The Effect of Methylphenidate on Three Forms of Response Inhibition in Boys With AD/HD

Anouk Scheres,[1,6] **Jaap Oosterlaan,**[1] **James Swanson,**[2] **Sharon Morein-Zamir,**[3]
Nachson Meiran,[3] **Harry Schut,**[4] **Laurens Vlasveld,**[5] **and Joseph A. Sergeant**[1]

The current study was aimed at (a) investigating the effect of three doses methylphenidate (MPH) and placebo on inhibition of a prepotent response, inhibition of an ongoing response, and interference control in Attention Deficit/Hyperactivity Disorder (AD/HD), and (b) studying dose-response relations for the three forms of response inhibition. To meet these aims, the following tasks were selected: two versions of the Stop Paradigm for inhibition of a prepotent response, a Circle Tracing Task and a recently developed Follow Task for inhibition of an ongoing response, and the Stroop Color-Word Test and an Eriksen Flanker Task for interference control. These tasks were administered to 23 boys with AD/HD during four treatment conditions: 5 mg MPH, 10 mg MPH, 20 mg MPH, and placebo. A pseudorandomized, multiple-blind, placebo-controlled, within-subject design was used. As hypothesized, inhibitory control in children with AD/HD improved under MPH compared to placebo. However, this effect was only significant for inhibition of a prepotent response and inhibition of an ongoing response (as measured by the Follow Task), but not for interference control. The relation between treatment condition and response was linear. However, this linear relation was due to improved inhibitory control under MPH compared to placebo, because no effects of MPH *dose* were observed for any of the response inhibition measures.

KEY WORDS: AD/HD; ADHD; response inhibition; inhibitory control; methylphenidate.

INTRODUCTION

Attention Deficit/Hyperactivity Disorder (AD/HD) is one of the most common child psychiatric disorders. In the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (*DSM-IV*; American Psychiatric Association, 1994), three subtypes are distinguished, reflecting the possible combinations of the dimensions inat-

tention and hyperactivity/impulsivity. Currently, the focus of research is on the domain of impulsivity, which is usually defined as a lack of response inhibition (e.g., Barkley, 1997a; Halperin, McKay, Matier, & Sharma, 1994). Barkley (1997a, 1997b) suggested that behavioral inhibition is the primary executive function (EF), necessary to perform other EFs. According to Barkley, a deficit in inhibition, which is seen as the core dysfunction in AD/HD, will lead to other EF problems. Pennington and Ozonoff (1996) hypothesized that children with AD/HD have a deficit in response inhibition, but not in other EFs.

Barkley (1997a, 1997b) assumed that children with AD/HD are deficient in three forms of inhibition: (a) inhibition of a prepotent response, that is, a response that is or has been previously associated with reinforcement, (b) inhibition of an ongoing response (which allows for a delay in the decision to continue responding), and (c) interference control, that is, protecting a response from

[1] Department of Clinical Neuropsychology, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.
[2] Child Development Centre, University of California at Irvine, Irvine.
[3] Department of Behavioral Science, Ben-Gurion University of the Negev, Beer-Sheva, Israel.
[4] Parnassia Psychomedical Centre, The Hague, The Netherlands.
[5] Department of Paediatrics, Reinier de Graaf Gasthuis, Voorburg, The Netherlands.
[6] Address all correspondence to Anouk Scheres, New York University Child Study Center, 577 1st Avenue, New York City, New York 10016; e-mail: anouk.scheres@med.nyu.edu.

disruption by competing responses or events. The operationalization of these three forms of inhibition is not clear (Nigg, 2001). For example, Barkley reported results obtained from studies of AD/HD children employing the Stop Paradigm (see for review Oosterlaan, Logan, & Sergeant, 1998) as evidence for a deficit in inhibition of a prepotent response and in inhibition of an ongoing response. Recently, Nigg (2000) proposed a taxonomy of forms of inhibition in developmental psychopathology. In this proposed taxonomy, inhibition of a prepotent response (to be measured with the Stop Paradigm) is distinguishable from interference control (as measured by the Stroop Color-Word Test and Flanker Task). Inhibition of an ongoing response as defined by Barkley (1997a, 1997b) is not included in the taxonomy proposed by Nigg (2000). Suggested neural circuits in inhibition of a prepotent response involve the lateral and orbital prefrontal cortex. A neural system proposed to be crucial to interference control involves the anterior cingulate, the dorsolateral prefrontal cortex, and the basal ganglia.

Methylphenidate (MPH) is the most frequently prescribed medication for children with AD/HD (Goldman, Genel, Bezman, & Slanetz, 1998; Swanson, McBurnett, Christian, & Wigal, 1995). It has been shown to reduce symptoms of inattention, hyperactivity and impulsivity, as observed by parents and/or teachers (e.g., MTA cooperative group, 1999; Schachar & Tannock, 1993). Furthermore, it has been demonstrated that MPH increases performance on a variety of cognitive tasks (Rapport & Kelly, 1991), including tasks measuring response inhibition (e.g., Tannock, Schachar, Carr, Chajczyk, & Logan, 1989; Tannock, Schachar, & Logan, 1995). Given the fact that theories of impaired response inhibition are among the most widely recognized ones in trying to understand the main symptoms in children with AD/HD, it is surprising that only a few studies have focused on the effect of MPH on measures of response inhibition. A systematic analysis of the effect of MPH on different forms of response inhibition, as defined by Barkley (1997a, 1997b) has not been conducted thus far. The current study was designed to measure the effect of MPH on these three forms of response inhibition.

Selected Tasks to Study Three Forms of Response Inhibition

Inhibition of a Prepotent Response

The Stop Paradigm was used as a task to measure inhibition of a prepotent response. Performing the Stop Paradigm requires a subject to respond to a "go stimu-

lus." However, occasionally, a stop signal is presented and the prepotent response has to be inhibited. Two versions of the Stop Paradigm, which both aim at estimating the latency of the response inhibition process, were administered: One with stop signals presented at fixed intervals, and one applying a tracking mechanism to vary the interval between the go and the stop signal (Logan, 1994; Logan, Schachar, & Tannock, 1997; Osman, Kornblum, & Meyer, 1986). The Stop Paradigm with stop signals presented at fixed intervals has been used frequently in research on AD/HD (see for review Oosterlaan et al., 1998). However, the Stop Paradigm with a tracking mechanism has several advantages over the Stop Paradigm with stop signals presented at fixed delays (Band, van der Molen, & Logan, in press). For example, it allows a more reliable estimate of the latency of the response inhibition process (Stop Signal Reaction Time [SSRT]), and a shorter test administration than the version with stop signals presented at fixed delays. The Stop Paradigm with a tracking mechanism has been employed in a few studies of children with AD/HD (Chhabildas, Pennington, & Willcutt, 2001; Nigg, 1999; Schachar, Mota, Logan, Tannock, & Klim, 2000; Scheres, Oosterlaan, & Sergeant, 2001a, 2001b). Although both versions of the paradigm aim at estimating the latency of the stop process (SSRT), it is not clear whether the two versions yield similar SSRTs. In theory, the latency of the stop process is constant. Thus, SSRTs in both versions of the Stop Paradigm are expected to be identical. The two versions of the Stop Paradigm have been compared in only one study (Kooijmans, Scheres, & Oosterlaan, 2001), and the tracking version of the Stop Paradigm has not been used in evaluating the effect of medication. The current study investigated whether both tasks are equally sensitive to the effect of medication.

Inhibition of an Ongoing Response

A Circle Tracing Task (Bachorowski & Newman, 1985, 1990) and a recently developed Follow Task with stop instructions (Morein-Zamir & Meiran, in press) were used to measure inhibition of an ongoing response. Although these tasks have not been used in research on AD/HD previously, we selected these tasks because they allow direct measurement of inhibition of an ongoing, or continuous, response.

Interference Control

The Stroop Color-Word Test (Stroop, 1935) and the Eriksen Flanker Task (Eriksen & Eriksen, 1974) were selected to measure interference control. In both of these

paradigms, a competing response to irrelevant information has to be inhibited. However, in the Stroop Color-Word Test, subjects have to suppress the response to a certain stimulus *feature*, whereas in the Eriksen Flanker Task, subjects have to suppress an automatic reading response to irrelevant stimuli, flanking the target. The combination of the Stroop Color-Word Test and an experimental task such as the Eriksen Flanker Task to measure interference control has been suggested by Nigg (2000).

Previous Research on Response Inhibition and the Effects of MPH in Children With AD/HD

Inhibition of a Prepotent Response

In numerous studies, children with AD/HD have been demonstrated to perform more poorly than normal children on tasks measuring different forms of response inhibition. Oosterlaan et al. (1998) performed a meta-analysis on studies employing the Stop Paradigm with AD/HD children. It was demonstrated that children with AD/HD exhibit significantly slower response inhibition times (SSRTs) than normal control children. Since that meta-analysis, a number of studies have replicated this finding (Chhabildas et al., 2001; Konrad, Gauggel, Manz, & Schöll, 2000; Nigg, 1999; Schachar et al., 2000; Solanto et al., 2001; Wilcutt et al., 2001) although six other studies have not differentiated AD/HD from control children on this task (Kuntsi, Oosterlaan, & Stevenson, 2001; Manassis, Tannock, & Barbosa, 2000; Pliszka, Liotti, & Woldorff, 2000; Rubia et al., 2001; Scheres et al., 2001a, 2001b).

Only two studies (Tannock et al., 1989, 1995) have investigated the effect of MPH on inhibition of a prepotent response using the Stop Paradigm (Logan, 1994). Tannock et al. (1989) showed that SSRT was significantly faster under 1.0 mg/kg MPH compared to 0.3 mg/kg or placebo. Subsequently, Tannock et al. (1995) investigated the dose-response relation for response inhibition by studying the effect of 0.3 mg/kg, 0.6 mg/kg, and 0.9 mg/kg MPH and placebo on SSRT, and found an inverted U-shape relation. The latter finding indicates that the effect of MPH on inhibition of a prepotent response did not increase linearly with dose, but that the medium dose was the optimal one. It is presently unclear whether the dose-response relationship for other forms of inhibition are linear or have an inverted U-shape in children with AD/HD.

Interference Control

Studies of interference control employing the Stroop Color-Word Test are usually referred to as providing sup-

portive evidence for a difficulty in interference control in children with AD/HD (e.g., Barkley, 1997a; Perugini, Harvey, Lovejoy, Sandstrom, & Webb, 2000). In the Stroop Color-Word Test, the color naming response has to be protected from disruption by the automatic reading response. Note that only a few studies found significant group differences, when performance on the interference condition was examined after controlling for performance on the color naming condition (Carter, Krener, Chaderjian, Northcutt, & Wolfe, 1995; Seidman, Biederman, Mounteaux, Weber, & Faraone, 2000). One study employing the Eriksen Flanker Task showed that the AD/HD group was more distracted by incongruent flankers as measured by hit rate (but not reaction times) than the normal control group (Jonkman et al., 1999).

In the only published study on the effect of MPH on interference control as measured by the Eriksen Flanker Task in AD/HD (Jonkman et al., 1999), it was shown that MPH did not reduce the interference problem in children with AD/HD. Everett, Thomas, Cote, Levesque, and Michaud (1991) studied hyperactive and normal children and their interference control in the Stroop Color-Word Test prior to a year of MPH treatment and after a year of MPH treatment. Although hyperactive children's performance improved after MPH, they still performed more poorly than normal controls.

Inhibition of an Ongoing Response

To date, inhibition of a continuous response as measured by the Circle Tracing Task and the Follow Task has not been studied in children with AD/HD. However, it has been shown that impulsive subjects are less able to slow down while tracing a circle than normal controls (Bachorowski & Newman, 1990). The relation between AD/HD and inhibition of an ongoing, continuous response as measured by the Follow Task still has to be established.

Aims

If a deficit in the three forms of response inhibition, that is, inhibition of a prepotent response, inhibition of an ongoing response, and interference control (Barkley, 1997a, 1997b) is the core problem in AD/HD leading to other EF deficits and behavioral problems, it would be of interest if MPH improves equally or differentially these three forms of response inhibition. This was the first aim of the current study. Secondly, because it is not yet known whether dose-response relations are identical for the three forms of response inhibition, dose response

relations were studied for each form of inhibition in children with AD/HD.

In order to address these issues, for each of the three inhibition domains, two inhibition tasks were administered to boys with AD/HD, under four treatment conditions (placebo, 5 mg MPH, 10 mg MPH, 15/20 mg MPH).

METHOD

Participants

Twenty-three boys with AD/HD in the age range of 6–12 years ($M = 8.7$ years, $SD = 1.7$ years) participated in this study. Children were referred to pediatricians and child psychiatrists at three clinics in The Netherlands. These children were all identified as meeting the *DSM-IV* criteria (APA, 1994) for AD/HD by the physician and/or a multidisciplinary team of professionals and treatment with MPH was suggested. The physician informed the parents about the possibility of participating in a standardized double-blind placebo-controlled evaluation procedure for the effect of MPH. Parents and children received a letter with information about the procedure and an informed consent form. When parents and children agreed to participate, they were invited to the first meeting (see below). A medical ethics committee approved the study.

Selection Procedure

During the first meeting parents were administered the Diagnostic Interview Schedule for Children (DISC)-IV, parent version (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). The DISC-IV is a structured interview that generates *DSM-IV* diagnoses. The following sections were administered: AD/HD, Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD). In order to be diagnosed with AD/HD based on the DISC-IV, the child had to demonstrate at least six symptoms of inattention and/or six symptoms of hyperactivity/impulsivity. Furthermore, in order to meet the pervasiveness criterion, at least two symptoms of AD/HD had to be observed at home *and* in school. Finally, the age of onset had to be before seven. While the parents were being interviewed, four subtests of the Revised Wechsler Intelligence Scale for children (WISC-R) were administered to the child to assess intelligence. These subtests were Vocabulary, Arithmetic, Block Design, and Picture Arrangement. The estimated IQ as obtained from these subtests correlates $r = .93$–$.95$ with the full scale IQ (Groth-Marnat, 1997).

Only children who met the *DSM-IV* criteria for AD/HD (DISC-IV) and had an IQ above 70 could enter the study. Children not meeting these criteria were referred back to the physician and received regular treatment. For all children who were diagnosed AD/HD by their physician and/or multidisciplinary team and referred to the study, the DISC-IV confirmed and sometimes refined the *DSM-IV* diagnosis (in terms of establishing AD/HD subtypes and comorbidity). Twenty-four children with AD/HD were selected for the study and participated. Because only one child in the AD/HD group was a girl, she was excluded from the sample.

The average IQ of the children was 97.6 (*SD* 14.7; see Table I). One child dropped out of the study after the interview, because parents withdrew consent. From the DISC-IV, it was determined that one child met criteria for AD/HD hyperactive/impulsive subtype, eight children were of the inattentive subtype, and 14 children met criteria for the combined subtype. Ten children (eight combined subtype, one inattentive subtype, and one hyperactive/impulsive subtype) also met criteria for a diagnosis of ODD, and one child (inattentive subtype) met criteria for CD. None of the children had been previously treated with MPH or another stimulant medication. Children did not receive any other form of treatment during the titration stage.

Table I. Group Characteristics and Diagnostic Data

Measure	AD/HD ($n = 23$)	
	M	*SD*
Age	8.7	1.7
IQ	97.6	14.7
DBD parent ($n = 22$)		
Inattention[a]	19.3	3.6
Hyperactivity/impulsivity[a]	17.9	5.1
ODD[a]	11.0	4.9
CD	2.6	2.1
DBD teacher		
Inattention[a]	18.7	5.4
Hyperactivity/impulsivity[a]	16.1	7.3
ODD	8.8	5.9
CD ($n = 22$)	2.9	3.5
DSM-IV screener parent		
AD/HD ($n = 21$)[a]	58.6	6.8
ODD ($n = 21$)	19.5	6.8
CD ($n = 22$)	40.8	5.8
DSM-IV screener teacher		
AD/HD[a]	58.3	11.7
ODD ($n = 22$)	16.9	8.9
CD	40.4	10.0

Note. DBD = Disruptive Behavior Disorder rating scale; ODD = oppositional defiant disorder; CD = conduct disorder.
[a] Average scale score is at or above the 95th percentile.

Rating Scale Scores

Parents and teachers of the participants completed the Disruptive Behavior Disorder Rating Scale (DBD; Pelham, Gnagy, Greenslade, & Milich, 1992; Oosterlaan, Scheres, Antrop, Roeyers, & Sergeant, 2000) and a *DSM-IV* screener (Hartman et al., 2001). The DBD consists of (a) two subscales composed of the *DSM-IV* items for AD/HD, that is, an Inattention subscale and a Hyperactivity/Impulsivity subscale, (b) a scale composed of the *DSM-IV* items for ODD, and (c) a scale composed of the *DSM-IV* items for CD. Items were rated on a scale from zero to three.

As can be seen in Table I, the average scores on the DBD Inattention subscale were in the clinical range (95th–100th percentile). Scores ranged between 8 and 27. These scores were expected on the basis of the DISC-IV, because all boys (except one) met *DSM-IV* criteria for AD/HD inattentive subtype or combined subtype. Average scores on the Hyperactivity/Impulsivity subscale were in the clinical range and varied between 3 and 27. This range of scores indicates that some boys fell in the clinical range, but others did not. This finding reflects that 15 boys met *DSM-IV* criteria for hyperactivity/impulsivity. Average scores on the parent DBD ODD scale were in the clinical range, but average scores on the teacher DBD ODD scale were not in the clinical range. Scores on the DBD ODD scales ranged between 1 and 20. Average scores on the CD scales were not in the clinical range and varied from 0 to 13. The range of scores on the ODD and CD scales reflects that 11 boys had comorbid ODD or CD.

The *DSM-IV* screener was developed to assess syndromes of childhood psychopathology based on the *DSM-IV* (Hartman et al., 2001). This screener was developed on the basis of results from a large-scale study on the internal construct validity of *DSM-IV* based questionnaires. The results of psychometric analyses showed that deductively derived questionnaires based on *DSM-IV* had better internal construct validity than more traditional questionnaires, such as the CBCL, which are developed inductively. The screener contains 181 items, which are grouped into seven scales. These seven scales are the following: (a) AD/HD, (b) ODD, (c) CD, (d) anxiety, (e) depression, (f) Pervasive Developmental Disorder (PDD), and (g) schizophrenia. Items were rated on a scale from zero to three. Average scale scores on the AD/HD scale for both the parent and the teacher questionnaire were above the 95th percentile (see Table I). Scores on all other scales were below the 95th percentile (data available from the first author).

Titration Stage

Medication Design

A pseudo-randomized, multiple-blind, placebo-controlled, within-subject design was used in which all participants received each of four treatment conditions: placebo, 5 mg of MPH, 10 mg of MPH, and 15/20 mg of MPH (see Table II). A combination of absolute doses and relative (mg/kg) doses was applied in this study. The low and medium doses were 5 and 10 mg respectively for each child. The high dose was 15 mg for boys with a body weight below 22 kg, and 20 mg for boys with a body weight of 22 kg or higher. This procedure ensured that the highest dose never exceeded 0.9 mg per kg body weight. All boys in the present study had a body weight higher than 22 kg and therefore the highest dose administered in this study was always 20 mg.

Each treatment condition was administered 7 days, twice daily, at breakfast (around 7:30 a.m.) and at lunch (around 12:30 a.m.). Within each week, all the four treatment conditions were administered and ordered such that one condition was never administered on two successive schooldays. The highest dose was never administered the day after placebo. After 4 weeks, each treatment condition had been administered on all days of the week, and the treatment condition on a fixed day was different in each week. This allowed for assessment of the child under the four treatment conditions on a fixed weekday. The order of the weeks (within which the treatment conditions are fixed) differed for children, and was implemented using a Latin square design (4 week orders were used: ABCD,

Table II. Medication Design (mg Methylphenidate)

	Saturday	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday
Lead-in				0	5	10	20
Week A	0	0	0	5	10	20	0
Week B	5	5	5	10	20	0	5
Week C	10	10	10	20	0	5	10
Week D	20	20	20	0	5	10	20

BCDA, CDAB, and DABC). However, due to practical constraints, the four orders were not exactly balanced over the group. Therefore, each medication condition was tested as to whether it was administered to an equal number of boys in each week. Chi-square tests for goodness of fit showed that for each medication condition, the number of participants tested did not differ significantly across weeks (χ^2s between 3.7 and 6.0, all p values > .10). The titration procedure started with a lead-in. The lead-in consisted of 4 days in which all the treatment conditions were administered in an ascending order, starting with placebo on the first day and ending with 20 mg on the fourth day (see Table II). Each week at arrival for the assessment of the child, parents were required to return empty medication boxes and blisters, and take home new tablets for the coming week.

Medication and placebo were prepared by the hospital pharmacy, and packed in identical tablets. Placebo tablets contained only a base granulate. The MPH tablets of 5 and 10 mg contained base granulate plus MPH granulate, and the tablets of 20 mg contained only MPH granulate.

Tasks

Inhibition of a Prepotent Response

The Stop Paradigm. The Stop Paradigm (Logan, 1994; Logan & Cowan, 1984) has been used in numerous studies on children with AD/HD in the age range of 6–12 years (see for review, Oosterlaan et al., 1998). The task involves two types of trials: go trials and stop trials. Go trials consisted of cartoon airplanes presented for a period of 1000 ms at the midpoint of the computer screen. Immediately before the go stimulus onset, a fixation point (500 ms in duration) appeared on the screen. If the plane pointed to the right, subjects were required to press the right response button. If the plane pointed to the left, subjects were instructed to press the left button. The inter-stimulus-interval (ISI) was 1,500 ms. The inter-trial-interval was 3000 ms. Stop trials consisted of a go trial and a stop signal (a 1000 Hz tone, 50 ms in duration), presented through earphones. The stop signal was usually presented shortly after the plane, but could also be presented concurrently with or shortly before the plane, depending on the child's performance (see below). Children were instructed not to press either of the two buttons, when they heard the tone. Seventy-five percent of the trials were go trials, and 25% were stop trials. The Stop Paradigm allows measurement of both response execution (go trials) and response inhibition (stop trials).

Trials were presented in blocks of 64 trials. Within a block, the plane pointed equally often to the right or to the left, and stop signals were balanced for right and left go trials. Stop trials were presented randomly within each block. A stop trial was always followed by a go trial. However, to prevent children from expecting that a stop trial would always be followed by a go trial, two stop trials were presented in succession in each block.

To ensure that the children were familiar with the paradigm, the task commenced with two practice blocks. In the first practice block only go trials were presented. During practice of the go task, children were encouraged with standardized instructions to respond as quickly and as accurately as possible. In the second practice block, 25% of the trials were stop trials. During practice of the stop task, children were instructed to work as quickly and accurately as possible and to try to suppress their response, when they heard the stop signal. After practice, participants were administered four experimental blocks of 64 trials.

The dependent variable that reflects the latency of the inhibitory process is SSRT. SSRT cannot be observed, because the response to a stop signal is a covert one. Therefore, SSRT has to be estimated. This can be done using the race model (Logan & Cowan, 1984). This model assumes that the go process and the stop process are independent. The go stimulus triggers the go process and the stop signal initiates the stop process. The process that finishes first wins the race. If the go process wins the race, the response is executed. If the stop process finishes first, the response is inhibited. The outcome of the race depends on the speed and the variability of the go process, the delay between go stimulus and stop signal, and the speed and the variability of the stop process.

In this study, two methods for estimating SSRT were employed: a method using fixed intervals between the go and the stop signal, and a method applying a tracking mechanism to vary the interval between the go and the stop signal.

In the Stop Paradigm, as it was originally developed (Logan, 1994; Logan & Cowan, 1984), stop signals are presented at *predetermined (fixed) intervals* before the subject's expected response. In this way, the ability to inhibit a response at different points in the response execution process can be determined. The shorter the time interval between the stop signal and the expected response, the more difficult it becomes to inhibit the response. In the current study, the interval was 50 ms, 200 ms, 350 ms, or 500 ms with each interval occurring on 25% of the stop trials. The following procedure was used to calculate SSRT for the Stop Paradigm with stop signals presented at fixed intervals. First, reaction times on go trials were rank ordered on a time axis. Reaction times were ordered from fastest to slowest. Second, the nth reaction time was

picked, where *n* is defined by the product of the number of reaction times in the distribution and the probability of responding given a stop signal (or 1 minus the probability of inhibition). For example, if there were 100 reaction times in the distribution and the probability of responding given a stop signal was .3, the *n*th reaction time would be the 30th in the rank-ordered distribution. The *n*th reaction time is an estimate of the time at which the stop process runs to completion, relative to the onset of the go signal. Third, the stop signal interval (the time interval between the stop signal and the subject's expected response) was subtracted from the *n*th reaction time to estimate SSRT. SSRT was calculated for each interval and then averaged.

The "fixed interval procedure" was adapted to allow for a more direct observation of SSRT (Logan et al., 1997; Osman et al., 1986). In the adapted procedure, a tracking mechanism was applied to vary the delay between the onset of the go signal and the stop signal dynamically, contingent on the subject's performance. The use of a tracking mechanism has several theoretical and practical advantages over the Stop Paradigm with stop signals presented at fixed intervals (Band et al., in press). For the Stop Paradigm with the tracking mechanism, SSRT can be observed almost directly. In the current study, the initial delay between go signal and stop signal was 250 ms. If the child succeeded in inhibiting his or her response, the delay on the next stop trial was increased by 50 ms. If the child did not succeed in inhibiting, the delay on the next stop trial was decreased by 50 ms. By using this tracking mechanism, it was established that a child has a 50% chance of response inhibition. This means that on average, the go and the stop process finish at the same time. In this way, the finishing time of the go process becomes an estimate of the finishing time of the stop process. SSRT can be calculated by subtracting the mean delay from the mean go signal reaction time.

For both versions of the Stop Paradigm, SSRT was the primary dependent variable, reflecting the latency of the inhibition process. In addition to SSRT, the latency and the variability of the response execution process were obtained. These variables were mean reaction time on go trials (MRT), and standard deviation of the reaction times on go trials (*SD*). MRT and *SD* were calculated across correct responses on go trials.

Inhibition of an Ongoing Response

Circle Tracing Task. The Circle Tracing Task is a task that requires subjects to trace a large printed circle with their index finger (Bachorowski & Newman, 1985, 1990). Although this task has not been used with children previously, it is a very simple task, which can be easily performed by children of 6 years of age. The circle was 50.80 cm (20 in.) in diameter, drawn on a cardboard square, and covered with Plexiglas. The circle had a small line indicating the starting and the finishing point of the tracing. The word START (in green ink) and STOP (in red ink) were printed on either side of this line. The task was administered under two conditions: first with neutral instructions ("trace the circle") followed by inhibition-instructions ("trace the circle again, but this time as slowly as you can"). A maximum of 12 min was allowed for both tracing conditions. Participants were not informed of this fact. The calculated inhibition variable was the time used to trace the circle in the slow condition minus the tracing time in the neutral condition. This dependent variable will be referred to as inhibition time. The larger the inhibition time, the better a participant is able to inhibit (slow down) the continuous tracing response.

Follow Task. A Follow Task (Morein-Zamir & Meiran, in press) has been developed recently to measure inhibition of a continuous response. Because this task has only been used with adults so far, we conducted a pilot study with children in the age range of 6–12 years (data available from the first author). The advantage of using a continuous response that has to be inhibited is that it enables *direct* observation of the SSRT (as opposed to indirect calculation as in the Stop Paradigm). Another advantage is that the SSRT can be observed for each trial. This procedure has not been previously carried out in studies on AD/HD.

Each trial began with the target (a green square) presented in the center of the screen. To start a trial, children pressed the left button of the mouse. The target moved randomly and children were instructed to follow it with the mouse cursor. The time the target was displayed on the screen for a given location along the trajectory (target speed) was set at 85 ms. This target speed was chosen based on the pilot study in children mentioned above. After a variable delay (ranging from 10 to 20 s with an average of 15 s) children heard a stop signal (a 1,000 Hz tone, 100 ms in duration) which instructed them to stop their continuous response immediately. Children were informed that, in order for their stop response to be considered successful, they had to refrain from moving the cursor until the next target appeared on the screen. The program defined a 500 ms pause in moving the cursor as a complete stop. The next trial started 4 s after the cursor had stopped moving completely.

Trials were presented in blocks of 10 trials. To ensure that the children were familiar with the procedure, the task commenced with a practice block. During practice, children were encouraged to follow the target very closely and to stop immediately when they heard the tone. It was emphasized that they should keep their hand completely

still after the stop signal. After practice, participants were administered four experimental blocks.

The dependent variable that reflects the latency of the inhibitory process is SSRT. SSRT in this task can be *observed* and was operationalized as follows: the time, computed by an analysis program, when the initial signs of stopping can be observed in the continuous following performance. The procedure was as follows: after the stop tone, the position of the cursor (two-dimensional spatial coordinates) was measured as many times as possible in batches of 20 ms. For each 20-ms period, the program computed the average distance between the present cursor position and the cursor position at which the stop signal was presented. This distance was plotted as a function of time elapsed, since the stop tone was presented (units of 20 ms). The function is first linear (indicating that the child is moving the cursor at a constant speed), but would then flatten out (indicating that the child had begun to stop). A linear regression analysis was performed on the first five measurements (first 100 ms) with the above defined distance as dependent variable and time bin as the independent variable. The resulting regression model was used to predict the distance at measurement 6. In the next iteration, the regression analysis included the first six measurements, to predict the distance at measurement 7, until the 105th observation was reached. This allowed 2,100 ms for the subjects to inhibit their response. Stopping initiation was defined as the point after which five consecutive positive deviations with respect to the predicted distance were identified. Five consecutive positive deviations were selected as the criterion, because the probability of this occurring by chance is $1/2^5$, or 0.03, which converges with conventional significance levels.

Interference Control

Stroop Color-Word Test. The Stroop Color-Word test (Stroop, 1935; Dutch version: Hammes, 1971) is a task that measures interference control (MacLeod, 1991). Because this test requires automatic reading skills, it was only administered to children aged 8 and higher. The test consists of three cards with 100 stimuli each, ordered in 10 rows and 10 columns. First, children were presented with the word card, on which the names of the colors red, green, yellow, and blue are printed in black in a random order. Participants were instructed to read the words as quickly as they could. Speed of reading was measured in this condition. On the second card (the color card) colored rectangles (red, yellow, blue, and green) were presented in a random order. Children were instructed to name the colors as quickly as possible. Speed of color naming was

measured with this card. On the third card (the color-word card), children were presented with color words in a random order. The color of the ink in which the word was printed differed from the meaning of the word. For example, the word green was printed in red ink. Children were instructed to name the color of the ink and not to read the word. To perform correctly on the last card, the automatic reading response must be inhibited, while the color of the ink is named. The main dependent variable in this task was the interference score for time (IS time), calculated by subtracting the speed of color naming (measured by card 2) from the time needed to name the colors in the interference condition (card 3).

Eriksen Flanker Task. In the Eriksen Flanker Task (Eriksen & Eriksen, 1974), the ability to inhibit a response to irrelevant, interfering stimuli is measured. Flanker tasks have been used in children as young as 5 years of age (e.g., Ridderinkhof, van der Molen, Band, & Bashore, 1997). During incongruent trials (target stimulus surrounded by incongruent flankers), competing, incorrect responses must be inhibited. Typically, incongruent trials induce slower reaction times and more errors compared to congruent trials (targets surrounded by congruent flankers; Ridderinkhof et al., 1997). In the present study, an arrow version of the flanker task was used. Target stimuli were arrows pointing to the right or to the left, presented at the center of the screen. The direction of the target arrow indicated whether the child had to press the left or the right response button. The target stimulus was surrounded by two distracters on both sides (left and right). The distracters were either arrows or rectangles. There were three types of trials in this task: neutral, congruent, and incongruent. A neutral trial consisted of the target arrow flanked by rectangles (==>== or ==<==). A congruent trial consisted of the target arrow flanked by arrows that pointed in the same direction as the target (>>>>> or <<<<<). An incongruent trial consisted of a target arrow flanked by arrows pointing in the opposite direction to the target (>><>> or <<><<). When responding to the incongruent trials, a child was required to inhibit the response to distracting, irrelevant stimuli.

The task commenced with four practice blocks of 45 trials (15 trials for each condition) each, followed by six experimental blocks, consisting of 60 trials each (20 trials for each condition). The three types of trials were presented randomly within each block. A warning signal, consisting of a cross (500 ms in duration), preceded the imperative stimulus (1,000 ms in duration). After the stimulus, the screen turned blank for 1,500 ms. The inter-trial-interval was 3,000 ms.

Before practice, children were encouraged with standardized instructions to respond as quickly and as

accurately as possible. Between blocks, in order to achieve an optimal balance between speed and accuracy for every child, instructions emphasized either speed or accuracy or both, dependent on the child's performance during the previous block: Children were encouraged (a) to work as fast as possible, when the percentage of errors was between 0 and 5%, (b) to work as accurately as possible, when the percentage of errors was higher than 10%, or (c) to work as fast and accurately as possible, when the percentage of errors was between 5 and 10%.

The dependent variables for this task were an interference score for mean reaction time (MRT on incongruent trials minus MRT on congruent trials) and an interference score for number of errors (number of errors on incongruent trials minus number of errors on congruent trials).

Procedure

Parents were informed of the study by the child psychiatrist or pediatrician. They were given an information leaflet about the purpose and the procedures used in this study. In addition, they received a letter with an informed consent form. When parents had read the information about the study and were willing to participate, they signed and returned the informed consent form. Parents were invited then for the first meeting. At any time during the study, parents could withdraw their consent.

During the first meeting, parents were interviewed and the child's intelligence was assessed. During the titration stage, children's inhibitory functioning was assessed during each of the four treatment conditions. Assessment took place on the same weekday once a week. Children were assessed in the clinic during the afternoon. On arrival, at 12:30 p.m., the coded tablet was administered and the child had lunch. Since the behavioral effect of MPH reaches a maximum between 1 and 2 hr after oral administration (Swanson et al., 1995), the assessment started exactly 1 hr after drug/placebo administration. Testing lasted between 2 and 3 hr. Hence, all testing was done between 1 and 4 hr after drug administration.

The order of the inhibition tasks was balanced over the AD/HD group, to control for a fatigue effect and for the peak time of MPH. Half of the AD/HD children performed block A (Stop Paradigm – Circle Tracing Task – Stop Paradigm) first, followed by block B (Eriksen Flanker Task – Stroop Color-Word Test – Follow Task). The other half of the group performed block B first, followed by block A. A 10-min break was scheduled between the two blocks. The order of the blocks was fixed within a subject across the weeks. Within block A, the order of the Stop

Paradigm with stop signals presented at fixed intervals and the Stop Paradigm with the tracking mechanism was balanced across children, in order to be able to compare performance on these two tasks.

Statistical Analyses

First, in order to study the effect of the three doses of MPH and placebo on the three forms of response inhibition, the dependent variables of the different tasks were analyzed with ANOVAs, with treatment condition (placebo, 5 mg, 10 mg, and 20 mg MPH) as within-subject factor (four levels). If there was a main effect of treatment condition, the shape of that effect was studied by applying polynomial contrasts. Furthermore, if there was a main effect of treatment condition, Helmert contrasts were performed to compare the effect of placebo to the effect of medication (average of the three doses MPH). Secondly, to study the effect of MPH *dose* (5 mg, 10 mg, and 20 mg), ANOVAs with dose as within-subject factor (three levels) were performed. In case of a significant dose effect, the shape of that effect was studied by applying polynomial contrasts.

Missing Data

Some cases were excluded for the analyses of the inhibition measures, either because of missing data due to technical problems or extreme scores (see Table III). In the Stop Paradigm with the tracking mechanism, the data of one boy were missing due to technical problems, and three cases were excluded because of extreme scores: One child showed an accuracy of 50% on go trials, one child showed a percentage inhibition of 12.5%, and one child had a calculated SSRT lower than 50 ms. In the Stop Paradigm with stop signals presented at fixed intervals, one case was excluded because of a low accuracy on go trials (50%), and one case was excluded because calculation of the SSRT was not possible due to perfect accuracy on stop trials. Data of one child were missing due to technical problems for the Follow Task. One child was excluded because of an extreme score for the analyses of the Circle Tracing Task. In the Eriksen Flanker Task, data of one child were missing due to technical problems, and one child was excluded because of an extreme score for the Eriksen Flanker Task. Nineteen children were included for the analyses of the Stroop Color-Word Test. Five children were younger than 8 years and therefore did not have the required automatic reading skills necessary to perform the Stroop Color-Word Test for the purpose of measuring interference control.

Table III. Group Means and Standard Deviations for Inhibition Measures in the Four Treatment Conditions (Placebo, 5 mg, 10 mg, or 20 mg Methylphenidate)

| | AD/HD | | | | | | | |
| | Placebo | | 5 mg | | 10 mg | | 20 mg | |
Measure	M	SD	M	SD	M	SD	M	SD
Inhibition of a prepotent response[a]								
SSRT fixed ($n = 21$)[b]	254.8	91.3	211.7	56.2	200.4	56.1	207.9	61.7
Percentage inhibition tracking ($n = 19$)[c]	48.6	1.5	50.1	1.3	49.9	1.9	50.3	1.5
SSRT tracking ($n = 19$)[d]	219.1	92.9	153.4	56.5	151.2	40.2	138.4	34.0
Inhibition of an ongoing response								
Circle inhibition time ($n = 22$)	156.5	170.9	149.5	137.9	160.0	155.7	143.3	127.1
Follow SSRT ($n = 22$)[b]	285.5	59.5	255.2	51.0	257.8	43.0	252.4	43.0
Interference control								
Stroop IS Time ($n = 18$)	60.8	44.1	42.6	21.2	52.5	29.6	41.3	19.9
Eriksen IS MRT ($n = 21$)	34.4	30.2	23.8	14.3	19.8	17.0	24.3	19.7
Eriksen IS Errors ($n = 21$)	5.8	6.0	4.2	6.1	3.8	5.3	4.5	3.9
Response execution								
Mean reaction time fixed ($n = 21$)[b]	435.1	96.1	405.7	93.1	399.3	80.0	395.0	71.7
Variability in responding fixed ($n = 21$)[d]	109.0	39.6	82.0	29.3	72.7	25.6	69.4	21.7
Mean reaction time tracking ($n = 19$)	430.2	88.8	403.0	75.2	402.4	95.3	393.8	55.4
Variability in responding tracking ($n = 19$)[d]	108.5	42.4	78.0	29.5	76.7	30.7	67.4	24.0

Note. AD/HD = Attention Deficit/Hyperactivity Disorder; SSRT = stop signal reaction time; IS = interference score; MRT = mean reaction time.

[a] Two versions of the Stop Paradigm were applied: a version with fixed intervals between the stop tone and the expected reaction time, and a version with a tracking mechanism that adjusts the delay between go stimulus and stop signal contingent on the participant's performance (for further details, see text).

[b] Main effect of treatment condition, $\alpha < .05$.

[c] Main effect of treatment condition, $\alpha < .01$.

[d] Main effect of treatment condition, $\alpha < .001$.

RESULTS

The group means and standard deviations on all the inhibition tasks are presented in Table III and Fig. 1.

Inhibition of a Prepotent Response

Stop Paradigm With Stop Signals Presented at Fixed Intervals

A main effect of treatment condition was found for SSRT, $F(3, 60) = 3.75$, $p < .05$; $\eta^2 = 0.16$. The shape of this effect was linear, $F(1, 20) = 6.24$, $p < .05$; $\eta^2 = 0.24$. A Helmert contrast showed that children exhibited faster SSRTs, when administered MPH compared to placebo, $F(1, 20) = 7.10$, $p < .05$; $\eta^2 = 0.26$. However, no significant differences for SSRT were observed among the three doses of MPH, $F(2, 40) = 0.28$, *ns*; $\eta^2 = 0.01$).

Stop Paradigm With the Tracking Mechanism

Over treatment conditions, the tracking mechanism was successful. The percentage inhibition was close to the expected 50%: 49.7%. Unexpectedly, there was an effect of treatment condition on the percentage inhibition, $F(3, 54) = 4.34$, $p < .01$; $\eta^2 = 0.19$. This effect was linear, $F(1, 18) = 9.35$, $p < .01$; $\eta^2 = 0.34$. This linear effect appeared to be due to a slightly higher percentage inhibition under MPH (50.1%) compared to placebo (48.6%), $F(1, 18) = 11.66$, $p < .01$; $\eta^2 = 0.39$. Slight variations in the percentage inhibition for the medication conditions and placebo do not pose a threat to the validity of SSRT as measured by this task. The percentage inhibition did not differ across doses of MPH, $F(2, 36) = 0.32$, *ns*; $\eta^2 = 0.02$. This means that the tracking algorithm ensured that children reached approximately 50% inhibition on the stop trials under each MPH dose.

A main effect of treatment condition was found for SSRT, $F(3, 54) = 8.25$, $p < .001$; $\eta^2 = 0.31$. This effect was linear, $F(1, 18) = 15.29$, $p = .001$; $\eta^2 = 0.46$. A Helmert contrast showed that MPH induced shorter SSRTs than placebo, $F(1, 18) = 11.31$, $p < .01$; $\eta^2 = 0.39$. However, no significant differences for SSRT were detected among the three doses of MPH, $F(2, 36) = 0.94$, *ns*; $\eta^2 = 0.05$.

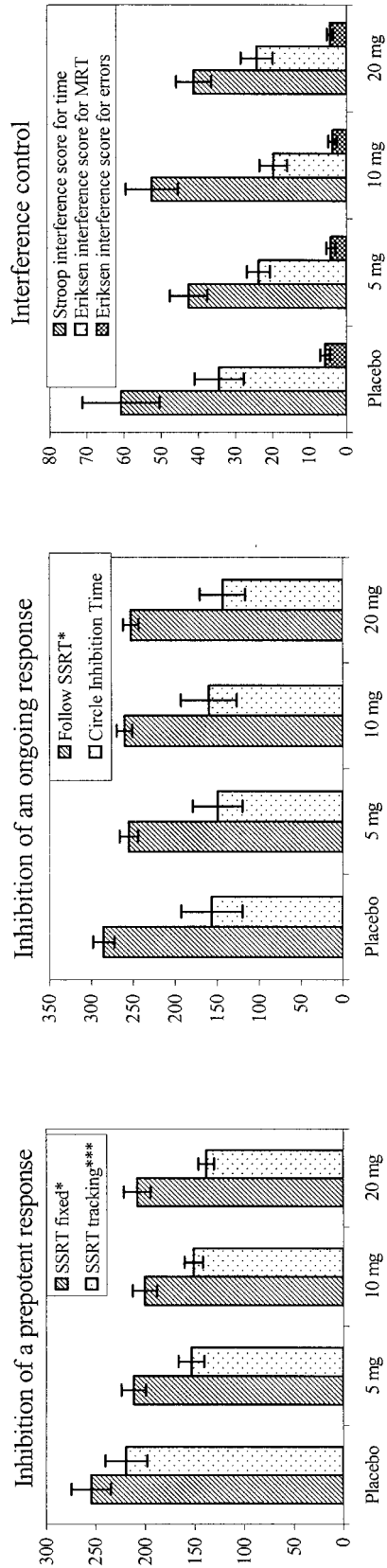The effect of methylphenidate on inhibition in AD/HD

Fig. 1. The inhibition variables as a function of treatment condition. Measures for inhibition of a prepotent response (stop signal reaction times [SSRT]) are depicted in the left panel, measures for inhibition of an ongoing response are depicted in the middle panel, and measures for interference control (interference scores for time [Stroop Color-Word Test], mean reaction time [MRT], and errors [Eriksen Flanker Task] are shown in the right panel. *Main effect of treatment condition, $\alpha < .05$; ***Main effect of treatment condition, $\alpha < .001$.

Inhibition of an Ongoing Response

Circle Tracing Task

No effect of treatment condition was observed for the inhibition time as measured by the Circle Tracing Task, $F(3, 63) = 0.16, ns; \eta^2 < 0.01$, or dose, $F(2, 42) = 0.26, ns; \eta^2 = 0.01$. Note that the scatter was large in this task.

Follow Task

A significant effect of treatment condition was found for SSRT as measured by the Follow Task, $F(3, 63) = 3.04, \quad p < .05; \eta^2 = 0.22$. This effect was linear, $F(1, 21) = 5.76; p < .05; \eta^2 = 0.22$. SSRTs were faster under MPH compared to placebo, $F(1, 21) = 6.19, p < .05; \eta^2 = 0.23$. No differences for SSRT were detected across the three doses of MPH, $F(2, 42) = 0.12, ns; \eta^2 < 0.01$.

Interference Control

Stroop Color-Word Test

The effect of treatment condition on the interference score for time was not statistically significant, $F(3, 51) = 2.36, p = .08; \eta^2 = 0.12$. No significant main effect of dose was observed on the interference score for time, $F(2, 34) = 1.93, ns; \eta^2 = 0.10$.

Eriksen Flanker Task

The task manipulation was effective. A main effect of trial type (congruent vs. incongruent) was observed for MRT, $F(1, 20) = 70.17, p < .001; \eta^2 = 0.78$, and for number of errors, $F(1, 20) = 38.92, p < .001; \eta^2 = 0.66$. Compared to congruent trials, incongruent trials led to slower reaction times and more errors.

The effect of treatment condition on the interference score for MRT failed to reach statistical significance, $F(3, 60) = 2.40, p = .08; \eta^2 = 0.11$. No effect of dose was found for the interference score for MRT, $F(2, 40) = 0.52, ns; \eta^2 = 0.03$. No effect of treatment condition was observed for the interference score for number of errors, $F(3, 60) = 0.67, ns; \eta^2 = 0.03$, nor was there an effect of dose, $F(2, 40) = 0.10, ns; \eta^2 < 0.01$.

Response Execution Measures

In the two versions of the Stop Paradigm, measures of response execution were obtained in addition to the measures of response inhibition.

Stop Paradigm With Stop Signals Presented at Fixed Intervals

A main effect of treatment condition was found for the response execution measures MRT and variability of reaction times, $F(3, 60) = 3.22, p < .05; \eta^2 = 0.14; F(3, 60) = 18.29, p < .001; \eta^2 = 0.48$, respectively. This effect was linear for both variables, $F(1, 20) = 5.80, p < .05; \eta^2 = 0.23; F(1, 20) = 37.00, p < .001; \eta^2 = 0.65$, respectively. A Helmert contrast showed that children exhibited faster MRTs, $F(1, 20) = 4.24, p = .05; \eta^2 = 0.17$, with smaller variability in responding, $F(1, 20) = 28.86, p < .001; \eta^2 = 0.59$, when administered MPH compared to placebo. No significant effect of dose was found for MRT, $F(2, 40) = 0.66, ns; \eta^2 = 0.03$. There was a significant effect of dose for variability in responding, $F(2, 40) = 3.81, p < .05; \eta^2 = 0.16$. This effect was linear, $F(1, 20) = 5.30, p < .05; \eta^2 = 0.21$.

Stop Paradigm With the Tracking Mechanism

For MRT, the effect of treatment condition fell short of significance, $F(3, 54) = 2.68, p = .06; \eta^2 = 0.13$. A significant effect of treatment condition was found for variability in responding, $F(3, 54) = 12.25, p < .001; \eta^2 = 0.41$. This effect was linear, $F(1, 18) = 18.31, p < .001; \eta^2 = 0.50$. A Helmert contrast showed that MPH induced less variability in responding compared with placebo, $F(1, 18) = 23.34, p < .001; \eta^2 = 0.57$. No significant effect of dose was found for MRT, $F(2, 36) = 0.29, ns; \eta^2 = 0.02$, or for variability in responding, $F(2, 36) = 1.67, ns; \eta^2 = 0.09$.

DISCUSSION

First, the findings of the current study indicate that there was a main effect of treatment condition (placebo, 5 mg, 10 mg, 20 mg MPH) on inhibitory control in boys with AD/HD. This effect was observed for inhibition of a prepotent response, and for inhibition of an ongoing response, but not for interference control. Furthermore, it was observed for only one of the two measures for

inhibition of an ongoing response. Generally, the effect of treatment condition was linear. Secondly, no effect of MPH dose (5 mg, 10 mg, 20 mg) on inhibition in children with AD/HD was observed. Therefore, the linear effect of treatment condition on inhibitory performance could be attributed largely to differences in inhibitory performance under MPH, on the one hand, and under placebo, on the other.

The finding of improved inhibition of a prepotent response in AD/HD children under MPH compared to placebo measured by SSRT in the Stop Paradigm is consistent with previous findings (Tannock et al., 1989, 1995). In those studies, MPH speeded up SSRTs as measured with the Stop Paradigm with stop signals presented at fixed intervals. In the current study, this finding was replicated, and extended for both versions of the Stop Paradigm. However, the inverted U-shaped dose-response relation reported by Tannock et al. (1995) in their second study was not replicated in the current study. One explanation for this discrepancy between studies could be due to differences in the dose regimen employed. Tannock and colleagues used relative doses of 0.3 mg/kg body weight as a low dose, 0.6 mg/kg body as a medium dose, and 0.9 mg/kg as a high dose. In our study, absolute doses of MPH were used: 5 mg as a low dose, 10 mg as a medium dose, and 20 mg as a high dose. The absolute high dose in the current study may have been lower than the absolute high dose in Tannock et al.'s study.

The Stop Paradigm with stop signals presented at fixed intervals and the Stop Paradigm with the tracking mechanism yielded comparable medication effects. This supports the convergence between these two versions of the Stop Paradigm. Note, however, that the size of the medication effect was larger for the paradigm with tracking mechanism ($\eta^2 = 0.41$) than for the version with fixed intervals ($\eta^2 = 0.28$). This suggests that the Stop Paradigm with the tracking mechanism is more sensitive to the effect of medication than the paradigm with fixed intervals. A second difference between the two versions of the Stop Paradigm was observed: SSRTs in the Stop Paradigm with the tracking mechanism were faster than SSRTs in the Stop Paradigm with stop signals presented at fixed intervals (see Table III). In a previous study in which these two versions of the Stop Paradigm were used, the Stop Paradigm with a tracking mechanism also yielded faster SSRTs than the Stop Paradigm with stop signals presented at fixed intervals (Kooijmans et al., 2001). In theory, the latency of the stop process is constant. Thus, SSRTs in both versions of the Stop Paradigm were expected to be identical. Band et al. (in press), however, showed that SSRT is most reliably estimated when the percentage inhibition is 50%.

In the Stop Paradigm with stop signals presented at fixed intervals, the percentage inhibition differs for the four intervals, and the average percentage inhibition is *not necessarily* 50%. Usually, SSRTs are underestimated when the percentage inhibition is lower than 50% and overestimated when the percentage inhibition is higher than 50% (Band et al., in press). When the percentage inhibition in the placebo condition was averaged over the four intervals, it appeared to be 66.26%. Therefore, SSRT was possibly *overestimated* in the Stop Paradigm with stop signals presented at fixed intervals.

In order to investigate this possibility, for the Stop Paradigm with stop signals presented at fixed intervals, SSRT was estimated for the point in the inhibition curve at which percentage inhibition was 50% in the placebo condition. This yielded an average SSRT of 199.3 ms, which is *shorter* than the SSRT averaged over the four intervals in the placebo condition (254.8 ms), and closer to the SSRT in the Stop Paradigm with the tracking mechanism in the placebo condition (219.1 ms; data available from the first author). These results suggest that SSRTs were not entirely similar for the two versions of the Stop Paradigm because SSRT was overestimated in the Stop Paradigm with stop signals presented at fixed intervals. Future work on these features of the two versions of the Stop Paradigm is recommended.

In requiring inhibition of an ongoing response, a significant effect of treatment condition was observed for the Follow Task, but not for the Circle Tracing Task. In the Follow Task, SSRT can be observed directly, as opposed to the Stop Paradigm, in which SSRT has to be estimated. This direct measure of inhibition of an ongoing response provided a clear effect of MPH compared to placebo. Similar to the findings obtained by the two versions of the Stop Paradigm, no effect of MPH dose was observed. The lack of treatment effect on the Circle Tracing Task could be due to the large differences in inhibition times between children in all treatment conditions. Inhibition times ranged from 5 to 700 s.

With respect to the domain of interference control, the interference score for number of errors in the Eriksen Flanker Paradigm did not change under MPH compared to placebo. Although children showed lower interference scores for MRT under MPH compared to placebo, this effect fell short of statistical significance. In another study on the effect of 15 mg MPH and placebo on the Eriksen Flanker Task in AD/HD, no significant effect of MPH on interference control was reported either (Jonkman et al., 1999). On the second task measuring interference control, the Stroop Color-Word Test, children showed a decrease in the interference effect for time, when on MPH compared

to placebo, but also here, the effect was nonsignificant. In other studies employing the Stroop Color-Word Test, an effect of MPH on Stroop performance has been reported. For example, Everett et al. (1991) reported an improvement on the interference score after 1 year of MPH treatment, compared to a pretreatment baseline assessment. In the current study, measures of interference control did not prove sensitive to the effect of medication in AD/HD.

The fact that MPH had a positive effect on inhibition of a prepotent response and inhibition of an ongoing response but not on interference control, has theoretical implications. First, it could be interpreted as support for the distinctiveness of interference control on the one hand, and the two other types of response inhibition on the other. Secondly, it may call into question the supposed deficit in interference control in AD/HD: If MPH improves symptoms in AD/HD children but not their performance on tasks measuring interference control, the primacy of an interference control deficit may be called into question.

In the two domains of inhibition where a significant effect of treatment condition was found (inhibition of a prepotent response and inhibition of an ongoing response), the shape of this effect was consistently linear. Note that this linear effect was due to better inhibitory control under MPH, compared to placebo, but not because of an effect of MPH dose. On the basis of current findings, it cannot be concluded that a low, medium, or a high dose is *more* effective than any other dose in improving inhibitory control in boys with AD/HD. However, Tannock et al. (1995) found a decrement in inhibitory performance with the high dose compared to the medium dose. Also other studies have reported an optimal response to medium or high doses of MPH in cognitive tasks (e.g., Douglas, Barr, Amin, O'Neill, & Britton, 1988; Sprague & Sleator, 1977). But in a review of 13 studies in which the effect of low and high doses of MPH on cognitive tasks were reported, no evidence was found to support the position that performance is optimal at a low dose compared to a high dose (Rapport & Kelly, 1991). In 38.5% of the tasks, a dose effect was found in favor of the high dose. However, for an equal percentage of tasks, no dose effect was found at all. The latter finding suggests that the current study is not the first one failing to find dose effects for cognitive tasks. Van der Meere, Gunning, and Stemerdink (1999) found neither an effect of MPH on inhibitory performance as measured in a go/no go test, nor a dose effect in AD/HD children. Similarly, O'Toole, Abramowitz, Morris, and Dulcan (1997) found no effect of MPH dose on impulsive responding as measured by errors of commission on a Continuous Performance Task.

Although the focus of the current study was on the effect of MPH on response inhibition in AD/HD, in the two versions of the Stop Paradigm measuring inhibition of a prepotent response, two measures of response execution (MRT and variability in responding) were obtained in addition to SSRT. Analyses showed that MPH improved not only inhibitory control, but also speed (in one version) and variability of the response execution process (in both versions), thus confirming the generalized effect of MPH as predicted by the cognitive–energetic model (Sergeant, Oosterlaan, & Van der Meere, 1999; Sergeant & Van der Meere, 2000). Furthermore, it was observed that the effect of MPH on variability in responding was larger than the effect of MPH on inhibitory control or speed of the response execution process. Moreover, a dose effect was observed for variability in responding in the Stop Paradigm with stop signals presented at fixed intervals. This was the only variable for which an effect of MPH dose was shown. These findings suggest that the effect of MPH is not specifically related to the domain of inhibition. These findings are of interest in that the variability in responding has been shown to be the variable with the highest heritability effect for AD/HD (Kuntsi et al., 2001). The current results show that variability in responding may be more sensitive to the effect of MPH than measures of response inhibition.

The current study included children with AD/HD of any subtype. However, Barkley's (1997a, 1997b) disinhibition hypothesis applies to the combined and the hyperactive/impulsive subtypes of AD/HD only, and not to the inattentive subtype. Little research has focused on possible differences between AD/HD subtypes in their response to MPH. There is some suggestion that children with only attention problems respond optimally to low and moderate doses, whereas children with the combined subtype respond optimally to moderate and high doses (McBurnett, 2000). However, because of power constraints, children with different subtypes of AD/HD were not compared with one another on their response to MPH in the current study. Future research is needed to show whether the effect of MPH on response inhibition may be different for children with different subtypes of AD/HD.

In sum, current findings showed that MPH improved inhibitory performance in two out of three domains of inhibition under study in boys with AD/HD. However, the measures of interference control and the Circle Tracing Task were not sensitive to the effect of MPH. Generally, treatment condition–response relations were linear. These linear relations were due to better inhibitory control under MPH compared to placebo, and not because of an effect of MPH dose on inhibitory performance. Finally, this study showed that the Stop Paradigm with the tracking mechanism is more sensitive to MPH effects than the Stop Paradigm with stop signals presented at fixed intervals,

and that MPH not only improved inhibitory control in AD/HD, but also reduced reaction times and variability in responding.

REFERENCES

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Bachorowski, J. A., & Newman, J. P. (1985). Impulsivity in adults: Motor inhibition and time-interval estimation. *Personality and Individual Differences*, 6, 133–136.

Bachorowski, J. A., & Newman, J. P. (1990). Impulsive motor behavior: Effects of personality and goal salience. *Journal of Personality and Social Psychology*, 58, 512–518.

Band, G. P. H., van der Molen, M. W., & Logan, G. D. (in press). Horse-race model simulations of stopping: Good news for stop-signal reaction time but bad news for slope of the inhibition function. *Acta Psychologica*, xxx, xxx–xxx.

Barkley, R. A. (1997a). *ADHD and the nature of self-control*. New York: Guilford Press.

Barkley, R. A. (1997b). Behavioural inhibition, sustained attention, and executive functions: Constructing a unifying theory of AD/HD. *Psychological Bulletin*, 121, 65–94.

Carter, C. S., Krener, P., Chaderjian, M., Northcutt, C., & Wolfe, V. (1995). Abnormal processing of irrelevant information in attention deficit hyperactivity disorder. *Psychiatry Research*, 56, 59–70.

Chhabildas, N., Pennington, B. F., & Willcutt, E. G. (2001). A comparison of the neuropsychological profiles of the DSM-IV subtypes of ADHD. *Journal of Abnormal Child Psychology*, 29, 52–540.

Douglas, V. I., Barr, R. G., Amin, K., O'Neill, M. E., & Britton, B. G. (1988). Dosage effects and individual responsivity to methylphenidate in attention deficit disorder. *Journal of Child Psychology and Psychiatry*, 29, 453–475.

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception and Psychophysics*, 16, 143–149.

Everett, J., Thomas, J., Cote, F., Levesque, J., & Michaud, D. (1991). Cognitive effects of psychostimulant medication in hyperactive children. *Child Psychiatry and Human Development*, 22, 79–87.

Goldman, L. S., Genel, M., Bezman, R. J., & Slanetz, P. J. (1998). Diagnosis and treatment of Attention-Deficit/Hyperactivity Disorder. *JAMA*, 279, 1100–1107.

Groth-Marnat, G. (1997). *Handbook of psychological assessment* (3rd ed.). New York: Wiley.

Halperin, J. M., McKay, K. E., Matier, K., & Sharma, V. (1994). Attention, response inhibition, and activity level in children: Developmental neuropsychological perspectives. In M. G. Tramontana & S. R. Hooper (Eds.), *Advances in child neuropsychology* (Vol. 2, pp. 1–54). New York: Springer-Verlag.

Hammes, J. W. G. (1971). *De Stroop Kleur-Woord Test. Handleiding* [The Stroop Color-Word Test: Manual]. Lisse: Swets & Zeitlinger.

Hartman, C. A., Hox, J., Mellenbergh, G. J., Boyle, M. H., Offord, D. R., Racine, Y., et al. (2001). DSM-IV internal construct validity: When a taxonomy meets data. *Journal of Child Psychology and Psychiatry*, 42, 817–836.

Jonkman, L. M., Kemner, C., Verbaten, M. N., van Engeland, H., Kenemans, J. L., Camferman, G., et al. (1999). Perceptual and response interference in children with attention-deficit hyperactivity disorder, and the effects of methylphenidate. *Psychophysiology*, 36, 419–429.

Konrad, K., Gauggel, S., Manz, A., & Schöll, M. (2000). Inhibitory control in children with traumatic brain injury (TBI) and children with attention deficit/hyperactivity disorder (ADHD). *Brain Injury*, 14, 859–875.

Kooijmans, R., Scheres, A., & Oosterlaan, J. (2001). Response inhibition and measures of psychopathology: A dimensional analysis. *Child Neuropsychology*, 6, 175–184.

Kuntsi, J., Oosterlaan, J., & Stevenson, J. (2001). Psychological mechanisms in hyperactivity: I. Response inhibition deficit, working memory impairment, delay aversion, or something else? *Journal of Child Psychology and Psychiatry*, 42, 199–210.

Logan, G. D. (1994). On the ability to inhibit thought and action: A users' guide to the stop signal paradigm. In D. Dagenbach & T. H. Carr (Eds.), *Inhibitory processes in attention, memory, and language* (pp. 189–239). San Diego: Academic Press.

Logan, G. D., & Cowan, W. B. (1984). On the ability to inhibit thought and action: A theory of an act of control. *Psychological Review*, 91, 295–327.

Logan, G. D., Schachar, R. J., & Tannock, R. (1997). Impulsivity and inhibitory control. *Psychological Science*, 8, 60–64.

MacLeod, C. M. (1991). Half a century of research on the Stroop effect: An integrative review. *Psychological Bulletin*, 109, 163–203.

Manassis, K., Tannock, R., & Barbosa, J. (2000). Dichotic listening and response inhibition in children with comorbid anxiety disorders and ADHD. *Journal of the American Academy for Child and Adolescent Psychiatry*, 39, 1152–1159.

McBurnett, K. (2000). Methylphenidate treatment of DSM-IV types of Attention Deficit Hyperactivity Disorder. In L. L. Greenhill & B. B. Osman (Eds.), *Ritalin: Theory and Practice* (2nd ed., pp. 253–263). Larchmont: Mary Ann Liebert.

Morein-Zamir, S., & Meiran, N. (in press). Individual stopping times and cognitive control: Converging evidence from a new stop signal paradigm. *Quarterly Journal of Experimental Psychology*, xx, xxx–xxx.

MTA cooperative group. (1999). A 14-month randomized clinical trial of treatment strategies for Attention-Deficit/Hyperactivity Disorder. *Archives of General Psychiatry*, 56, 1073–1086.

Nigg, J. T. (1999). The ADHD response-inhibition deficit as measured by the stop task: Replication with DSM-IV combined type, extension, and qualification. *Journal of Abnormal Child Psychology*, 27, 393–402.

Nigg, J. T. (2000). On inhibition/disinhibition in developmental psychopathology: Views from cognitive and personal psychology and a working inhibition taxonomy. *Psychological Bulletin*, 126, 1–27.

Nigg, J. T. (2001). Is ADHD a disinhibitory disorder? *Psychological Bulletin*, 127, 571–598.

Oosterlaan, J., Logan, G. D., & Sergeant, J. A. (1998). Response inhibition in AD/HD, CD, comorbid AD/HD+CD, anxious, and control children: A meta-analysis of studies with the stop task. *Journal of Child Psychology and Psychiatry*, 39, 411–425.

Oosterlaan, J., Scheres, A., Antrop, I., Roeyers, H., & Sergeant, J. A. (2000). *Vragenlijst voor Gedragsproblemen bij Kinderen (VvGK). Nederlandse bewerking van de Disruptive Behavior Disorders Rating Scale* [Disruptive Behavior Disorder Rating Scale. Dutch translation of the Disruptive Behavior Disorders Rating Scale]. Lisse: Swets Test Publishers.

Osman, A., Kornblum, S., & Meyer, D. E. (1986). The point of no return in choice reaction time: Controlled and ballistic stages of response preparation. *Journal of Experimental Psychology: Human Perception and Performance*, 12, 243–258.

O'Toole, K., Abramowitz, A., Morris, R., & Dulcan, M. (1997). Effects of methylphenidate on attention and nonverbal learning in children with Attention-Deficit Hyperactivity Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36,* 531–538.

Pelham, W., Gnagy, E. M., Greenslade, K. E., & Milich, R. (1992). Teacher ratings of DSM-III-R symptoms for the disruptive behavior disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, *31,* 210–218.

Pennington, B. F., & Ozonoff, S. (1996). Executive functions and developmental psychopathology. *Journal of Child Psychology and Psychiatry*, *37,* 51–87.

Perugini, E. A., Harvey, E. A., Lovejoy, D. W., Sandstrom, K., & Webb, A. H. (2000). The predictive power of combined neuropsychological measures for Attention-Deficit/Hyperactivity Disorder in children. *Child Neuropsychology*, *6,* 101–114.

Pliszka, S. R., Liotti, M., & Woldorff, M. G. (2000). Inhibitory control in children with Attention-Deficit/Hyperactivity Disorder: Event-related potentials identify the processing component and timing of an impaired right-frontal response-inhibition mechanism. *Biological Psychiatry*, *48,* 238–246.

Rapport, M. D., & Kelly, K. L. (1991). Psychostimulant effects on learning and cognitive function: Findings and implications for children with Attention Deficit Hyperactivity Disorder. *Clinical Psychology Review*, *11,* 61–92.

Ridderinkhof, K. R., van der Molen, W., Band, G., & Bashore, T. R. (1997). Sources of interference from irrelevant information: A developmental study. *Journal of Experimental Child Psychology*, *65,* 315–341.

Rubia, K., Taylor, E., Smith, A. B., Oksannen, H., Overmeyer, S., & Newman, S. (2001). Neuropsychological analyses of impulsiveness in childhood hyperactivity. *British Journal of Psychiatry*, *179,* 138–143.

Schachar, R., Mota, V. L., Logan, G. D., Tannock, R., & Klim, P. (2000). Conformation of an inhibitory control deficit in Attention-Deficit/Hyperactivity Disorder. *Journal of Abnormal Child Psychology*, *28,* 227–235.

Schachar, R., & Tannock, R. (1993). Childhood hyperactivity and psychostimulants: A review of extended treatment studies. *Journal of Child and Adolescent Psychopharmacology*, *3,* 81–97.

Scheres, A., Oosterlaan, J., & Sergeant, J. A. (2001a). Response execution and inhibition in children with AD/HD and other disruptive disorders: The role of behavioural activation. *Journal of Child Psychology and Psychiatry*, *42,* 347–357.

Scheres, A., Oosterlaan, J., & Sergeant, J. A. (2001b). Response inhibition in children with DSM-IV subtypes of AD/HD and related disruptive disorders: The role of reward. *Child Neuropsychology*, *7,* 172–191.

Seidman, L. J., Biederman, J., Mounteaux, M. C., Weber, W., & Faraone, S. V. (2000). Neuropsychological functioning in nonreferred siblings of children with Attention Deficit/Hyperactivity Disorder. *Journal of Abnormal Psychology*, *109,* 252–265.

Sergeant, J. A., Oosterlaan, J., & Van der Meere, J. (1999). Information processing in Attention-Deficit/Hyperactivity Disorder. In H. C. Quay & A. E. Hogan (Eds.), *Handbook of Disruptive Behavior Disorders* (pp. 75–104). New York: Plenum.

Sergeant, J. A., & van der Meere, J. J. (2000). Ritalin: An energetic factor? In L. L. Greenhill & B. B. Osman (Eds.), *Ritalin: Theory and practice*, (2nd ed., pp. 321–340). Larchmont: Mary Ann Liebert.

Shaffer, D., Fisher, P., Lucas, C. P., Dulcan, M. K., & Schwab-Stone, M. E. (2000). NIMH Diagnostic Interview Schedule for Children version IV (NIMH DISC-IV): Description, differences from previous versions, and reliability of some common diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry*, *39,* 28–38.

Solanto, M. V., Abikoff, H., Sonuga-Barke, E., Schachar, R., Logan, G. D., Wigal, T., et al. (2001). The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD: A supplement to the NIMH multimodal treatment study of AD/HD. *Journal of Abnormal Child Psychology*, *29,* 215–228.

Sprague, R. L., & Sleator, E. K. (1977). Methylphenidate in hyperkinetic children: Difference in dose effects on learning and social behavior. *Science*, *198,* 1274–1276.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *18,* 643–662.

Swanson, J. M., McBurnett, K., Christian, D. L., & Wigal, T. (1995). Stimulant medications and the treatment of children with ADHD. In T. H. Ollendick & R. J. Prinz (Eds.), *Advances in clinical child psychology*. New York: Plenum .

Tannock, R., Schachar, R. J., Carr, R. P., Chajczyk, D., & Logan, G. (1989). Effects of methylphenidate on inhibitory control in hyperactive children. *Journal of Abnormal Child Psychology*, *17,* 473–491.

Tannock, R., Schachar, R., & Logan, G. (1995). Methylphenidate and cognitive flexibility: Dissociated dose effects in hyperactive children. *Journal of Abnormal Child Psychology*, *23,* 235–266.

Van der Meere, J., Gunning, B., & Stemerdink, N. (1999). The effect of methylphenidate and clonidine on response inhibition and state regulation in children with ADHD. *Journal of Child Psychology and Psychiatry*, *40,* 291–298.

Wilcutt, E. G., Pennington, B. F., Boada, R., Ogline, J. S., Tunick, R. A., Chhabildas, N. A., et al. (2001). A comparison of the cognitive deficits in reading disability and Attention-Deficit/Hyperactivity Disorder. *Journal of Abnormal Psychology*, *110,* 157–172.