24 hours (at least six half-lives, Gualtieri et al 1982) before assessment.

Thirteen control subjects (8 male, mean age: 30.5 ± 5.0 years, age range: 25–40, IQ: 114 ± 4.3) were selected from nonclinical settings to match the patients as closely as possible for age [$t(24) = 1.63$, $p > .10$], gender, and IQ [$t(24) = 1.60$, $p > .10$]. Control subjects were not taking medication and had no previous contact with psychiatric services. The study was approved by the Cambridge Local Ethics Committee, and all subjects gave written informed consent.

Patients with ADHD were tested on 2 separate days in a double-blind design while taking and while not taking MPH. A standard dose of methylphenidate hydrochloride 30 mg (Spencer et al 1998) or placebo (lactose) was administered 75 min before the start of testing. Seven patients received drug first and then placebo, and six patients received placebo first, then drug, thus counterbalancing for potential practice effects. For the "placebo" comparison, six control subjects were tested once only, and seven were tested twice (with only second-session results used). The tests were 3 days apart on average.

The "tracking" stop-signal test was used (Figures 1 and 2). On each trial, a left- or right-pointing arrow stimulus was displayed on a computer screen. The subject responded with a left or right key press as quickly as possible (Go task) unless they heard a beep (a random 25% of trials), in which case they tried to withhold a response (Stop task). The stop-signal delay (SSD) varied. Each subject performed five blocks of 64 trials per block. The stop-signal paradigm allows a sensitive estimate of inhibitory control—the stop signal reaction time (SSRT)—reflecting the time it takes to internally suppress a response. Additional dependent measures were median Go reaction time (RT) (i.e., no-signal trials) and number of discrimination errors on such no-signal trials (e.g., a left key-press to a rightward arrow).

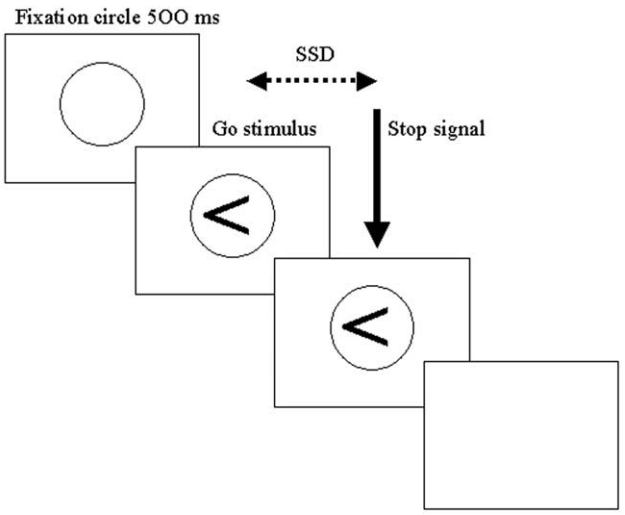

Figure 1. Composition of a single trial. The subject responds as fast as possible to the left- (or right-) pointing arrow with a left (or right) button press. On a minority of trials, a stop-signal beep sounds at the stop-signal delay (SSD).

Results

Stop-signal reaction time for unmedicated adults with ADHD (mean 195 ± 55 msec; P(inhibit) = 47%) was slower than for control subjects (153 ± 27 msec; P(inhibit) = 49%); a statistically significant difference [$t(1,17.3) = 2.5$, $p < .05$, two-tailed t test with Greenhouse-Geisser correction] (Figure 3), reflecting a large effect size of .97. Unmedicated adults with ADHD responded faster on no-signal trials (426 ± 86 msec) than control subjects (450 ± 99 msec), but this was not a significant difference; [$t(1,24) < 1$, ns]. Unmedicated adults made significantly more discrimination errors on no-signal trials (2.5%) compared with control subjects (.4%) ($U = 34.5$, $p < .05$, nonparametric test for unequal variances).

A pairwise t test (two-tailed) showed that adults with ADHD were significantly faster when medicated for SSRT (165 ± 50 msec) than when unmedicated (Figure 3) (195 ± 55 msec) [$t(1,12) = 4.2$, $p < .05$]; but this was not the case for no-signal RT (medicated: 426 ± 81 msec; unmedicated: 426 ± 86 msec) or for discrimination errors (medicated: 1.6%; unmedicated: 2.5%) [$t(1,12) = 1.3$, ns].

A split-half analysis of SSD after convergence on ~50% P(inhibit) (see Figure 2) (taking the average of staircases 1 and 3 vs. average of staircases 2 and 4) showed highly significant correlations within all three groups (medicated ADHD: $r = .94$; unmedicated ADHD: $r = .90$; control subjects: $r = .91$; all $p < .0001$), indicating good internal consistency of average SSD estimation. High reliability of SSRT estimation with the current method was confirmed by comparison between the current control group and a different control group in a different study in which the same stop-signal test was used (Turner et al 2002) (mean age: 28 years, mean SSRT: 160 msec [c.f. 153 msec for current study]).

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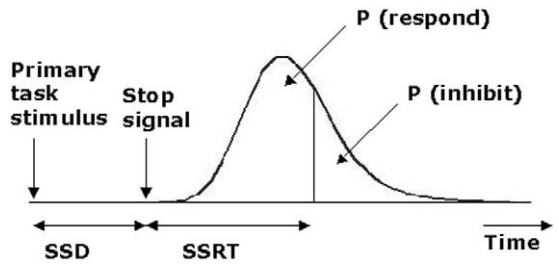

Figure 2. Race-Model estimation of stop-signal reaction time (SSRT) (Logan and Cowan 1984). A distribution of no-signal RTs (Go trials) is shown beneath the curve. On Stop trials, a tone occurs after the primary stimulus at a particular stop-signal delay (SSD). The stop-signal divides the no-signal RT distribution into two probabilities: A left part consisting of responses fast enough to escape inhibition P(respond), and a right part corresponding to P(inhibit). Provided SSD is varied to yield 50% P(inhibit)—the point of median no-signal RT—SSRT is estimable by subtracting average SSD from median no-signal RT. Convergence to 50% P(inhibit) is ensured by use of ("tracking") step-up and step-down interleaved staircases: If the subject inhibited successfully on a previous stop trial, then inhibition was made more difficult on the current stop trial by increasing the SSD by 50 msec; if the subject did not successfully inhibit on a previous stop trial, then SSD was decreased by 50 msec. Average SSD was computed from the values of four staircases after convergence on 50% P(inhibit).

Finally, in view of apparent executive function differences between subtypes of adult ADHD (Gansler et al 1998), descriptive measures are provided for the three patients with ADHD/I and the eight with ADHD/C. On placebo, SSRT was slower for ADHD/I (208 ± 61 msec) than for ADHD/C (187 ± 50 msec), and this was also the case while medicated (ADHD/I: 187 ± 17 msec; ADHD/C: 153 ± 28 msec). The reduction in SSRT with drug treatment was therefore greater for the ADHD/C group (34 ± 48 msec) than for the ADHD/I group (20 ± 51 msec).

Discussion

This study confirmed prior reports (Dinn et al 2001; Murphy 2002) of a response inhibition deficit in adult ADHD and showed that it can be ameliorated by MPH. Because studies with structural MRI (Castellanos et al 1994, 1996, 2002), fMRI (Casey et al 1997; Vaidya et al 1998), and electroencephalogram (Overtoom et al 2002; Pliszka et al 2000) strongly suggest a right frontal deficit underlying poor response inhibition in childhood ADHD, and because lesions of the right inferior frontal cortex in adults produce a response inhibition deficit on the same stop-signal test (Aron et al 2003), and two fMRI studies showed reduced frontal activation in adult ADHD (Bush et al 1999; Schweitzer et al 2000), adult ADHD might relate to right frontal pathology. This, however, requires direct confirmation through structural

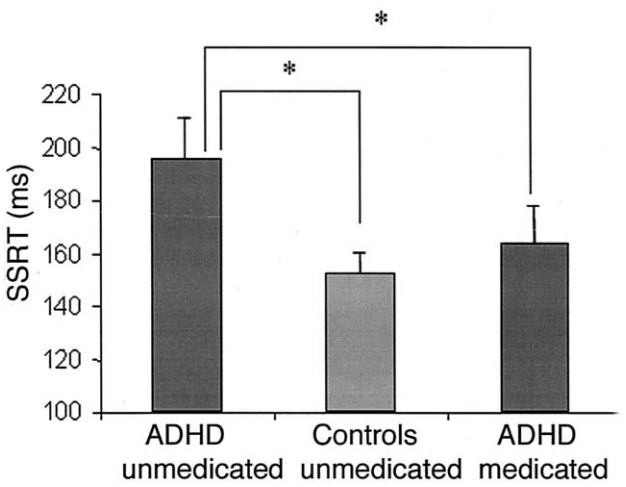

Figure 3. Response inhibition results. Unmedicated adults with attention-deficit/hyperactivity disorder (ADHD) were significantly slower in inhibiting a response to a stop-signal than healthy, unmedicated, age- and intelligence quotient–matched control subjects (*$p < .05$). Methylphenidate, a stimulant drug, led to significantly improved response inhibition performance for the adult ADHD subjects relative to when they were unmedicated (*$p < .05$). SSRT, stop-signal reaction time. Error bars represent SEM.

and functional studies. Additionally, pharmacologic neuroimaging might elucidate MPH effects in adult ADHD. Such a study in children established increased inferior frontal activation associated with MPH in both healthy and ADHD subjects performing a response inhibition task (Vaidya et al 1998).

Although the current sample was small, and, like other studies (Pliszka 1998), manifested comorbidity, the SSRT difference between unmedicated ADHD adults and control subjects represented a large effect size. Future studies, with much larger samples, might be capable of assessing to what extent personality, mood, and anxiety, as opposed to a purer deficit in executive function, might contribute to such a robust response inhibition deficit, and whether there is really a difference between the predominantly inattentive type and the "combined" type (inattentive/hyperactive-impulsive) of ADHD. If future studies establish that MPH speeds SSRT in adult ADHD to a greater degree than in matched control subjects, then the stop-signal test might assist classification and the evaluation of treatment response.

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