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Does Methylphenidate Improve Inhibition and Other Cognitive Abilities in Adults with  
Childhood-Onset ADHD?

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## ABSTRACT

We examined the effect of methylphenidate (Mph) on inhibition and several other cognitive abilities in 43 adults with Attention Deficit Hyperactivity Disorder (ADHD) by use of Conners' Continuous Performance Test (CPT) and the Change Task (ChT), an extension of the Stop Signal Test (SST). In a double blind, cross-over, placebo controlled study with Mph, tests were administered during the third week of individually titrated treatment with Mph (maximum dose 1 mg / kg / day) and during the third week of treatment with placebo. We established large medication effects for commission errors, standard error of mean reaction time, and attentiveness on the CPT, as well as moderate medication effects for mean reaction time on the CPT and response re-engagement speed on the ChT. For Stop Signal Reaction Time (SSRT) on the ChT, we also established large effects of Mph, but only in a group of participants who showed slow SSRTs on placebo. Mph indeed ameliorates inhibition, which is the core problem of ADHD, and certain other cognitive abilities in adults with ADHD.

For decades, Attention Deficit Hyperactivity Disorder (ADHD) has been thought to affect only children. In the last fifteen years or so, however, researchers have established that children do not always outgrow their problems with attention, hyperactivity, and impulsivity once they reach adulthood. Rather, between 30 to 50% of children with ADHD still meet the requirements for the diagnosis in adulthood (Biederman, Mick, & Faraone, 2000; Manuzza, Klein, Bessler, Malloy, & LaPadula, 1998; Weiss, Hechtman, Milroy, & Perlman, 1985). This has lead to prevalence estimates for the United States of 1-6% of the general population (Wender, Wolf, & Wasserstein, 2001). Epidemiologic studies have confirmed these figures in adults applying for a driver's license (Murphy & Barkley, 1996) and in college students (Heiligenstein, Conyers, Berns, Miller, & Smith, 1998).

For a long time, attention problems and hyperactivity have been the most researched symptoms of this disorder, but recently impulsivity is increasingly seen as the symptom of greatest significance (Taylor, 1998). According to several theories, impulsivity or decreased inhibition of behavior even is the central impairment of ADHD (Barkley, 1997; Nigg, 2001; Pennington & Ozonoff, 1996; Schachar, Tannock, & Logan, 1993). A possible explanation for this shift may be found in the current thought that inhibitory control plays an important role in attentional systems, which makes the inattention in ADHD a secondary symptom. As Rubia, Oosterlaan, Sergeant, Brandeis and van Leeuwen (1998) stated it: "For example, failure to sustain attention may be due to failure to inhibit interfering activities and distractibility may be caused by not inhibiting attention to irrelevant information" (p. 25). The extensive empirical evidence for deficits in inhibition in children with ADHD is derived from studies using different inhibition paradigms, for instance the Stop Signal Test (SST). In a meta analysis on SST data in ADHD children, Oosterlaan, Logan, and Sergeant (1998) demonstrated that children with ADHD exhibit significantly slower response inhibition times

than normal control children. This finding was confirmed in a more recent review of SST studies in children (Sergeant, Geurts, & Oosterlaan, 2002). Another paradigm that has often been employed in successfully establishing inhibition deficits in children with ADHD is the Continuous Performance Test (CPT) (Brandeis et al., 1998; Kerns, McInerney, & Wilde, 2001). For reviews of CPT studies in children with ADHD, see Corkum and Siegel (1993), Losier, McGrath, and Klein (1996), and Riccio, Waldrop, Reynolds, and Lowe (2001). Deficits in inhibition have also been established for adults with ADHD, using both the SST (Epstein, Johnson, Indira, & Conners, 2001; Murphy, 2002; Ossmann & Mulligan, 2003; Wodushek & Neuman, 2003), and the CPT (Barkley, Grodzinsky, & DuPaul, 1992; Epstein, Conners, Sitarenios, & Erhardt, 1998; Epstein et al., 2001; Ossmann & Mulligan, 2003; Riccio & Reynolds, 2001; Walker, Shores, Trollor, Lee, & Sachdev, 2000).

The stimulant methylphenidate (Mph) is one of the most effective and safe medications for the treatment of ADHD in children. Approximately 70% of ADHD children show a therapeutic response to stimulant medication (Schachter, Pham, King, Langford, & Moher, 2001; Wilens & Spencer, 2000). In adults with ADHD, stimulant medication has received far less attention than in children. In a recent review, (Wilens, Spencer, & Biederman, 2002) seven Mph studies were mentioned, in which the weighted mean clinical response to Mph treatment was 56%. In a recent meta analysis, Faraone, Spencer, Aleardi, Pagano, and Biederman (2004) mentioned a mean effect size of 0.9 for six double-blind placebo-controlled Mph treatment studies in adults with ADHD.

Mph has been shown to improve inhibition on several laboratory tasks in children with ADHD, such as the CPT (for a review see Losier et al., 1996), and the SST (Scheres et al., 2003; Tannock, Schachar, Carr, Chajczyk, & Logan, 1989; Tannock et al., 1995). Information on the effect of Mph on inhibition and other cognitive variables tested by the CPT in an adult ADHD population is limited. Riordan et al. (1999) established a decrease in visual

distractibility with Mph on a CPT. Kuperman et al. (2001) mentioned improvement with Mph on attentiveness (one of the signal detection parameters) on a CPT in adults with ADHD, but no other parameters were reported. In the only study mentioning an effect of Mph on the inhibition parameter of a CPT, the effect was not significant (Gualtieri, Ondrusek, & Finley, 1985). The effect of Mph on the Change Task (ChT, which is an extended version of the SST) in an adult ADHD sample has not been reported thus far. Given the current emphasis on inhibition in ADHD, this shortage of studies into the effect of Mph on inhibition in adult ADHD is surprising. This is why in the present study, we hypothesized that Mph would improve inhibition in adults with ADHD, both on the CPT and the ChT, compared to placebo.

In addition to inhibition, the CPT and the ChT measure several other variables of cognitive functioning. The CPT provides information on processes related to response execution (speed and variability), as well as measures that are related to signal detection theory (perceptual sensitivity in discriminating targets from non-targets and response style). Another interesting feature of the CPT is that stimuli may be presented with different event rates, for instance 1, 2 or 4 s between stimuli. This allows for analysis of the involvement of behavioral activation in response execution. An optimal behavioral activation state influences motor adjustment, thus affecting response execution (Sanders, 1998). The influence of activation level has been repeatedly indicated in ADHD in children (Scheres, Oosterlaan, & Sergeant, 2001; Sergeant, 2000; Van der Meere, 1996).

The ChT provides information on similar response execution processes as the CPT. Moreover, by instructing subjects to perform another action after they have inhibited their prepotent response, it also supplies information on response re-engagement processes. Performance on many of these variables has been shown to differ between children with ADHD and normal controls (see Losier et al., 1996; Oosterlaan et al., 1998, Riccio et al.

2001). Similar information on adults with ADHD is sparse, but available studies indicate that they also may show difficulties on some of the abilities mentioned above, such as speed of response execution, and attentiveness (Epstein et al., 1998; Epstein et al., 2001).

Besides its positive effect on the clinical symptoms of ADHD and on inhibition, stimulant medication seems to improve specific other cognitive abilities. In children, it has been shown to enhance response speed and accuracy (Klorman et al., 1988; Reid & Borkowski, 1984), response variability (Tannock et al., 1995), and response re-engagement (Barnett et al., 2001; Berman, Douglas, & Barr, 1999; Kempton et al., 1999; Solanto, 1997; Tannock et al., 1995). Studies with Mph in adults with ADHD have suggested that the drug may also improve specific cognitive abilities in this group. Kuperman et al. (2001) showed advanced response re-engagement abilities and increased fluency with Mph. Other researchers have found evidence of increase in working memory ability (Kinsbourne, De Quiros, & Tocci Rufo, 2001), motor speed, and processing speed, as well as decreases in distractibility (Riordan et al., 1999).

Our first hypothesis stated that Mph would improve inhibition in adults with ADHD, both on the CPT and the ChT, compared to placebo. In order to extend the knowledge of the effect of Mph on cognitive abilities, other than inhibition, in adult ADHD, we further hypothesized that several cognitive processes (speed of response execution, variability of response execution, response re-engagement, attentiveness) measured by the CPT and the ChT would improve with Mph, compared to placebo.

## METHOD

### Participants

Forty-three adults with ADHD between 20 and 55 years of age ( $M = 38.9$  years;  $SD = 10.1$ ), 21 men and 22 women, participated in this study. Two of these participants were diagnosed with ADHD hyperactive / impulsive subtype, the other 41 were diagnosed with

ADHD combined subtype. None of the participants had been treated with Mph prior to this study. The average IQ was 100.3 (*SD* 17.9; minimum 76, maximum 142). The participants were either self-referred or referred by other clinicians for assessment of ADHD to an outpatient clinic in the Netherlands. Prior to inclusion in the study, participants underwent a standardized clinical assessment consisting of a psychiatric evaluation by one of two experienced psychiatrists. The following instruments were used: a semi-structured clinical diagnostic interview for ADHD and co morbid disorders; several sections from the Dutch version of the Diagnostic Interview Schedule (Robins et al., 1995): section L (for the retrospective diagnosis of ADHD in childhood), section N (for the retrospective diagnosis of oppositional defiant disorder), section O (for the retrospective diagnosis of conduct disorder), and section P (for current antisocial personality disorder); the Dutch version of the Composite International Diagnostic Interview (CIDI) (version 2.1, lifetime; Robins et al., 1988) for Axis I psychiatric disorders; the Dutch version of the International Personality Disorder Examination (IPDE) (Loranger, Sartorius, Andreoli, & Berger, 1994) for borderline and antisocial personality disorders. For current ADHD-symptoms during the last 6 months, we used the Dutch version of the ADHD-Rating Scale (DuPaul, Power, Anastopoulos, & Reid, 1998), based on the 18 DSM-IV symptom criteria for ADHD. The level of associated impairment was assessed using the Dutch version of the Sheehan Disability Scale (SDS) (Sheehan, Harnett-Sheehan, & Rai, 1996) and the Global Assessment of Functioning Scale (GAF) (APA, 1994). A medical history, a physical examination (blood pressure, pulse and weight), and laboratory assessments (complete blood cell count, liver, kidney, thyroid, glucose function tests, and electrocardiogram) were also obtained.

To be given a diagnosis of adult ADHD, subjects had to (1) currently meet at least 5 of 9 DSM-IV criteria of inattention and / or at least 5 of 9 DSM-IV criteria of hyperactivity / impulsivity (based on the ADHD Rating Scale), (2) meet at least 6 of 9 DSM-IV criteria of

inattention and / or at least 6 of 9 DSM-IV criteria of hyperactivity / impulsivity in childhood (based on the DIS- section L), (3) describe a chronic persisting course of ADHD symptoms from childhood to adulthood, and (4) endorse a moderate to severe level of impairment attributed to ADHD symptoms. The cutoff point of 5 of 9 hyperactive / impulsive symptoms and / or 5 of 9 inattention symptoms for adult diagnosis of ADHD is in line with previous research (Biederman et al., 2000; Murphy & Barkley, 1996). In order to obtain information about lifetime ADHD symptoms and impairment, the participant, the partner (if available), and (if possible) the parents were interviewed. Information on school reports was examined in order to substantiate the diagnosis in childhood. We estimated the IQ of participants based on four subtests of the Dutch version of the Wechsler Adult Intelligence Scale-III: Vocabulary, Arithmetic, Block Design, and Picture Arrangement. The reliability of this short form has not been established for the WAIS-III yet, but for the WAIS-R these four tests have been found to estimate Full Scale IQ with greater accuracy than other variations (Boone, 1990). Data for several diagnostic measures are provided in Table 1.

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 Insert Table 1 about here  
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Subjects with co morbid psychiatric disorders were included, unless these disorders required to be treated first (for instance severe depression or anxiety) or when treatment with Mph was contra-indicated (for instance with hypertension). The number of eligible participants was 108. Before study entry, 15 people withdrew consent for the trial. We excluded 41 participants: four with clinically significant medical conditions, one with abnormal baseline laboratory values, seven with other psychiatric conditions that required to be treated first, 11 because of current use of psychotropics, and 18 because of prior use of Mph or amphetamines. Other exclusion criteria were: a history of tic disorders, IQ below 75,



any neurological condition that could interfere with a diagnosis of ADHD (such as concussion, meningitis, traumatic brain injury), suicidal behavior, psychosis, mania, physical aggression, and pregnancy or nursing. No participants had to be excluded based on these criteria. After study entry and full diagnostic assessment, seven participants were ineligible: five due to current substance abuse, one due to hypertension, and one due to severe depression that urgently required treatment. In the end, 45 participants were randomized and completed the trial. Data of two participants could not be used for the neuropsychological part of the study due to incompleteness ( $n = 1$ ) and positive urine screening for opiates ( $n = 1$ ). The study was approved by the local Medical Ethical Committee, and all subjects completed a written informed consent form before inclusion in the study.

## **Materials**

### *Continuous Performance Test*

Computerized CPTs are often used to study vigilance in ADHD populations. Most CPTs require a subject to press a key in response to a target stimulus (for instance the letter X, or the letter A followed by an X) and to ignore non-target stimuli. The version used in this study is the Conners' Continuous Performance Test (Conners, 1995), which differs from traditional (X and A-X) CPT paradigms (Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956). In Conners' CPT, the response required for the critical signal of X is to withhold a discrete and repetitive motor response, rather than to respond to it. For all other stimuli, a response of pressing the space bar is required. This means that omission errors indicate a failure to execute the required response, whereas commission errors suggest an inability to inhibit the prepotent response. Next to sustained attention, the main measurement objective of traditional CPTs, the Conners' CPT may invoke executive or controlled attention (Ballard, 2001). As far as we know, this version of the test has only been used in one study with Mph

in an adult ADHD population (Kuperman et al., 2001). However, this study only reported medication effects on the dependent variable attentiveness ( $d'$ ).

The task consisted of six blocks of 60 trials. Each block contained three sub-blocks of 20 trials each. Stimuli presented were letters of approximately 1 inch in size. Ten percent of stimuli in each block were Xs, with a total of 36 Xs for the entire test. Other letters presented were A, B, C, D, E, F, H, I, L, M, N, O, T, Y, and Z. For each block, the sub-blocks had different inter-stimulus intervals (ISIs): 1, 2, or 4 s. The order of sub-blocks randomly varied between blocks. Each letter was displayed for 250 ms. The most often reported (and therefore also chosen for this study) dependent variables are: 1) the number of commission errors, measuring inhibitive behavior (high error rates indicate poor inhibitive control), 2) mean reaction time for hits (to measure the latency of the response execution process), 3) the standard error of the mean hit reaction time (an indication of the consistency with which respondents can focus their attention), 4) attentiveness ( $d'$ ), which is an indication of the ability to discriminate between targets and non-targets, and 5) risk taking ( $\beta$ ) (an indication of a person's response style: high values point to cautious response styles, whereas low values suggest more risk taking). Omission errors were not analyzed for this study, since the participants made hardly any errors of this type ( $M$  (placebo) = 2.4;  $M$  (Mph) = 1.8).

### *Change Task*

The Change Task (ChT) (Logan & Burkell, 1986) is an extension of the Stop Signal Test (SST) (Logan, Cowan, & Davis, 1984). The SST measures response execution and response inhibition processes, while the extended ChT is also used to investigate response re-engagement. To our knowledge, this test has not been used previously in any studies with adults with ADHD.

The ChT used in this study consisted of go trials and stop trials. For both types of trials, an aeroplane was presented for 1000 ms at either the left or the right side of the screen.

Immediately before stimulus onset, a fixation point (500 ms in duration) appeared at the center of the screen. A right sided stimulus required subjects to press the right response button as quickly as possible. If the aeroplane was presented on the left, the left response button had to be pressed. Subjects were instructed to use the index and middle fingers of their dominant hand. Between trials the screen turned blank for 1500 ms. Stop trials were identical to go trials, but in addition a stop signal (a 1000 Hz tone, 50 ms in duration) was presented through stereo earphones. When a stop signal was presented, participants were to withhold their response (i.e., not to press any button with their dominant hand). In addition, they had to press a different button with their non-dominant thumb as quickly as possible. This is the Change Response, a measure of response re-engagement. Seventy-five percent of trials were go-trials, and 25% were stop trials. Trials were presented in blocks of 64 trials. Stop signals were presented at predetermined intervals before the subject's expected response. This provides the opportunity to ascertain the ability to inhibit a response at different points in the response execution process. The shorter the time interval between the stop signal and the expected response, the more difficult it becomes to inhibit this response. Intervals between stop signal and expected response were set at 50 ms, 200 ms, 350 ms, or 500 ms with each interval occurring on 25% of the stop trials. The expected moment of response was based on the mean reaction time in the previous block. The task started with three practice blocks to familiarize participants with the paradigm. In the first block only go trials were presented (primary task). In the second practice block, 25% of trials were stop trials, which only required inhibition of response. In the last practice block, stop signals required both response inhibition and response re-engagement. After practice, participants were administered four experimental blocks of 64 trials each. Standardized instructions pressed participants not to wait for the stop signal, but to continue pressing the buttons as quickly as they could.

The main dependent measure for this task is Stop Signal Reaction Time (SSRT). This is an estimate of the time it takes before the inhibition process is engaged. SSRT cannot be measured directly, but it can be estimated using the Race Model (Logan, 1994). According to the Race Model response inhibition depends on the outcomes of a race between two sets of processes that operate independently. One set starts with the onset of the go-stimulus (the aero plane at the left or right side of the screen) and results in the activation and execution of the response, whereas the other set starts with the onset of the stop signal and results in the onset of the inhibitory process (Logan & Cowan, 1984). The response is made or withheld, depending on which set of processes wins the race. In practice, SSRT is calculated as follows: first, reaction times on go-trials are rank ordered on a time axis. Then, the  $n$ th reaction time is picked, whereby  $n$  is defined by the product of the number of reaction times in the distribution and the probability of responding given a stop signal. This gives an estimate for the time at which the inhibition process runs to completion, relative to the onset of the primary task stimulus. Third, the delay between onset of the primary task stimulus and the stop signal is subtracted from the  $n$ th reaction time and thus SSRT is estimated. For more detailed information on the calculation of SSRT, the reader is referred to Logan et al. (1984). In addition to SSRT, other dependent variables included in the analyses were: 1) the mean reaction time on go-trials of the primary task (measuring latency of response execution), 2) the standard deviation of the reaction times on go-trials of the primary task (measuring variability in the latency of the response execution process), 3) the mean reaction time on the Change Response of the task (an indication of the speed of the response re-engagement process), and 4) the standard deviation of the Change Response latencies (to measure variability in the speed of the response re-engagement process). Another measure often reported in research using the SST is the slope of inhibition function. Recently however,

Band, Van der Molen, and Logan (2002) indicated that this variable is not a reliable indicator of differences in inhibition. Therefore, this variable was not analyzed in the current study.

## **Procedure**

Participants entered a double blind, placebo controlled, cross over trial of Mph. The design of this trial and clinical outcomes are described in detail elsewhere (see Kooij et al., in press). We designed the trial based on the medication study by Spencer et al. (1995). There were two 3-week treatment periods for each participant, one period of three weeks for Mph and one period of three weeks for placebo, with 1 week of washout in between.

The order of treatment (Mph-placebo or placebo-Mph) was randomized. Weekly supplies of Mph (10 mg per tablet) or placebo were prepared and dispensed by the hospital pharmacy in identically appearing tablets. Placebo tablets contained only a base granulate. Mph tablets contained only Mph granulate. Medication was prescribed in four times or five times a day dosing, depending on whether rebound occurred. Study medication was titrated up from low to high doses, to avoid exposure to high initial doses of active medication and to minimize side effects. Participants started with 0.5 mg / kg per day in week 1, followed by 0.75 mg / kg per day in week 2, and up to 1.0 mg / kg per day in week 3, unless adverse effects emerged. A dose of 1.0 mg / kg has been shown to be a reasonable upper limit dosage for clinical purposes (Sachdev & Trollor, 2000). To control for possible substance use during the trial, patients were asked unannounced twice to hand over a urine sample.

Repeated administrations of the inhibition tasks described above were obtained in week 3 (highest dose of Mph, or placebo) and in week 7 (highest dose of Mph, or placebo). Testing started one hour and fifteen minutes after tablet intake. Mph peak concentrations in the brain are reached after approximately 60 minutes (Volkow et al., 1995). Maximal therapeutic effects are reached within approximately 2 hours after ingestion (Swanson, McBurnett, Christian, & Wigal, 1995; Wilens, Biederman, Spencer, & Prince, 1995). The

behavioral half-life of the drug is approximately 3 hours (Solanto & Conners, 1982).

Administration of the inhibition battery took approximately 1 hour, so testing was completed between the moment of peak Mph levels in the brain and the behavioral half-life value.

Besides two treatment orders (Mph-placebo or placebo-Mph), inhibition tasks were also administered in two different test orders (CPT-ChT or ChT-CPT), to be able to control for possible effects of fatigue and for effects of declining medication efficacy.

### **Statistical Approach**

In order to check whether treatment order or test order interacted with the effect of treatment condition, separate MANOVAs were conducted for the dependent variables of the CPT and the ChT, with treatment condition (Mph or placebo) as within subject factor and treatment order (Mph-plac or plac-Mph) and test order (CPT-ChT or ChT-CPT) as between subjects factors. If no overall interactions between treatment condition and treatment order or test order were found, the effects of medication on the dependent variables were further analyzed with ANOVAs with treatment condition as within subject factor. If, however, overall interactions between treatment condition and treatment order or test order were significant, univariate cross-over results were interpreted only for those variables that did not show an interaction. For variables that did show a univariate interaction, only data from the parallel trial (the first three weeks of treatment) were analyzed in an ANOVA with treatment condition as between subjects factor. Our alpha level was set at .05.

The data of one participant were excluded from the analyses for the ChT, because mean scores on several dependent variables deviated more than 1.5 times the interquartile range from the 25<sup>th</sup> or 75<sup>th</sup> percentile.

### **RESULTS**

Group characteristics for the two treatment order groups are shown in Table 2. Statistical analyses confirmed that there were no differences between the two groups in

number of participants, gender distribution, age, IQ, absolute dose (in mg / day), or relative dose (in mg / kg / day) of Mph at time of testing.

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 Insert Table 2 about here  
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## Main analyses

### *Continuous Performance Test*

There was no interaction between treatment condition and treatment order (Wilks'  $\Lambda = .77$ ,  $F(5, 35) = 2.12$ ,  $p = .086$ ), nor between treatment condition and test order (Wilks'  $\Lambda = .93$ ,  $F(5, 35) = .49$ ,  $p = .779$ ). Therefore, the effects of treatment condition on the dependent variables of the CPT were further analyzed without taking either treatment order or test order into account. A MANOVA with treatment condition as within subject factor showed an overall significant effect of treatment (Wilks'  $\Lambda = .60$ ,  $F(5, 38) = 4.98$ ,  $p = .001$ ,  $\eta^2 = .40$ ). Separate ANOVAs with treatment condition as within subject factor (see Table 3 for means and standard deviations) revealed a significant decrease of commission errors with Mph ( $F(1,42) = 10.88$ ,  $p = .002$ ). The accompanying effect size ( $\eta^2 = .21$ ) was large (Cohen, 1988). We also established a significant increase in mean reaction time with medication ( $F(1,42) = 5.10$ ,  $p = .029$ ) with a medium effect size ( $\eta^2 = .11$ ). Standard error of hits significantly decreased with Mph ( $F(1,42) = 7.15$ ,  $p = .011$ ), with a large effect size ( $\eta^2 = .15$ ). There was a significant improvement in attentiveness ( $d'$ ) ( $F(1,42) = 8.17$ ,  $p = .007$ ). The effect size of the latter increase was large ( $\eta^2 = .16$ ). The only CPT variable that did not show a change with medication was risk taking ( $\beta$ ) ( $F(1,42) = .43$ ,  $p = .837$ ,  $\eta^2 = .00$ ).

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 Insert Table 3 about here  
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*CPT – Analyses of ISI*

For several variables (commission errors, mean hit reaction time, and standard error of reaction time) of the CPT, separate data are available for the three different ISIs. These variables were analyzed in ANOVAs with two within subject factors: ISI (three levels: 1, 2, or 4s) and treatment condition with two levels, to check if Mph has a different effect for different ISIs. Because of possible violations of the sphericity assumption, degrees of freedom and related  $p$ -values were corrected according to the Greenhouse-Geisser method. For commission errors, there was no significant interaction between treatment condition and ISI ( $F(1.89, 79.21) = .54, p = .940, \eta^2 = .00$ ). Mph did not change the number of commission errors made over the different ISIs. As can be seen in Figure 1, there was a significant interaction effect of ISI and treatment condition for mean hit reaction time ( $F(1.75, 73.53) = 5.15, p = .011, \eta^2 = .11$ ). Post hoc paired samples  $t$ -tests revealed that the difference between placebo and Mph was significant only for an ISI of 1 s ( $t(42) = 3.95, p = .000$ ). Mph significantly slowed down the mean hit reaction time for an ISI of 1s.

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 Insert Figure 1 about here  
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Figure 2 displays the standard error of mean hit reaction time. For this variable we established a significant interaction of ISI and treatment condition ( $F(1.88, 79.06) = 5.07, p = .010, \eta^2 = .11$ ). Post hoc paired samples  $t$ -tests showed the effect of Mph to be significant only for an ISI of 4 s ( $t(42) = -3.14, p = .003$ ). So Mph lead to less variability in responding at a large ISI.

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*Change Task*

There was no significant interaction between medication treatment condition and test order (Wilks'  $\Lambda = .91$ ,  $F(5, 34) = .67$ ,  $p = .628$ ). Therefore, the effects of medication for this test were further analyzed without taking test order into account. There was, however, a significant interaction between treatment condition and treatment order (Wilks'  $\Lambda = .51$ ,  $F(5, 34) = 6.60$ ,  $p = .000$ ). Univariate tests revealed significant interactions of treatment condition and treatment order for mean reaction time ( $F(1, 38) = 12.20$ ,  $p = .001$ ), and standard deviation of reaction times ( $F(1, 38) = 21.00$ ,  $p = .000$ ). Apparently, for these variables it made a difference whether Mph or placebo was administered first. For these variables, main effects of treatment condition were therefore analyzed only for the parallel trial (after three weeks of treatment, during the highest dose of Mph or placebo).

The variables that did not show univariate interactions of treatment order and treatment condition were further analyzed with ANOVAs with treatment condition as within subject factor (see Table 4 for means and standard deviations). For SSRT, no decrease with medication was found ( $F(1, 41) = 3.08$ ,  $p = .087$ ,  $\eta^2 = .07$ ). Inhibition as measured by this variable, did not improve with Mph. A significant decrease in mean reaction time on the Change Response with Mph was established ( $F(1, 41) = 4.84$ ,  $p = .033$ ). The accompanying effect size was medium ( $\eta^2 = .11$ ). This indicates an improvement in response re-engagement with Mph. The standard deviation of these Change Response reaction times was not different under medication or placebo ( $F(1, 41) = .26$ ,  $p = .615$ ,  $\eta^2 = .01$ ).

For the two variables that showed significant interactions between treatment order and treatment condition, data for the first point of measurement (after three weeks) were compared in an ANOVA with treatment condition as a between subjects factor (see Table 4 for means and standard deviations). There was no significant effect of Mph on mean reaction

time ( $F(1, 40) = .91, p = .346, \eta^2 = .02$ ). A marginally significant decrease with Mph could be established for the standard deviation of reaction times ( $F(1, 40) = 4.02, p = .052, \eta^2 = .09$ ).

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#### *Post-hoc analyses*

Several exploratory analyses were conducted to characterize the results more completely. In order for a medication effect to be not only statistically but also clinically significant, one would like medication to normalize scores on dependent variables. To check whether this was the case for our sample, we compared the mean of our medicated ADHD group with the group mean of a normal control sample from another study for the variable that showed the largest effect size in our study: commission errors on the CPT. The normal control participants in a study by Murphy, Barkley, and Bush (2001) carried out the exact same version of the CPT as our ADHD participants. A one sample  $t$ -test showed no differences ( $t(42) = -.28, p = .78$ ) between the mean number of commission errors of our medicated ADHD sample ( $M = 10.7$ ) and the mean of the normal control sample ( $n = 64, M = 11$ ), indicating a similar level of inhibition in both groups. When we compared our ADHD sample off medication (placebo scores) and the same normal control group, the difference was significant ( $t(42) = 2.23, p = .03$ ): the ADHD group showed worse inhibition capacities than the normal control group from Murphy et al.

It is possible that medication effects are found only when there is room for improvement. To check this possibility, we compared medication effects (difference scores between placebo and Mph) on CPT commissions and on ChT SSRT for participants with placebo scores below and above the means of these variables. For CPT commissions, the group ( $n = 18$ ) who made a larger number of commission errors (compared to the mean

placebo commission score) improved significantly more with Mph than the group who made a smaller number of errors ( $n = 25$ ; again compared to the mean placebo score) ( $F(1, 41) = 8.21, p = .007, \eta^2 = .17$ ). For SSRT on the ChT, the effect of high versus low placebo scores was even larger. Participants who showed slower than average SSRTs on placebo ( $n = 22$ ) improved much more with medication than participants who responded faster than average to begin with ( $n = 20$ ) ( $F(1, 40) = 25.15, p = .000, \eta^2 = .39$ ). This latter result is in contrast with the non-significant results in the total sample. Apparently, Mph does significantly improve inhibition as measured by the ChT in participants who show low scores on SSRT to begin with.

To check what the predictive value of improvement on cognitive tests is for clinical respondership, we conducted a discriminant analysis to determine whether the difference between placebo and medication scores for the two most often reported dependent variables for our neuropsychological tests (commission errors and SSRT) could predict clinical respondership. Clinical respondership for each participant was determined according to Kooij et al. (in press), who defined clinical response as a decrease of at least two points on the investigator based Clinical Global Impression Scale for ADHD over the total treatment period (three weeks), *and* a 30% or more symptom reduction on the selfreported ADHD Rating Scale. The overall Wilks' lambda was significant for change in commission errors on the CPT ( $\Lambda = .79, \chi^2(2, N = 43) = 9.15, p = .010$ ), but not for the SSRT of the ChT. Only the significant discriminant function was interpreted. Clinical respondership could be correctly classified based on decrease of commission errors in 79% of the cases. Ten of 16 responders were correctly classified, leading to a sensitivity of 63%. Twenty-three of 26 non-responders were correctly classified as such, indicating a specificity of 89%. Positive predictive power of the decrease in commission errors on clinical respondership was 78%, negative predictive power was 79%. In order to take into account chance agreement, we computed a kappa

coefficient and obtained a value of .53, which can be considered moderate (Landis & Koch, 1977).

Finally, we performed a partial correlation analysis to check whether the amount of commission errors on the CPT during Mph was related to several clinical variables rather than to Mph, when placebo-commission errors were partialled out. There were no significant correlations between Mph-commission errors and any of the following variables: severity of ADHD (number of DSM-IV symptoms;  $r = -.14$ ,  $p = .37$ ), relative Mph dose at endpoint (in mg / kg;  $r = -.03$ ,  $p = .86$ ), absolute dose at endpoint (mg;  $r = -.00$ ,  $p = .99$ ), co morbid anxiety disorder ( $r = .27$ ,  $p = .09$ ), number of co morbid disorders ( $r = .28$ ,  $p = .07$ ), or IQ ( $r = .06$ ,  $p = .71$ ).

## DISCUSSION

The present study was designed to examine the effects of Mph on inhibition and other cognitive measures in a sample of adults with ADHD. The group analyses indicated rather strong effects of Mph on inhibition and response measures on the CPT. However, no group effect on inhibition and only modest effects on other response measures were found on the ChT.

With respect to the CPT, the inhibition results confirm our hypothesis and they are in line with previous research in ADHD children (Losier, 1996). For adults, very few medication studies of commission errors on the CPT are available. Results by Gualtieri et al. (1985) indicate a decrease in commission errors on a CPT, although this decrease just fell short of significance. However, our study provides more reliable changes, since Gualtieri and colleagues tested after a single dose of Mph, rather than an entire week of medication. When breaking down commission errors into number of errors for different ISIs, the results indicate that the commission errors occur independently of event rate, both in the placebo and the Mph condition. This result may underline the suggestion that inhibition is not influenced by a behavioral activation level (Sergeant, Oosterlaan, & Van der Meere, 1999). When we compared a subgroup of our participants whose placebo score on commission errors was worse than that of a normal control group from the study by Murphy et al. (2001), the effect of Mph on commission errors was even larger.

We hypothesized the effect of Mph on SSRT of the ChT to be stronger than what we actually found. Our finding cannot be compared with adult ADHD data, since the effect of Mph on SSRT has not been studied in this population before. In children with ADHD, three studies reported substantial faster SSRTs with Mph (Scheres et al., 2003; Tannock et al., 1989, 1995), while Overtom and colleagues (in press) did not observe changes in SSRT with Mph. Post hoc analyses of our data indicated that Mph does induce a large improvement in

SSRT for a subgroup of our participants whose SSRT on placebo was slower (indicating worse inhibition) than the mean placebo SSRT score of the entire group. However, this does not explain why we did not find an improvement of SSRT in the entire ADHD group, whereas we did find a decrease of commission errors on the CPT. Possible explanations for this deviance will be explored later in this discussion.

Other cognitive processes measured by the two paradigms used in this study include latency and variability of response execution processes (mean reaction time and variability in reaction times on both CPT and ChT), attentiveness ( $d'$ ; CPT), response style ( $\beta$ ; CPT) and response re-engagement (MRT and SD; only in the ChT). Reaction times became slower with medication on the CPT. This is in contrast with research in children (Klorman, Brumaghim, Fitzpatrick, & Borgstedt, 1991; Riccio et al., 2001) and adults with ADHD (Riordan et al., 1999), in which faster rather than slower MRTs with medication have been established. When breaking down the MRT effect on the CPT into effects for different ISIs, we found the expected slowing of MRT with longer ISIs (ADHD subjects have been shown before to show slower RTs with longer ISIs, see Scheres et al. 2001). Only with the shortest ISI, however, did medication slow RT significantly. The overall slowing of MRT with medication seems to be best and solely explained by a slower MRT with the shortest ISI. Apparently, Mph allows ADHD participants to respond less impulsively at short ISIs. This is in accordance with research by Berman et al. (1999), which showed that Mph slowed down RT only on the most difficult, high load test conditions (the shortest ISI can be considered to be a high load). This result implies that Mph improves self-regulatory abilities, as suggested by Douglas (1988, 1999).

We also found that treatment with Mph decreased variability of mean reaction times on both the CPT and the ChT. This is in agreement with earlier studies in children with ADHD (Tannock et al., 1989, 1995). No comparable research is available for adults with

ADHD. The overall decrease of variability in reaction times on the CPT could be broken down into different effects for different ISIs. Mph effects on variability seem to be larger for longer ISIs. This is propitious, since ADHD is known to lead to increasing variability in response execution with slow event rates (i.e., longer ISIs) (Scheres et al., 2001; Van der Meere, Shalev, Borger, & Gross-Tsur, 1995). Apparently Mph increased the behavioral activation level (Sanders, 1998), which allowed participants to respond more evenly.

Response re-engagement on the ChT (the Change Response) was sped up by Mph. This concurs with a recent study, showing that Mph enhanced task switching performance in ADHD children (Kramer, Cepeda, and Cepeda, 2001), and it is in line with earlier findings on the effect of Mph on the Change Response (see the Materials section for an explanation of the Change Response) in children with ADHD (Tannock, 1995). No data on the effect of Mph adult performance on this variable are available. Variability in response re-engagement reaction times was not affected by medication. No previous studies have reported on this measure in adults with ADHD, but based on decreased response variability in primary reaction times with Mph, one might expect this variability on a secondary task to decrease as well. This was indeed found in a child ADHD sample (Tannock, 1995). Possible explanations for this divergence will be explored later on in the discussion.

Attentiveness ( $d'$ ) on the CPT increased with medication, which is in keeping with medication studies in children with ADHD (Losier, 1996), and with studies in adults with ADHD (Kuperman et al., 2001). Risk taking ( $\beta$ ) did not change with Mph treatment, which also in line with previous studies in children (Losier, 1996). In adults with ADHD, the effect of Mph on this variable has not been reported before. It should be mentioned, however, that the standard deviation of this parameter was about as large as the mean, which makes interpreting any results with this variable difficult. It also raises questions about the accuracy

of the calculation of this measure by the scoring program. Similar observations were made by Epstein et al. (1998).

Exploratory analyses indicated that Mph may indeed normalize the number of commission errors made on the CPT by ADHD participants to the level of a normal control group. We only compared data for one dependent variable, so we cannot generalize this result to other cognitive abilities, but it is a promising result for clinical practice. Future research should compare other processes, preferably with a normal control group recruited especially for that study, since the normal control sample in the study by Murphy et al. (2001) was younger than our ADHD sample. If other variables of the CPT also normalize with Mph, this may render this test suitable for quantitatively establishing the effect of Mph on an individual level. This would be a valuable contribution to the entire ADHD population (both children and adults), since changes in symptoms are now indicated by either observers, who may not always be as objective as necessary, or by patients themselves, who may not have an accurate perception of these changes (Barkley, Fisher, Smallish, & Fletcher, 2002). The clinical value of a decrease in commission errors is also substantiated by the receiver operating characteristic analyses we performed. We ascertained that the overall predictive value of the difference between placebo and medication commission errors on the CPT was 79%. The related sensitivity of 63% indicates that the decrease in commission errors from placebo to Mph has a moderate predictive value for clinical respondership. The specificity of this decrease seems to be better: 88% of participants who did not show a large decrease, were not clinical responders. Elwood (1993) argues that a more accurate measure of utility of neuropsychological variables is the positive and negative predictive power. Positive predictive power for the change in commission errors indicates that of those participants who showed large decreases in this type of errors, 78% were responders. Conversely, 79% of



participants who showed a smaller decrease of commission errors, were correctly classified as non-responders.

We found no significant correlations between medication commission errors on the CPT and several clinical variables, while partialing out placebo commission errors. This indicates that improvement in commission errors with medication is not influenced to a significant extent by the severity of ADHD, the administered dose of Mph (either relative or absolute), the number of co morbid disorders, co morbid anxiety disorder, and IQ. Of course these analyses are only superficial, and no definitive conclusions can be drawn based upon these results. Larger groups of participants would allow for more substantial analyses into these issues. However, the results do suggest that the effect of Mph on commission errors on the CPT takes place rather independently of the variables mentioned. For all the exploratory analyses, it should be stressed that only a few variables were used in the analyses. So exploratory results only play up to future research: of course other variables and other tests should be evaluated before firm conclusions can be drawn.

All in all, many of the effects found in our study are in accordance with previous Mph studies with either adults with ADHD and / or children with ADHD. However, two deviant results were established. The first deviant result is lack of reduced variability in the reaction times on the Change Response. This may be due to large within group variability for this variable. The decrease in mean reaction time of the Change Response is significant, while the decrease in the standard deviation of reaction times is not. Proportionally, however, these decreases are similar for both variables. The within group variance is, again proportionally seen, much larger for the standard deviation of mean reaction times on the Change Response than for the mean reaction time of the Change Response, which could easily lead to lack of significant ANOVA results.

The second and main divergent result is a lack of robust decreases in SSRT on the ChT for the total ADHD group. Several explanations can be given for this deviation. A possible explanation can be found in the work of Tannock and colleagues (1995), who found an inverse U-shaped dose-response curve for SSRT in a ChT: Mph induced the largest reduction in SSRT with a medium dose (0.6 mg / kg). Decreases in SSRT were not established with low (0.3 mg / kg) nor with high (0.9 mg / kg) doses. In our study, the mean relative dose (0.9 mg / kg) was similar to the high dose in Tannock's study. Future research with different doses of Mph should prove whether medium doses improve inhibition on the ChT in adults with ADHD.

Another elucidation for our absence of a robust reduction in SSRT may be offered by Scheres et al. (2003), who indicated that a Stop Task with a tracking mechanism may be more sensitive to medication effects than the version with a fixed intervals method, used here. The version with a tracking mechanism assures a constant inhibition probability of 50%, which provides the most reliable estimation of SSRT (Band et al., 2002). When the percentage inhibition is lower or higher than 50%, estimations of SSRT may be underestimated or overestimated, respectively. The results of a recent study (Aron, Dowson, Sahakian, & Robbins, 2003) indicate that Mph may indeed improve inhibition as measured with a tracking version of the SST in adults with ADHD. Our data evoke the important question of why Mph has a robust effect on commission errors on the CPT, and not on SSRT on the ChT, while both variables are supposed to measure inhibition. It may be the case that the two operationalizations of response inhibition actually tap into slightly different abilities. This suggestion is underpinned by the low correlation between SSRT and commission errors ( $r = .21$ ). The nature of the two tasks also indicates several differences. First of all, in the CPT, the signal to withhold a response is given before the actual response is started up, while the ChT requires withholding a response that has already commenced in a large part of the trials.

Secondly, there is a difference in the percentage of targets in both tasks. In the ChT, 25% of trials require withholding a response, while this is only called for in 10% of the trials in the CPT. This discrepancy may cause differences in the state of arousal that participants are in while performing both tasks, which may influence the effect of Mph on both tasks.

A third difference between the two tasks is the nature of the stop signal. In the CPT, this signal is visual, and similar to the target signals. In the ChT, the stop signal is auditory. It has been suggested that children with ADHD have particular difficulties with processing information in the auditory modality (Riccio, Hynd, Cohen, Hall, & Molt, 1994). If this is also the case in adult ADHD, this factor may interfere with improvement on the ChT with medication.

Yet another, important difference can be found in the level of difficulty of both tasks. Inhibition on the ChT requires withholding a response while being in a more or less alerted state. The participant is anticipating a plane on either side of the screen and has to actually pay continuous attention in order to give the correct response in this two-choice reaction time task. With the CPT, it seems easier to drift into a semi-alert state of attention, since this is a simple go- no go task. Every stimulus requires the same response, i.e., pressing the space bar. Besides this difference in difficulty, the ChT requires response re-engagement after inhibition of the primary response. This also makes the inhibition process in this task a different, and more difficult process from inhibition in the CPT. Tannock et al. (1995) have indeed found smaller Mph effects on SSRT in the more demanding ChT, compared to the easier SST (used in their 1989 study). Increased cognitive load may reduce the magnitude of the effect of stimulants. This is in line with previous research, where performance decrements at high doses have been found on tasks that were complex, or on the most difficult level of tasks (Berman et al., 1999; Douglas, 1988; Tannock & Schachar, 1992). This underscores the importance of studying the effects of different doses in adults with ADHD, since the optimal

dose for ameliorating behavioral symptoms, may not necessarily be the most effective dose for several cognitive abilities (Cantwell & Swanson, 1997).

We tried to establish the effect of Mph on inhibition in adults with ADHD. Although our data suggest positive effects of the drug on inhibition, we did not test whether this holds for all forms of inhibition. As noted by Evenden (1999), “there is not one unitary impulsivity or only one type of impulsive behavior” (p. 348). Different researchers have proposed different taxonomies for subdividing inhibition (Barkley, 1997; Nigg, 2001). So further studies are necessary to determine which form of inhibition is improved by Mph and to better operationalize different forms of inhibition.

In sum, current findings showed that, in adults with ADHD, Mph has large beneficial effects on inhibition as measured by the CPT. It also has a large effect on inhibition as measured by the ChT, but only in those subjects who show slow inhibition times off-medication. In addition to improving inhibition, Mph decreases variability in response execution processes on the CPT, and it improves the ability to distinguish signal from noise on the CPT. Finally, Mph has a positive effect on response re-engagement, as measured by the ChT. Thus, Mph does not only effectively ameliorate clinical symptoms in an adult ADHD population, as shown by several researchers (for a review, see Wilens et al., 2002), but its positive effects can also be demonstrated on several cognitive processes important in daily life.

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Table 1

*Group Characteristics on Diagnostic Measures*

Measure	value <i>M</i> ( <i>SD</i> )
Number of currently endorsed DSM-IV criteria for ADHD	15.5 (2.1)
Number of DSM-IV criteria for ADHD endorsed in childhood (DIS-L)	12.0 (4.1)
Sheehan Disability Scale (minimum 0, maximum 30)	22.8 (3.3)
Global Assessment of Functioning (minimum 0, maximum 100) *	57.3 (6.1)
Axis I co morbid disorders (CIDI Lifetime)	
▪ any co morbid disorder	79%
▪ multiple co morbid disorders ( ≥ 2)	53%
▪ any anxiety disorder	51%
▪ any mood disorder	53%
Axis II co morbid disorders	
▪ Antisocial Personality Disorder (IPDE)	9.3%
▪ Borderline Personality Disorder (IPDE)	16.3%

*Note.* CIDI = Composite International Diagnostic Interview; IPDE = International Personality Disorder Examination.

\* Scores above 70 indicate normal functioning.

Table 2

*Characteristics of Two Treatment Order Groups and of Total Group*

	Mph – Plac		Plac – Mph		Total group	
	(n = 24)		(n = 19)		(N = 43)	
men / women	14 / 10		8 / 11		22 / 21	
age (M, SD)	38.5	(9.9)	38.3	(10.6)	38.4	(10.1)
IQ (M, SD)	100.3	(17.6)	100.2	(18.7)	100.3	(17.9)
dose (mg)	74.8	(15.6)	65.3	(16.9)	70.6	(16.7)
(M, SD)						
dose (mg / kg)	.97	(.13)	.88	(.23)	.93	(.18)
(M, SD)						

*Note.* Mph = methylphenidate; Plac = placebo.

Table 3

*Descriptives and Statistics for Continuous Performance Test Variables*

Variable	Placebo		Mph		<i>F</i>	<i>p</i>	$\eta^2$
mean hit reaction time ( <i>M, SD</i> )	333.5	(48.7)	342.6	(48.7)	5.10	.029	.11
standard error ( <i>M, SD</i> )	6.0	(3.3)	4.9	(2.4)	7.15	.011	.15
commissions ( <i>M, SD</i> )	13.6	(7.6)	10.7	(7.2)	10.88	.002	.21
attentiveness ( <i>d'</i> ) ( <i>M, SD</i> )	3.1	(0.9)	3.4	(0.9)	8.17	.007	.16
risk taking ( $\beta$ ) ( <i>M, SD</i> )	.06	(.05)	.07	(.06)	.43	.837	.00

Table 4

*Descriptives and Statistics for Change Task Variables*

Variable	Placebo		Mph		<i>F</i>	<i>p</i>	$\eta^2$
SSRT ( <i>M, SD</i> )	220.0	(56.4)	202.3	(50.5)	3.08	.087	.07
MRT ( <i>M, SD</i> )*	434.1	(82.7)	407.4	(95.9)	.91	.346	.02
SD RT ( <i>M, SD</i> )*	96.9	(32.3)	78.2	(28.4)	4.02	.052	.09
Change Response MRT ( <i>M, SD</i> )	475.3	(89.7)	457.1	(71.1)	4.84	.033	.11
Change Response SD RT ( <i>M, SD</i> )	117.0	(43.4)	113.2	(43.8)	.26	.615	.01

*Note.* SSRT = Stop Signal Reaction Time; MRT = mean reaction time; SD = standard deviation; RT = reaction time.

\* Placebo: *n* = 19; Methylphenidate: *n* = 23 (parallel trial analysis only).

Figure Caption

*Figure 1.* Mean Hit Reaction Time (HRT) (in ms) on CPT as a Measure of ISI and Treatment Condition.

Figure 1 is provided in a separate file 'Figure1.tif'.

Figure Caption

*Figure 2.* Standard Error of Hit Reaction Time (SE HRT) (in ms) on CPT as a Measure of ISI and Treatment Condition.

Figure 2 is provided in a separate file 'Figure2.tif'.