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## Speed of Inhibition Predicts Teacher-rated Medication Response in Boys with Attention Deficit Hyperactivity Disorder

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This study aimed at investigating whether one of the key deficits in Attention Deficit Hyperactivity Disorder (ADHD), slow response inhibition, predicted the response to methylphenidate (MPH) treatment. In order to address this issue, we used Stop Signal Reaction Times (SSRTs) measured at baseline in 20 medication-naïve boys with ADHD as predictor, and parent and teacher ratings that were collected during a double-blind, placebo-controlled titration trial of MPH in the same group as outcome measures. Parent and teacher ratings were collected on primary scales, measuring ADHD symptoms, and secondary scales, measuring oppositional and disruptive behaviour. Placebo response and ADHD/Oppositional Defiant Disorder symptom severity at baseline were controlled for in the analyses. The SSRT did not predict the MPH response as measured by parent ratings, but it did predict the MPH response as measured by teacher ratings. This effect was specific for the ADHD scales. The slower SSRTs were, the less children benefited from MPH. Moreover, children with longer SSRTs needed higher doses of MPH for optimal symptom relief than children with shorter SSRTs. These findings have implications for clinicians who face the decision of which MPH dose to prescribe.

## Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a common behavioural disorder characterised by symptoms of inattention, hyperactivity, and impulsivity

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(American Psychiatric Association, 1994). A deficit in inhibitory control has been proposed to be the key executive function that is impaired in ADHD, which in turn leads to other executive function deficits (Barkley, 1997). Two meta-analyses on studies that have used the Stop Paradigm to measure inhibitory control show that, indeed, children and adults with ADHD suffer from slow response inhibition (long Stop Signal Reaction Times [SSRTs]) measured with the Stop Paradigm (Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; Oosterlaan, Logan, & Sergeant, 1998). It should be noted, however, that effect sizes are modest: $d = 0.64$ (Oosterlaan et al., 1998), $d = 0.58$ (Lijffijt et al., 2005), and $d = 0.68$ for the inattentive type and 0.86 for the combined type (Willcutt, Dole, Nigg, Faraone, & Pennington, 2005). Recent research has indicated that poor response inhibition is not the only underlying mechanism involved in symptoms of ADHD. In a study that compared the Stop Paradigm and the Choice Delay Task (measuring delay aversion) in children with ADHD, it was shown that performance on both tasks explained significant proportions of the variance in ADHD symptoms, and that performance on these tasks did not correlate (Solanto et al., 2001). This finding led Sonuga-Barke (2002) to propose a dual-pathway model for ADHD, suggesting that there are at least two independent pathways leading to symptoms of ADHD: an executive one, and a motivational one. More recently, other researchers have also reported that only a subset of children with ADHD suffer from poor inhibition (see Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005), and multiple candidate endophenotypes have been proposed (Castellanos & Tannock, 2002).

Given that slow response inhibition appears to be one key factor associated with symptoms of ADHD, it is surprising that relatively little research has focused on the link between response inhibition and the beneficial effects of psychostimulant drugs. Psychostimulant drugs improve symptoms of ADHD in the majority of children with this disorder (e.g., Greenhill et al., 2001). It may be hypothesised that one way in which methylphenidate (MPH) exerts its beneficial effects on ADHD symptoms is by improving inhibitory control. A number of studies have examined the effects of MPH on response inhibition in ADHD (Aron, Dowson, Sahakian, & Robbins, 2003; Barkley, Murphy, O'Connell, & Connor, 2005; Bedard et al., 2003; Boonstra, Kooij, Oosterlaan, Sergeant, & Buitelaar, 2005; Jonkman et al., 1999; O'Driscoll et al., 2005; Overtoom et al., 2003; Ridderinkhof, Scheres, Oosterlaan, & Sergeant, 2005; Scheres et al., 2003; Tannock, Schachar, Carr, Chajczyk, & Logan, 1989; Tannock, Schachar, & Logan, 1995; Vaidya et al., 1998; Van der Meere, Gunning, & Stemerdink, 1999). All but three of these studies (Jonkman et al., 1999; Overtoom et al., 2003; Van der Meere et al., 1999) found that MPH significantly improved response inhibition during MPH treatment. Thus, research has shown that MPH not only alleviates symptoms of ADHD, but also positively affects one key deficit of this disorder, slow response inhibition.

Another potential link between response inhibition and MPH, that of a predictive association between response inhibition and MPH response as measured by symptom improvement, has not so far been investigated. This is somewhat

surprising, since a substantial body of research has focused on identifying predictors for MPH response. The following factors have been identified as predicting a positive response to MPH: higher levels of inattentive behaviour (Buitelaar, Van der Gaag, Swaab-Barneveld, & Kuiper, 1995; Taylor et al., 1987; Thomson & Varley, 1998), higher levels of hyperactive behaviour (Barkley, 1976; Thomson & Varley, 1998; Taylor et al., 1987), lower overall severity of the disorder (Buitelaar et al., 1995), poor performance on tests of attention and concentration (Barkley, 1976), younger age (Taylor et al., 1987), high IQ (Buitelaar et al., 1995), presence of a neurological disorder such as seizures (Thomson & Varley, 1998), positive parent cognitions (Hoza et al., 2000), being male (Handen, Janosky, McAuliffe, Breaux, & Feldman, 1994), higher socio-economic status (Handen et al., 1994), and having the 10-repeat DAT1 allele (Kirley et al., 2003). Thus, poor performance on some cognitive tasks (mainly measuring attention and concentration) has been identified as a predictor, but to our knowledge nobody has studied whether performance on a response inhibition task predicts MPH response.

Because poor response inhibition is a key feature of ADHD, and because response inhibition can be ameliorated with MPH, it may be hypothesised that the ability to inhibit responses is predictive of how well someone will respond to medication in terms of symptom improvement. Therefore, our aim was to investigate whether response inhibition, as measured with the most reliable dependent variable of the Stop Paradigm (Logan, 1994; Logan & Cowan, 1984; Logan, Schachar, & Tannock, 1997)—SSRT—predicts the extent of symptom improvement during MPH treatment in children with ADHD. Although group findings of medication trials indicate that MPH has a positive effect on ADHD symptoms, and that higher doses work better, the optimal dose is highly idiosyncratic (Rapport & Denny, 2000; Rapport et al., 1987; Swanson, McBurnett, Christian, & Wigal, 1995). Therefore, group findings are only of limited value to a clinician when facing the decision whether or not to prescribe MPH, and, if prescribed, which dose to prescribe to an individual with ADHD. For this reason, it is helpful to identify predictors, so that clinicians can estimate the likelihood of an individual with specific characteristics to respond well to medication, and, if this likelihood is high, which dose will most probably be optimal for this individual.

We addressed this issue using SSRT as a predictor, and parent and teacher ratings as outcome measures. SSRTs were collected during a baseline assessment in a medication-naïve group of children with ADHD (Scheres et al., 2004), and parent and teacher ratings were collected during a double-blind, placebo-controlled titration trial of MPH in the same group (Scheres et al., 2003). In order to examine whether the SSRT predicted the MPH response in terms of ADHD symptoms specifically, or whether it also predicted improvement in behaviour not directly related to ADHD, we included the Conners, Loney, and Milich (CLAM) Inattention/Overactivity Scale (Loney & Milich, 1982; Pelham, Milich, Murphy, & Murphy, 1989; Swanson, 1992) and the McBurnett, Swanson, Kotkin, Atkins, M-Flynn, and Pelham (McSKAMP) Attention Index (Wigal et al., 1998) as primary ADHD outcome measures, and the CLAM Aggression/Defiance Scale and the

McSKAMP Deportment Index as secondary outcome measures related to oppositional behaviour and disruption.

## Methods

This study was approved by the Institutional Review Boards of the University of Amsterdam and the three participating clinics.

### Participants

Children were referred by paediatricians and child psychiatrists at three Dutch clinics. These children were all identified as meeting the DSM-IV criteria (American Psychiatric Association, 1994) for ADHD by the physician and/or a multidisciplinary team of professionals, and advised to start treatment with MPH. All children were medication-naïve. Twenty-three boys with ADHD in the age range of 6–12 years participated in this study (Scheres et al., 2003). Twenty boys were included for data analyses (see below), with a mean age of 8.8 years ($SD$ = 1.7) and a mean IQ of 98.4 ($SD$ = 15.3).

### Group Selection and Characteristics

After establishment of the diagnosis by the physician, the parents and children received a letter with information about the study and an informed-consent form. If the parents and children decided to participate and they had signed the consent forms, they were invited to participate in the study. Parents were administered the Diagnostic Interview Schedule for Children—Parent version (DISC-IV) (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). The section for Disruptive Behavior Disorders was administered. For all participants, the DISC-IV confirmed the DSM-IV diagnosis as established by the physician. According to the DISC-IV, 13 boys met DSM-IV criteria for ADHD-combined type and seven boys for ADHD-inattentive type. Ten boys also met the criteria for Oppositional Defiant Disorder.

Participants performed four subtests of the Revised Wechsler Intelligence Scale for Children, while parents were interviewed. These subtests were Vocabulary, Arithmetic, Block Design, and Picture Arrangement. The estimation of IQ as obtained on these subtests correlates $r$ = 0.93–0.95 with the full-scale IQ (Groth-Marnat, 1997). Only when the DSM-IV criteria for ADHD were met, and when the child's IQ was above 70, could the child enter the study.

Parent and teacher ratings were taken at baseline, and were used as descriptive measures. Scores were available for the following instruments: the Disruptive Behavioral Disorder Rating Scale (Pelham, Gnagy, Greenslade, & Milich, 1992), the DSM–IV screener (Hartman et al., 2001), the McSKAMP and the CLAM. Scores on the ADHD scales confirmed the DISC-IV to the DISC-IV scores. This sample demonstrated elevated scores on all ADHD scales as well as on some related scales (see Table 1 and Figure 1).

Table 1.  Means and standard deviations for age, IQ, and baseline symptoms

| Measure | M | SD |
|---|---|---|
| DBD parent[a] | | |
|   Inattention | 19.2[b] | 3.8 |
|   Hyperactivity/impulsivity | 17.8[b] | 5.4 |
|   Oppositional Defiant Disorder | 10.9[b] | 5.1 |
|   Conduct Disorder | 2.4 | 2.0 |
| DBD teacher | | |
|   Inattention[c] | 18.8[b] | 5.8 |
|   Hyperactivity/impulsivity[c] | 16.0[b] | 7.3 |
|   Oppositional Defiant Disorder[c] | 8.3 | 5.7 |
|   Conduct Disorder[a] | 2.8 | 3.6 |
| DSM-IV screener parent | | |
|   ADHD[d] | 59.1[b] | 7.2 |
|   Oppositional Defiant Disorder[d] | 19.7 | 7.2 |
|   Conduct Disorder[a] | 40.4 | 5.7 |
|   Anxiety[a] | 44.1 | 4.0 |
|   Schizophrenia[a] | 13.2 | 1.7 |
|   PDD[a] | 28.8 | 4.4 |
|   Depression[a] | 22.0 | 2.4 |
| DSM-IV screener teacher | | |
|   ADHD[c] | 58.1[b] | 12.4 |
|   Oppositional Defiant Disorder[a] | 16.2 | 9.0 |
|   Conduct Disorder[c] | 39.9 | 10.2 |
|   Anxiety[c] | 43.4 | 7.0 |
|   Schizophrenia[c] | 13.0 | 2.7 |
|   PDD[c] | 28.1 | 6.8 |
|   Depression[c] | 21.9 | 4.3 |

*Note*: DBD = Disruptive Behavior Disorder Rating Scale; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*; PDD = Pervasive Developmental Disorder. [a]*n* = 19. [b]Average scale score is at or above the 95th percentile. [c]*n* = 20. [d]*n* = 18.

*Stop Paradigm with Tracking Algorithm at Baseline*

Before entering the double-blind placebo-controlled medication titration stage, participants performed a battery of executive function tasks, among which was the Stop Paradigm with tracking mechanism (for a detailed description of this task, see Scheres et al., 2003, 2004). Briefly, the Stop Paradigm (Logan, 1994; Logan & Cowan, 1984) involves two types of trials: go trials, and stop trials. Go trials were airplanes presented for 1000 ms in the centre of the computer screen. A fixation point (500 ms in duration) preceded the go stimulus. Subjects were required to press the response button that corresponded to the direction in which the plane was
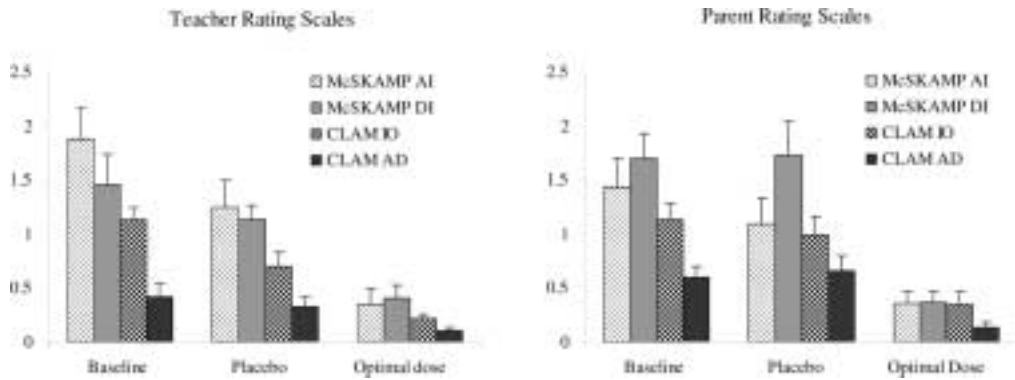
Figure 1.    Average item scores for teacher and parent rating scales during baseline, placebo, and the most effective MPH dose

pointing. The inter-stimulus interval was 1500 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 airplane. Children were instructed not to press either button when they heard the tone. The delay between the go and the stop signal varied. The longer this delay, the harder it is to inhibit the response. Seventy-five per cent of the trials were go trials, and 25% were stop trials.

The dependent variable that reflects the latency of the inhibitory process is the SSRT. The SSRT cannot be observed because the response to a stop signal is a covert one. Therefore, the SSRT is estimated. This can be done using the race model (Logan & Cowan, 1984), which 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. The advantage of the Stop Paradigm with tracking algorithm is that it achieves a success rate on inhibition trials of 0.5. Consequently, the SSRT can be simply estimated by subtracting the mean delay from the mean reaction time (see Logan et al., 1997). SSRTs as estimated with this procedure are more reliable than SSRTs as estimated based on the Stop Paradigm with fixed intervals (Band, Van der Molen, & Logan, 2003). Therefore, we focused on the SSRT as obtained with the Stop Paradigm with tracking algorithm for this study.

*Medication Titration*

Within a week after the baseline assessment, participants started the titration stage. A pseudo-randomised, multiple-blind, placebo-controlled crossover design was used in which all participants received each of four treatment conditions: placebo, 5, 10, and

Table 2.    Medication design (mg of 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     |

20 mg of MPH (see Table 2). Medication and placebo were prepared by the hospital pharmacy and packed in identical tablets (placebo tablets contained only a base granulate). The highest dose never exceeded 0.9 mg per kg body weight. Each treatment condition was administered over 7 days, twice daily, at breakfast (around 7:30 a.m.) and at lunch (around 12:30 p.m.). The order of the weeks was balanced using a Latin square design. Within each week, all four treatment conditions were administered and ordered such that one condition was never administered on two successive weekdays. Weekend doses were randomised by week; that is, the weekend dose was constant within weekends. Medication compliance was verified throughout the medication period. Parents were carefully instructed about medication administration, and they handed in empty medication boxes and took home new ones on a weekly basis. Children did not receive any other form of treatment during the titration stage.

### Parent and Teacher Observations during Titration

In order to measure medication effects on the child's behaviour, parents and teachers completed morning and afternoon rating scales during weekends at home and during weekdays in school, respectively. The informants observed the child's behaviour for 3.5 h, starting 1 h after administration, and rating scales were completed immediately following the observation period. Parents were carefully instructed about the use of the rating scales. One parent was selected to complete all rating scales. Teachers were visited to carefully instruct them about the titration procedure and rating scale completion. When possible, one teacher was selected to complete the rating scales.

    The following rating scales were used: as primary ADHD outcome measures, we used the CLAM Inattention/Overactivity (IO) Scale and the McSKAMP Attention Index (AI) for parents and teachers. As secondary oppositional/disruptive outcome measures, we used the CLAM Aggression Defiance (AD) Scale and the McSKAMP Deportment Index (DI) for parents and teachers. All items were scored on a 4-point scale, with higher scores reflecting higher severity of symptoms.

### Statistical Analyses

*Outliers and missing data.*  Prior to data analyses, data for two children were excluded due to extremely slow SSRTs. The SSRT of another child was missing due

to technical failure. Therefore, statistical analyses were conducted with a sample of 20 boys with ADHD.

*Analyses of variance.* As a first analysis, we investigated whether, on average, children responded to MPH treatment as rated by teachers and parents. We performed two analyses of variance (ANOVAs) (one for teacher ratings and one for parent ratings) with Condition as within group factor. Condition had three levels in this analysis: baseline, placebo, and the most effective dose (which could be 5, 10, or 20 mg, depending on the individual and on the informant). For each rating scale, the most effective dose was defined as the dose that resulted in the lowest score on that rating scale. Simple contrasts were used to examine whether symptoms as observed during the most effective medication condition significantly differed from symptoms during baseline and during placebo.

*Stepwise regression.* Regression analyses were performed to measure whether the SSRT at baseline predicted the response to MPH. Eight separate stepwise regression analyses were performed for each scale per informant. Within informants, regression analyses were performed for the CLAM IO Scale, the CLAM AD Scale, the McSKAMP AI, and the McSKAMP DI. The dependent variable in each of these analyses was the average item score on that scale during the most effective medication condition. For each rating scale, the most effective medication condition was defined as the MPH dose that resulted in the lowest score on that rating scale. The main predictor of interest was the SSRT at baseline. For each regression, the average of baseline and placebo rating scale scores for that particular scale and informant was entered as predictor at Step 1 in order to control for the confounding influence of severity of symptoms at baseline and for placebo effects. The baseline SSRT was entered as predictor at Step 2. With these stepwise regression analyses, we investigated whether the baseline SSRT predicted the MPH response while controlling for behavioural ratings during baseline and placebo (see Table 3).

*Exploratory inspection of the SSRT–optimal dose relationship.* For those outcome measures that were predicted significantly by SSRT, we were interested in exploring whether there was also a relation between SSRT at baseline and which dose was the most effective medication condition. To this end, we divided the group into three subgroups: children for whom 20 mg, 10 mg, or 5 mg was the most effective dose, respectively. ANOVA was used to compare optimal dose groups with SSRT as the dependent variable.

## Results

*Analyses of variance*

ANOVAs showed that, across subjects, symptoms of ADHD were reduced during the most effective dose as compared with baseline and placebo (see Figure 1). Main effects

Table 3. Stepwise regression analyses with the SSRT as the main predictor and the MPH response (as rated by teachers and parents) as the dependent measure

|  | Dependent measures | | | | | | | | | | | |
|  | Primary: ADHD Scales | | | | | | Secondary: Oppositional/Disruptive Scales | | | | | |
|  | CLAM IO | | | McSKAMP AI | | | CLAM AD | | | McSKAMP DI | | |
|  | $B$ | $R^2$ | $\Delta R^2$ | $B$ | $R^2$ | $\Delta R^2$ | $B$ | $R^2$ | $\Delta R^2$ | $B$ | $R^2$ | $\Delta R^2$ |
| Parent |  |  |  |  |  |  |  |  |  |  |  |  |
| Step 1, B/P Rating | 0.87 | 0.71 | 0.71** | 0.71 | 0.50 | 0.50** | 0.62 | 0.38 | 0.38** | 0.68 | 0.45 | 0.45** |
| Step 2, Baseline SSRT | 0.16 | 0.73 | 0.03 | −0.04 | 0.50 | 0.001 | 0.10 | 0.39 | 0.01 | 0.08 | 0.46 | 0.01 |
| Teacher |  |  |  |  |  |  |  |  |  |  |  |  |
| Step 1, B/P Rating | 0.04 | 0.12 | 0.12 | 0.55 | 0.47 | 0.47** | 0.61 | 0.61 | 0.61** | 0.49 | 0.47 | 0.47** |
| Step 2, Baseline SSRT | 0.62 | 0.42 | 0.30** | 0.42 | 0.63 | 0.16* | 0.29 | 0.66 | 0.05 | 0.34 | 0.54 | 0.08 |

*Note:* CLAM = Conners, Loney, and Milich; IO = Inattention/Overactivity; McSKAMP = McBurnett, Swanson, Kotkin, Atkins, M-Flynn, and Pelham; AI = Attention Index; AD = Aggression/Defiance; DI = Deportment Index; B/P = Combined effect of baseline and placebo ratings. *$p$ < .05, **$p$ < .01.

of Condition were found for all four teacher rating scales, including the primary ADHD scales ($F(2,34) = 40.9$, $p < .001$, $\eta^2 = .71$ for the CLAM IO scale; $F(2,34) = 23.8$, $p < .001$, $\eta^2 = .58$ for the McSKAMP AI) and the secondary oppositional/disruptive scales ($F(2,34) = 6.8$, $p < .01$, $\eta^2 = .29$ for the CLAM AD Scale; $F(2,34) = 12.8$, $p < .001$, $\eta^2 = .43$ for the McSKAMP DI). Main effects of Condition were also found for all four parent rating scales, including the primary ADHD scales ($F(2,36)=27.1$, $p < .001$, $\eta^2 = .60$ for the CLAM IO Scale; $F(2,36) = 14.9$, $p < .001$, $\eta^2 = .45$ for the McSKAMP AI) and the secondary oppositional/disruptive scales ($F(2,36) = 11.4$, $p < .001$, $\eta^2 = .39$ for the CLAM AD Scale; $F(2,36) = 18.7$, $p < .001$, $\eta^2 = .51$ for the McSKAMP DI). Contrast tests showed that scores during the most effective medication dose differed significantly from scores during baseline (all $F$ values $> 9.0$; all $\eta^2$ values $> .35$) and placebo (all $F$ values $> 9.6$; all $\eta^2$ values $> .36$).

*Stepwise Regression*

Regression analyses showed that the SSRT accounted for significant proportions of the variance in teacher-rated MPH response on the primary ADHD rating scales: 30% for the CLAM IO Scale ($p < .001$) and 16% for the McSKAMP AI ($p < .05$). Note that this effect was specific for the ADHD scales: the SSRT did not predict teacher-rated MPH response on the oppositional/disruptive outcome measures (see Table 3 and Figures 2 and 3). The association between SSRT and teacher-rated ADHD symptoms during the most effective dose was positive, indicating that, in terms of ADHD symptoms, children with faster SSRTs at baseline improved more during the optimal MPH dose than children with relatively slow SSRTs (see Figure 2).

The predictive power of the SSRT was specifically related to teacher-rated MPH response, as no significant portion of the variance in parent-rated MPH response was accounted for by the SSRT (see Table 3 and Figures 2 and 3).

*Exploratory Inspection of the SSRT–optimal Dose Relationship*

Since there was a significant association between the SSRT at baseline and the response to MPH during the most effective medication condition for the teacher CLAM IO Scale and the teacher McSKAMP AI, we explored whether there was also a relation between the SSRT and which dose was the most effective medication condition based on these ratings. SSRTs are plotted per optimal dose group in Figure 4. Note that the SSRTs as displayed in this figure are corrected for teacher ratings at baseline and placebo (entered as covariate), in order to control for a potential difference between subgroups in baseline/placebo teacher ratings. Figure 4 shows that increases in optimal dose were associated with increases in SSRT, after controlling for baseline and placebo teacher ratings. In other words, children for whom the teacher determined higher doses to be most effective for ADHD symptoms in school had longer SSRTs at baseline than children for whom teachers determined that a lower dose was optimal.
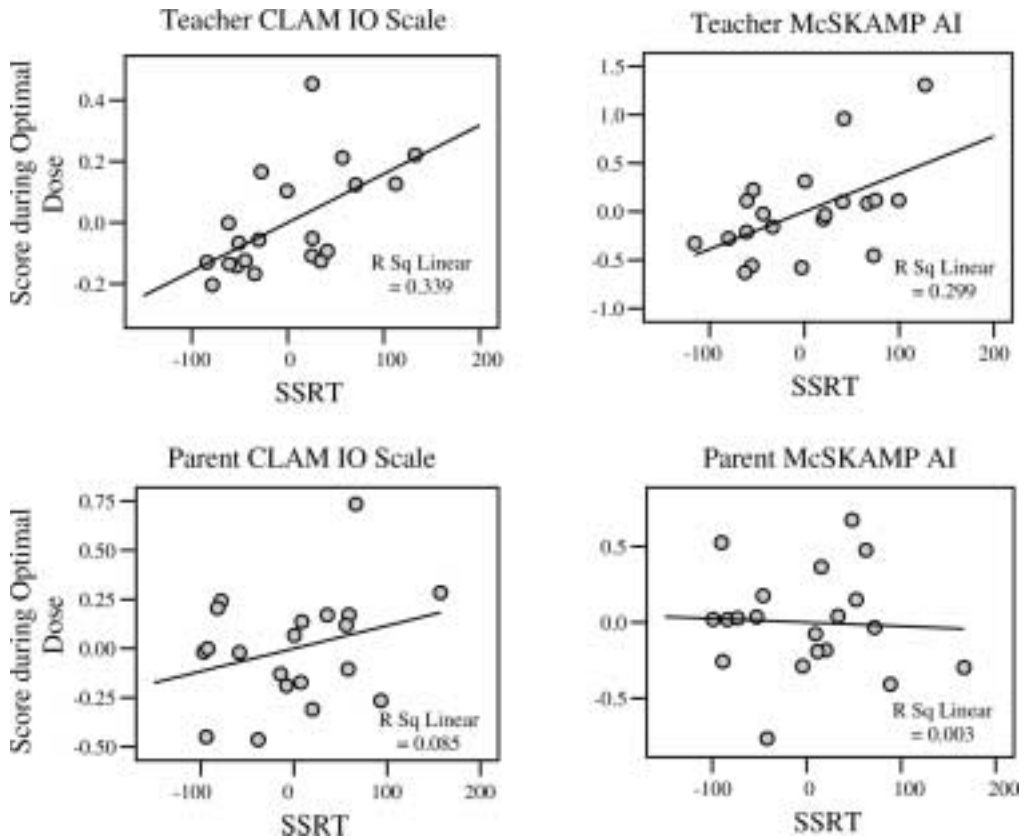
Figure 2. Partial correlation plots, reflecting the association between the SSRT at baseline and ratings during the best medication condition on the primary ADHD outcome measures, after controlling for ratings at baseline and placebo

Given the unequal and small sample sizes of these optimal dose groups, significant effects were not really to be expected. However, a large effect was observed for the CLAM IO Scale ($F(2,20) = 3.2$, $p < .07$, $\eta^2 = .29$), with contrast analyses showing a significant difference between SSRTs for the 5 mg optimal dose group and the 10 mg optimal dose group ($p < .05$). The effect for the McSKAMP AI was non-significant, but had a medium effect size ($F(2,20) = 1.0$, *ns*, $\eta^2 = .11$).

## Discussion

The goal of this study was to investigate whether the SSRT, a measure of inhibitory control as determined at baseline using the Stop Paradigm, predicted the MPH response. Teacher and parent ratings were used as outcome variables. Primary outcome measures were ADHD rating scales, and secondary outcome measures were oppositional/disruptive rating scales. Ratings as obtained during baseline and placebo
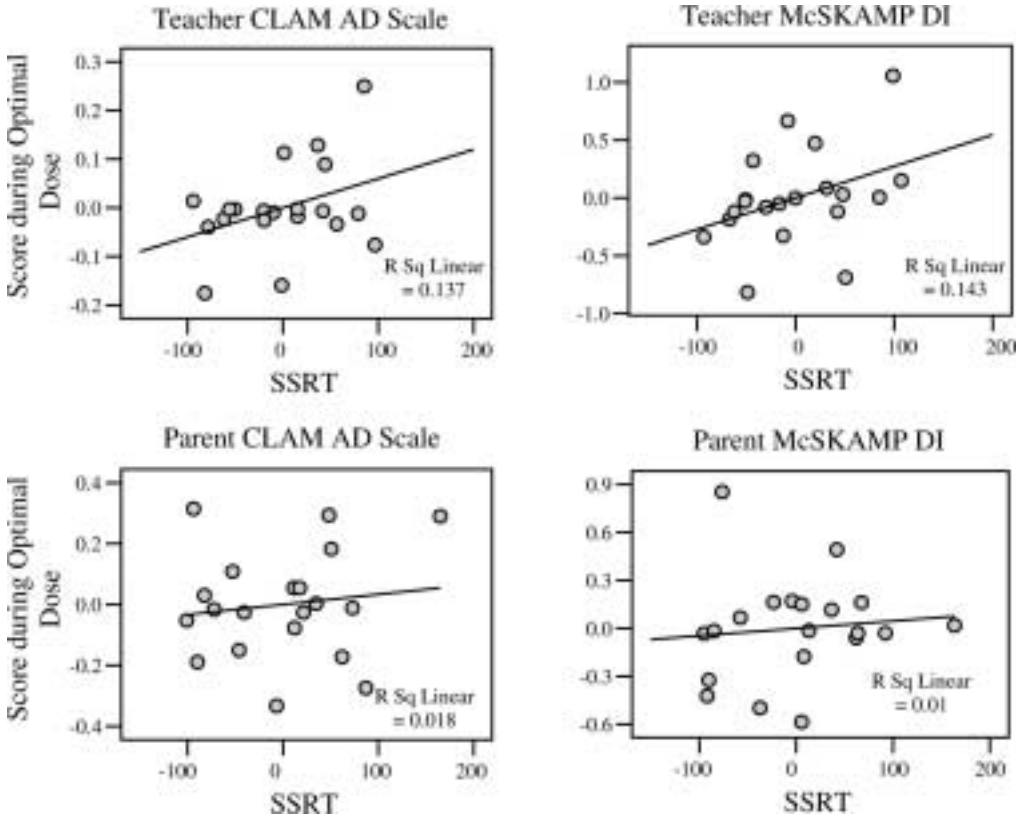
Figure 3.   Partial correlation plots, reflecting the association between the SSRT at baseline and ratings during the best medication condition on the secondary oppositional/disruptive outcome measures, after controlling for ratings at baseline and placebo
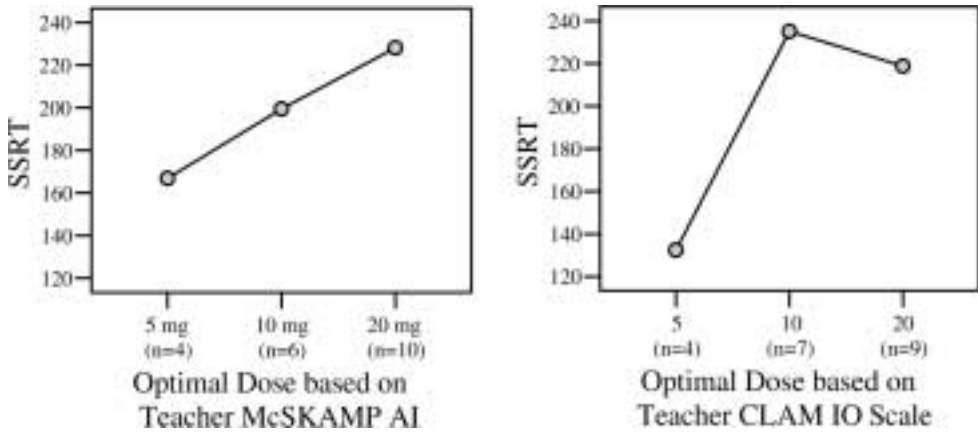


Figure 4.   SSRTs at baseline plotted for each of the three optimal dose groups

were controlled for in the analyses. We found that the SSRT predicted the MPH response as rated by teachers on the primary ADHD scales, but not as rated by parents.

Before we discuss these findings, it should be noted that the main limitation of this study is the small sample size. The findings need to be interpreted with that in mind. For example, the small sample size did not allow us to investigate any other potentially interesting predictors. Moreover, the lack of a significant association between the SSRT at baseline and the MPH response as measured with parent rating scales may have been due to low power (see later). Therefore, future work with a larger sample will need to replicate the findings reported here.

The predictive association between the SSRT and the MPH response is potentially interesting, since this may give clinicians a tool to work with when they have to estimate the likelihood of an individual's response to MPH, and when they have to decide which dose to prescribe. This study showed that children with relatively poor inhibitory control at baseline (showing slow SSRTs) have relatively high levels of ADHD symptoms during the most effective medication condition. Thus, in terms of symptoms of ADHD, children with relatively fast SSRTs improved more while on the most effective MPH dose than children with relatively slow SSRTs. Importantly, this effect was independent of severity of symptoms at baseline, and independent of placebo response, and therefore could not be explained by more room for symptom improvement in children with relatively slow SSRTs.

The SSRT predicted the MPH response as measured by teacher-rated ADHD outcome measures (i.e., the McSKAMP AI and CLAM IO Scale, but not the McSKAMP DI and CLAM AD Scale). The lack of an association with these oppositional/disruptive scales may be meaningful in the sense that the SSRT may be a MPH response predictor specifically related to symptoms of ADHD. However, this may also have been due to restriction of range in the oppositional/disruptive scores, especially for the CLAM AD Scale. Note that scores on this scale were below 1 even at baseline and placebo. There was therefore not much room for improvement on this scale. There was enough room for improvement on the McSKAMP DI, however, and yet no significant association between the SSRT and the MPH response on this scale was found.

The SSRT did not significantly predict the MPH response as measured by parent ratings. This may be explained by the possibility that inhibitory control is a skill that is required less to function well at home than to function well in the classroom. Although the small sample size used here should temper any definite conclusion about specificity of the association between the SSRT and teacher outcome measures, the effect sizes for the parent-rated MPH response were small. Therefore, it is unlikely that effects this small in size would become significant in a substantial sample. This informant-specific finding is mirrored in previous studies establishing that executive functioning measures relate to teacher ratings of ADHD, but not to parent ratings. For example, Oosterlaan, Scheres, and Sergeant (2005) found that only teacher ratings predicted performance on a number of executive functioning measures including measures of planning and working memory. Riccio, Hynd, Cohen, and Gonzalez (1993) found that teacher ratings of ADHD and other

behavioural problems predicted performance on a measure of set-shifting, whereas parent ratings failed to do so. Together with these earlier studies, the present study fits with the finding that teachers, as opposed to children and parents, are the optimal informants for ADHD symptoms (Loeber, Green, & Lahey, 1990; Loeber, Green, Lahey, & Stouthamer-Loeber, 1989, 1991; Power et al., 1998).

Although the SSRT predicted significantly how much children's ADHD symptoms improved during the most effective MPH dose as measured by teacher ratings, and effect sizes were large, an important question is whether this finding is clinically relevant. Inspection of the individual teacher scale scores during the most effective MPH dose shows that for most children (19 for the McSKAMP DI, 18 for the McSKAMP AI, and all 20 for both CLAM Scales), symptoms were normalised (average item scores between 0 and 1). Thus, although children with faster SSRTs improved more than children with slower SSRTs during the most effective dose, symptoms were within the normal range for virtually all children during the optimal MPH dose. Therefore, the relation between the SSRT and the teacher-rated MPH response may be only of limited clinical relevance.

The finding that children with longer SSRTs need higher doses for optimal symptoms improvement may be a more clinically relevant one, as it can potentially help in the decision related to which dose to prescribe. However, this finding needs to be replicated in a larger sample before it can be interpreted as being reliable. The fact that there was a significant difference for the SSRT between optimal dose groups with such small subgroup sample sizes (for the CLAM IO Scale) was surprising and a reflection of the large size of this effect.

In summary, this is the first study that reports on a significant association between inhibitory control and the MPH response as measured with teacher-rated ADHD scales. Moreover, the SSRT also had predictive value in terms of which MPH dose would be optimal. Although this study suffered from a small sample size, effect sizes reported here were large and, if replicated, the SSRT may be an important predictor for MPH response, and for the optimal MPH dose in particular.

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