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Stimulant Treatment Reduces Lapses in Attention among Children with ADHD:

The Effects of Methylphenidate on Intra-Individual Response Time Distributions

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Abstract

Recent research has suggested that intra-individual variability in reaction time (RT) distributions of children with ADHD is characterized by a particularly large rightward skew that may reflect lapses in attention. The purpose of the study was to provide the first randomized, placebo-controlled test of the effects of the stimulant methylphenidate (MPH) on this tail and other RT distribution characteristics. Participants were 49 9- to 12-year-old children with ADHD. Children participated in a 3-day double-blind, placebo-controlled medication assessment during which they received long-acting MPH (Concerta®), with the nearest equivalents of .3 and .6 mg/kg t.i.d. immediate-release MPH. Children completed a simple two-choice speeded discrimination task on and off of medication. Mode RT and deviation from the mode were used to examine the peak and skew, respectively, of RT distributions. MPH significantly reduced the peak and skew of RT distributions. Importantly, the two medication effects were uncorrelated suggesting that MPH works to improve both the speed and variability in responding. The improvement in variability with stimulant treatment is interpreted as a reduction in lapses in attention. This, in turn, may reflect stimulant enhancement of self-regulatory processes theorized to be at the core of ADHD.

Introduction

Attention-Deficit and Hyperactivity Disorder (ADHD), characterized by developmentally inappropriate degrees of inattention and/or hyperactive/impulsive behavior (Barkley, 2004), is one of the most commonly diagnosed childhood disorders (for a review see Smith, Barkley & Shapiro, 2006). To account for the behavioral symptoms that characterize the disorder, many theorists have focused on neuropsychological processes including inhibitory control, working memory, planning, set-shifting, and vigilance (e.g., Barkley, 2004; Douglas, 1999; Nigg, 2006; Wilcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Although research on ADHD and the executive functions has elucidated several key processes that are impaired, on average, in groups of children with ADHD, single-deficit neuropsychological theories fail to account for the heterogeneous nature of the disorder (Douglas, 1999; Nigg & Casey, 2005).

In an effort to better account for the heterogeneity in symptom presentation and neurocognitive functioning present in children with ADHD, some researchers have argued that ADHD symptoms are driven by more general regulatory or processing deficits rather than specific neurocognitive factors (see Douglas, 1999; Sergeant, Oosterlaan, & Van der Meere, 1999). For example, Virginia Douglas posits that ADHD is driven by a dysfunctional self-regulatory system which produces patterns of inconsistent or erratic allocation of attention and effort, referred to as deficient cognitive control (Douglas, 1999). Similarly, the cognitive-energetic model proposed by Sergeant and colleagues (Sergeant, 2005; Sergeant et al., 1999) implicates executive control and regulatory processes in ADHD.

Interestingly, although the different etiological theories of ADHD described above emphasize a variety of core cognitive processes and neuropsychological deficits, one of the most consistent findings in the ADHD literature is that these children demonstrate, across a range of measures, slower and more variable response patterns compared to children without ADHD (Douglas, 1999; Leth-Steensen, Elbaz, & Douglas, 2000). Variable response patterns within the cognitive literature refer to moment-to-moment fluctuations in task performance that occur on a time scale of seconds (Russell et al., 2006). This inconsistency in the performance of children with ADHD has been described as a ubiquitous finding across tasks, laboratories, and cultures (Castellanos & Tannock, 2002, p. 624). Although there are a variety of hypotheses for why children with ADHD have such variable response patterns, many researchers posit that variable responding reflects fluctuations and lapses in attention (Leth-Steensen et al., 2000; Van der Molen, 1996). Importantly, the discussion of variability in relation to ADHD is not limited to the cognitive literature. Researchers have long noted that ADHD symptoms appear to interact with the environment as they show considerable variability and fluctuations across settings, caregivers, and reinforcement schedules (e.g., Guevremont & Barkely, 1992). As a result, an understanding of intra-individual response variability at the cognitive level may have important clinical implications for children with ADHD.

However, despite the apparent importance of intra-individual variability or moment-to-moment fluctuations in task performance in children with ADHD, the majority of cognitive and neuropsychological research on these children has focused on global measures of performance such as mean differences in response speed (Castellanos & Tannock, 2002; MacDonald, Nyberg, & Backman, 2006). In addition, when variability is measured, the most common method is with a single-point estimate of the standard deviation around the mean for each individual (Russell et al., 2006). Unfortunately, these global measures obscure moment-to-moment processes and are limited in the information they provide. Furthermore, there is strong covariation between the mean and standard deviation of the mean (Wagenmakers & Brown, 2007) with correlations frequently in the .7 to .9 range, suggesting that the two variables do not really measure separate processes.

Recently, researchers have begun to utilize more fine-grained analyses to examine the overall shapes of reaction time (RT) distributions (Aase & Sagvolden, 2006; Castellanos & Tannock, 2002; Douglas, 1999; Leth-Steensen et al., 2000; MacDonald et al., 2006). In these analyses, separate parameters describe the leading edge (i.e., speed) as well as the size of the tail (i.e., variability) of the distribution (e.g., Acheson & de Wit, 2008; Leth-Steensen et al., 2000). In the seminal work in this area, Leth-Steensen and colleagues (2000) employed a four-choice RT task and demonstrated that although children with ADHD were not significantly slower, their distributions were characterized by a greater rightward skew (or tail) compared to children without ADHD. This effect is consistent with theories postulating that children with ADHD have periodic lapses in attention, characteristic of an underlying deficit in the allocation of attention and effort in order to meet task demands (Douglas, 1999; Leth-Steensen et al., 2000). Group differences in RT skew have been recently replicated by Hervey and colleagues (2006) using the Conners' Continuous Performance Test (CPT; Conners, 1994) as well as by

Williams and colleagues (2007) using a stop signal paradigm. Thus, a small but growing literature supports the hypothesis that the RT distributions of children with ADHD are characterized by a rightward skew, consistent with a self-regulatory deficit. An example of the rightward skew that is apparent in the response distributions of children with ADHD is illustrated in Figure 2 (A, D). Notably, the positive skew of the distributions is driven by a large number of abnormally slow responses.

As with any proposed core process in ADHD, an important next question is whether the RT skew is reduced by treatments for the disorder. To our knowledge, the present study is the first controlled investigation of the effects of stimulant medication on RT skew. The stimulant methylphenidate (MPH) is a first-line pharmacotherapy for ADHD (American Academy of Pediatrics, 2001; Pliszka, 2007), with a large literature demonstrating clinical therapeutic effects (e.g., Greenhill, Pliszka, Dulcan, Barnet, Arnold, & Beitchman, 2002; Pelham, Wheeler, & Chronis, 1998; Schachar, Tannock, Cunningham, & Corkum, 1997). In addition, there is evidence that MPH improves neurocognitive functioning. For example, MPH generally has positive effects on inhibitory control (Aron, Dowson, Sahakian, & Robbins, 2003; Tannock, Carr, Chajczyk, & Logan, 1989), visual-spatial working memory (Bedard, Martinussen, Ickowicz, & Tannock, 2004), and sustained attention (see review by Losier, McGrath, & Klein, 1996) in children with ADHD.

Although there is a wealth of data on the effects of MPH on neurocognitive functioning, very little research has examined stimulant effects on measures of specific aspects of intra-individual variability. The work that has been done in this area suggests that stimulant medication has beneficial effects on the speed (e.g., Bedard et al., 2003; Riccio, Waldrop, Reynolds, & Lowe, 2001) and variability (e.g., Boonstra, Kooij, Oosterlaan, Sergeant, & Buitelaar, 2005; Tannock, Schachar, & Logan, 1995) of responding. However, these studies have generally relied on the highly correlated mean and standard deviation indices. As a result, it remains unclear whether MPH reduces variability in responding by reducing the positive skew in RT distributions or whether MPH is speeding responding more generally.

There is currently only one published study that examined the effects of stimulant medication on intra-individual RT parameters among children with ADHD. Epstein and colleagues (2006) addressed this issue using the Conners' CPT (Conners, 1994), which requires a response on the vast majority of trials. In this study, RT skew was reduced among medicated children compared to un-medicated children, suggesting that stimulants selectively reduced the variability in responding. Similar to Leth-Steensen et al. (2000), the authors suggested that the reduction in variability was the result of fewer and less severe lapses in attention.

Although the study of Epstein and colleagues (2006) is an important first step in understanding treatment effects on intra-individual response distribution parameters, the study was methodologically limited. Most importantly, medication was not randomized at the time of assessment. Rather, parents reported whether or not their child had taken a stimulant on the day of testing, and dosing was not controlled. Consequently, no cause-and-effect relationship could be demonstrated.

The goal of the current study was to extend the emerging literature on intra-individual RT distributions in children with ADHD by examining the controlled effects of methylphenidate on intra-individual RT parameters. Specifically, we evaluated the effects of two doses of long-acting MPH (Concerta®) on the speed of responding and intra-individual variability using a within-subject, double-blind, randomized, placebo-controlled assessment. Mode-based analyses, described in more detail below, were used to investigate whether MPH affected the peak and/or skew of intra-individual RT distributions.

Consistent with previous research (see Bedard et al., 2003; Boonstra et al., 2005; Tannock et al., 1989), we expected that MPH would reduce mean RT and the standard deviation of RT. More critically, we predicted that MPH would improve more specific metrics of response speed, evident in a reduction in modal RT, and would decrease lapses in attention, evident in a reduction in deviation from the mode. We also hypothesized that medication effects on mode-based indices of response speed and variability would be weakly correlated or uncorrelated, suggesting separable effects of MPH on processing speed and lapses in attention.

Methods

Participants

Participants were 49 children between the ages of 9-12 years diagnosed with ADHD. The majority of participants (76%) were Caucasian, while the remaining participants were African-American (14%), mixed race (8%), and American-Indian or Alaska Native (2%). Most participants were taking stimulant medication at the time of the study or had taken stimulants prior to participating (82%). Additional sample characteristics are listed in Table 1.

Participants were recruited from the Center for Children and Families at the University at Buffalo as well as from the community through flyers placed in the offices of pediatricians. All participants were recruited to attend a week-long summer research program designed to examine the effects of stimulant medication on neurocognitive processes implicated in ADHD. Parents were remunerated for their participation in the form of money. Children were rewarded with toys and gift cards for their participation in the week-long program. All parents provided informed consent and all children provided informed assent, in accordance with procedures approved by the University at Buffalo Children and Youth Institutional Review Board.

Exclusion criteria included (1) Full Scale IQ below 80¹; (2) history of seizures and/or current medication to prevent seizures; (3) history of other medical problems for which psychostimulant treatment may involve considerable risk; (4) current use of psychotropic medications other than stimulants or atomoxetine (i.e., antipsychotics, mood stabilizers, antidepressants, and anxiolytics) (5) history or concurrent diagnosis of pervasive developmental disorder, schizophrenia or other psychotic disorders, or other serious mood/anxiety disorders requiring pharmacological treatment (6) absence of functional impairment related to ADHD; or (7) vision or hearing problems that would make it difficult to complete study tasks.

Diagnostic Assessment

All participants had a DSM-IV (APA, 1994) diagnosis of ADHD. The diagnostic assessment involved a structured computerized clinical interview of one or both parents (Diagnostic Interview Schedule for Children Version IV (DISC-IV); Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). In addition, parents and teachers completed two standardized rating scales: the Disruptive Behavior Disorder (DBD) rating scale (Pelham, Gnagy, Greenslade, & Milich, 1992; Pelham, Fabiano, & Massetti, 2005) and the Impairment Rating Scale (Fabiano et al., 2006). The DBD measures all DSM-3R and -IV symptoms of ADHD, Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD), on a 0-3 Likert scale. The DBD has been previously shown to have sound psychometrics and has been used extensively in studies of children with ADHD (see Pelham et al., 1992; Pelham et al., 2005). The IRS is an eight item visual-analogue scale that evaluates the child's problem level and need for treatment in developmentally important areas, such as peer relationships, adult-child relationships,

¹One child exhibited a marked discrepancy between the verbal and performance subscales, limiting the reliability of the brief assessment. Because the estimated IQ of 77 was very near our cutoff, the child was allowed to participate.

academic performance, classroom behavior, and self-esteem. The IRS has been previously shown to be reliable and valid in ADHD and normative populations (see Fabiano et al., 2006).

In order to meet diagnostic criteria, children were required to exhibit six or more symptoms of inattention and/or six or more symptoms of hyperactivity/impulsivity according to the diagnostic interview and/or the DBD rating scale based on reports from the parent and teacher². In addition, cross-situational impairment had to be present according to the IRS and/or the DISC. Seventy-one percent of the children were diagnosed with ADHD-Combined Type ($n = 29$ boys, 6 girls), 23% were diagnosed with ADHD-Inattentive Subtype ($n = 8$ boys, 4 girls), and 6% were diagnosed with ADHD-Hyperactive/Impulsive Subtype ($n = 2$ boys). Subtypes were based on examining the symptoms endorsed across the DBD rating scales and the DISC. As expected, comorbidity with externalizing disorders was common, with 65% of the sample meeting criteria for ODD, and 22% of the sample meeting provisional criteria for CD. Parents also completed the Child Behavior Checklist (CBCL; Achenbach, 1991; see Table 1).

Standardized measures of intellectual ability and achievement were administered including the Vocabulary and Block Design subtests from the Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV; Wechsler, Kaplan, Fein, Kramer, Morris, & Delis, 2004) and the Reading, Mathematics, and Spelling subtests from the Woodcock-Johnson Test of Achievement (WJTA; Woodcock, McGrew, & Mather, 2001). Full Scale IQ was determined by prorating scores based on performance on the Vocabulary and Block Design subtests from the WISC-IV. As shown in Table 1, the sample was generally in the average range on measures of IQ and achievement³.

Setting

The Summer Research Camp was held from 7:30 am to 5pm Monday through Friday and consisted of groups of five children each week. On Monday through Thursday children completed a variety of computerized tasks and participated in three 30-minute academic periods. Recreational activities, meals, and snacks were intermingled with testing. Children earned points throughout the day for task participation and appropriate behavior. These points were exchanged for toys and gift cards at the end of each day.

Task order was randomized between participants, but it remained consistent within a child across testing days. Data from the current analyses is limited to one of these tasks, the X and O Discrimination Task, described below.

X and O Discrimination Task

Intra-individual response distributions were assessed with a simple computerized letter discrimination task programmed in E-prime (Psychology Software Tools, Pittsburgh, PA). In the task, children were asked to discriminate between an X and an O that appeared on the screen by pressing one of two labeled buttons on a response box as quickly as possible while maintaining accuracy. The task consisted of 10 practice trials followed by 100 task trials. Each letter was presented on the screen for 3000ms separated by a 1000ms inter-stimulus interval. Only responses during the 3000ms stimulus presentation were recorded. An audible click occurred the first time a button was pressed during each trial.

²Teacher reports were missing from 5 children. Analyses were re-run with these 5 children excluded and results remained the same.

³One child met provisional criteria for having a math learning disability (math standard score 1.5 standard deviation below the mean for the child's age; see Martinussen & Tannock, 2006).

Medication Assessment

After an initial practice day, each child participated in a 3-day double-blind, placebo-controlled medication assessment. Participants taking stimulant medication were asked to discontinue their medication at least 24 hours prior to the practice day. Those participants taking Strattera completed a 1-week washout period prior to participating in the medication assessment. Active doses were long-acting MPH (Concerta®) with the nearest commercially available equivalents of 0.3 and 0.6 mg/kg t.i.d. immediate-release MPH. The medication was purchased through our research pharmacy and was not supplied by the manufacturer. Doses ranged from 18 to 90 mg (dose was capped at 90 mg for safety reasons). The mean of the low dose was 39.24 mg ($SD = 9.75$) and the mean of the high dose was 73.44 mg ($SD = 15.78$). Sixteen out of 49 children were order restricted so that they received the low dose prior to receiving the high dose. These restrictions occurred with children who were naïve to stimulant medication or in cases where the low dose provided in the study was two or more times greater than the child's current dose. Medication was administered when the child arrived in the morning, 90 minutes prior to the initial cognitive task. Subjects were given the same number of blinded capsules per day regardless of actual MPH dose to maintain blinding.

Adverse events were rated daily by camp counselors and parents using the Pittsburgh Side Effect Rating Scale, which inquires about common side effects seen with stimulants (rated none to severe) (Pelham, 1993). Blood pressure and pulse were also measured daily during times of peak medication effects. Any subject reporting significant distress or exhibiting marked side effects was evaluated by the study nurse or physician.

Procedure

Children were brought in to the testing rooms and were reminded of the laboratory rules. Children were told that they would earn 100 points for following the rules and completing the tasks during the activity period. These rules included 1) follow directions, 2) stay in your assigned area, 3) use material and possessions appropriately, and 4) try your best. Children were also informed that, following a single warning, they would lose 25 points per rule violation.

Data Reduction

RT for each of the 100 trials was the basic unit of data. Only responses for correct discriminations were included in the analyses. Responses that occurred within the first 150ms of stimulus presentation were considered anticipatory responses and excluded from analyses. Omissions were replaced with a value of 3000ms (total trial length).

The primary dependent variables of interest included within-subject mode and deviation from the mode. However, we also computed mean RT and standard deviation of RT given their common usage in the literature. Accuracy, anticipatory responses, and omissions were examined in supplementary analyses.

Several studies that have examined the shapes of RT distributions have used ex-Gaussian models to examine response distributions in ADHD (Douglas, 1999; Epstein et al., 2006; Hervey et al., 2006; Leth-Steensen et al., 2000). These models utilize a theoretical distribution characterized as a convolution of the normal and exponential distribution functions (see Castellanos, Sonuga-Barke, Milham, & Tannock, 2006). Parameter values are chosen that best describe the leading edge (i.e., speed) as well as the size of the tail (i.e., variability) of the distribution (Douglas, 1999; Leth-Steensen et al., 2000). However, in the current study we used a mode-based approach rather than the ex-Gaussian method to examine RT distributions. This decision was based on a number of limitations of the ex-Gaussian method including 1) ex-Gaussian distributions do not always adequately fit individual data (e.g., 13% in Leth-Steensen

et al., 2000), 2) the ex-Gaussian method makes specific assumptions about the shape of the distribution (e.g. the inclusion of an exponential distribution) which may not be true of the data set, and 3) the ex-Gaussian method involves fairly complex computations and curve-fitting procedures (Hausknecht et al., 2005), with no apparent advantage resulting from this complexity.

Mode and deviation from the mode provide a useful way to quantify the typical speed of an individual's responses (e.g., the peak of the distribution) and the variability of responses (e.g., the skew of the distribution), respectively (Acheson & de Wit, 2008; Hausknecht et al., 2005; Sabol, Richards, Broom, Roach, & Hausknecht, 2003). The mode is a preferred measure of speed as it is unaffected by distributional skew. Conversely, deviation from the mode assesses the skew of the distribution and is easily calculated by subtracting the modal RT from the mean RT (Hausknecht et al., 2005; Sabol et al., 2003). To estimate the mode of response distributions, we used the Half-Range Mode method (HRM), as in other recent work (Acheson & de Wit, 2008; Hausknecht et al., 2005; Sabol et al., 2003). The HRM method produces mode values that are asymptotically unbiased and are more resistant to distributional skew (Bickel, 2002; Bickel, 2003; Hedges & Shah, 2003). HRM involves dividing a data set into two halves and selecting the densest side (e.g. the side with the greatest number of data points). This side is then split in half, the density of the halves is evaluated, and the densest side is again selected. The splitting of the data continues until the half-sample is less than three data points. The mean of this final sample is the mode of the original data set (Hedges & Shah, 2003). In the current study, HRM was programmed in Microsoft Excel.

Data Analysis

Bivariate correlations were used to examine the relations between the dependent variables within each of the different medication conditions as well as between the different medication effects. To examine the effects of MPH on the dependent variables, separate repeated measures ANOVAs were conducted. Orthogonal contrasts of placebo vs. both active medication doses and of low vs. high doses were employed to assess medication effects⁴. Effect sizes were computed as Cohen's *d* (Cohen, 1988).

Results

Correlational analyses demonstrated that mean RT and standard deviation of RT were significantly and positively correlated in the placebo, low MPH (0.3 mg/kg/day), and high MPH (0.6 mg/kg/day) conditions, $r_s = .90, .82$, and $.83$, respectively, $ps < .001$. These correlations indicated that across medication conditions mean RT and standard deviation of RT share on average 72% of their variance with one another. In contrast, and consistent with our predictions, mode RT and deviation from the mode were not significantly correlated in the placebo, low MPH, or high MPH conditions, $r = -.03, -.09$, and $.27$, respectively, $ps > .06$. These correlations indicated that across medication conditions mode RT and deviation from the mode share on average only 2.7% of their variance with one another.

As expected, mean RT and standard deviation of RT were significantly reduced under active medication conditions compared to placebo, $F_s(1,48) = 83.01$ and 64.64 , $ps < .001$, $ds = .88$

⁴As a result of the relatively small number of girls ($n = 10$) and children with ADHD-Inattentive ($n = 12$) and ADHD-Hyperactive/Impulsive subtype ($n = 2$) we conducted only exploratory tests of sex and subtype differences. Girls were slower and more variable overall, and unpredicted interactions with medication dose suggested that the higher dose of MPH was necessary to achieve similar reductions in mode RT and deviation from the mode in girls compared to the low dose of MPH for boys. Exploratory analyses with subtype (ADHD-C vs. ADHD-I) revealed no reliable differences between subtypes for mode RT and deviation from the mode; of course, the present study was underpowered to detect such effects. It is important to note that 40% of girls ($n = 4$) but only 22% of males ($n = 8$) were of the inattentive subtype, further muddying the interpretation of the sex effects above. Future work with larger samples will be necessary to thoroughly evaluate sex and subtype differences.

and .94, respectively (see Figure 1A and Figure 1B). Moreover, the high dose of MPH resulted in significantly lower mean RT and standard deviation of RT than did the low dose of MPH, $F_s(1,48) = 8.14$ and 6.64 , $p_s < .007$ and $.02$, $d_s = .24$ and $.34$, respectively. Lastly, an examination of correlations between the medication effects (mean of low and high doses of MPH vs. placebo) for mean RT and standard deviation of RT revealed that they were significantly and positively related, $r = .80$, $p < .001$. Scatter plots were examined in order to see whether these effects were driven by outliers, defined as any participants with medication effects that were three standard deviations above or below the mean. No participants met this criterion.

As expected, mode RT was significantly reduced under active medication compared to placebo, $F(1,48) = 19.23$, $p < .001$, $d = .46$ (see Figure 1C). Although the means were in the expected direction, the high dose of MPH did not result in a significantly lower mode RT compared to the low dose of MPH, high $F(1,48) = 2.55$, $p = .12$, $d = .2$. Most importantly and as predicted, deviation from the mode was significantly attenuated under active medication conditions compared to placebo, $F(1,48) = 35.37$, $p < .001$, $d = .89$ (see Figure 1D). The high dose of MPH did not significantly reduce deviation from the mode compared to the low dose of MPH, $F(1,48) = .692$, $p = .41$, $d = .14$.

Although Figure 1 illustrates the average effect, it is also interesting to examine the actual RT distributions for individual subjects. Figure 2 presents such distributions for a 9-year-old male (first panel) and an 11-year-old male (second panel) for each of the medication conditions. Consistent with our inferential statistics, you can see at the individual level that medication reduces both the mode and the deviation from the mode RT, relative to placebo. In addition, a developmental trend is suggested, with both mode and deviation from the mode reduced in the older child relative to the younger child. Consistent with the pattern suggested by Figure 2, age in the overall sample was negatively correlated with deviation from the mode during the placebo session, $r = -.34$, $p < .02$ although it was not significantly correlated with mode RT, $r = -.18$, $p = .22$.

As done for the mean and standard deviation, we examined the correlation between the medication effects (mean of high and low MPH vs. placebo) on mode RT and deviation from the mode. Contrary to expectations, the medication effects were moderately negatively correlated, $r = -.36$, $p < .02$, though not nearly as highly as for the mean and standard deviation of RT. However, after excluding the two children who had medication effects on mode RT or deviation from the mode that were greater than three standard deviations above the mean, the medication effect on mode RT was no longer significantly correlated with the medication effect on deviation from the mode, $r = -.13$, $p = .38$.

Supplementary analyses examined accuracy and the numbers of anticipatory responses and omitted responses in order to evaluate whether beneficial effects of MPH on speed were the result of a speed-accuracy tradeoff. Compared to accuracy during the placebo session ($M = .94$), accuracy improved significantly under active medication, $F(1,48) = 4.31$, $p < .05$ and tended to be better during the high compared to the low dose of MPH ($M_s = .97$ and $.96$, respectively, $F(1,48) = 3.27$, $p = .08$). The mean numbers of anticipatory responses and omitted responses were low in all conditions (for anticipatory responses, $M_s = .5$, $.3$, and $.1$; for omissions, $M_s = 1.2$, $.4$, and $.2$, for placebo, low MPH, and high MPH respectively). The reductions during active medication compared to placebo were marginally significant, $F_s(1,48) = 3.15$ and 3.65 , $p_s = .08$ and $.06$, for anticipatory responses and omissions, respectively, but the differences between the high and low dose of MPH did not approach traditional levels of statistical significance, $p_s > .2$. Thus, there did not appear to be any speed-accuracy tradeoff; rather, children were faster, less variable, and more accurate under active MPH.

Discussion

Intra-individual variability has been increasingly discussed in the literature as an important regulatory deficit in children with ADHD (e.g., Castellanos et al., 2006; Castellanos & Tannock, 2002; Douglas, 1999; Leth-Steensen et al., 2000). However, despite the apparent importance of intra-individual variability in children with ADHD, there is a paucity of research on the effects of common treatments for ADHD, such as stimulant medication, on intra-individual response speed and variability. The current study was the first study to date to examine the placebo-controlled effects of the stimulant medication methylphenidate (MPH) on the peak and skew of intra-individual response time (RT) distributions.

Consistent with previous research, we observed robust MPH effects on mean RT and standard deviation of the mean RT (Bedard et al., 2003; Boonstra et al., 2005; Riccio et al., 2001; Tannock et al., 1989). Importantly, however, correlational analyses demonstrated that the medication effects on mean RT and standard deviation of RT were very strongly and positively correlated, suggesting that mean RT and standard deviation of RT do not reflect dissociable processes.

Our focus was on the mode RT and deviation from the mode in order to quantify the average speed and variability, respectively, of an individual's responses (Hausknecht et al., 2005; Sabol et al., 2003). Specifically, mode is thought to reflect sensory motor processing whereas deviation from the mode is thought to reflect distributional skew (Sabol et al., 2003). Mode and deviation from the mode are thought to be more precise measures of speed and variability, respectively, given that the mode is believed to be unaffected by distributional skew (Hausknecht et al., 2005). In support of this idea, we found that mode RT and deviation from the mode were not reliably correlated with one another.

We hypothesized that MPH would reliably speed responses evident in faster modal RT. As expected, we found that modal RT was reliably reduced under active medication suggesting that MPH speeds sensory motor processing. In addition, this decrease in response speed was not consistent with a speed-accuracy trade-off as accuracy also improved under active medication. The effect of medication on modal RT is clearly depicted in Figure 2 and illustrates the leftward distributional shift that occurred when children were medicated. Interestingly, this leftward shift was more pronounced for the older child suggesting that medication may be more effective at improving speed and reducing lapses in attention in older samples. Importantly, however, our sample included a narrow age range (9-12 years) and all children were diagnosed with ADHD. As a result, future work is needed to fully understand developmental trends associated with medication. Although the effect of MPH on sensory motor processing has been previously demonstrated (Bedard et al., 2003; Boonstra et al., 2005; Tannock et al., 1989), our focus on the effect of MPH on mode-based RT measures allowed us to examine whether MPH was specifically affecting response speed.

Although we examined the effects of MPH on both the speed and variability of RT distributions, our primary interest was on the effect that medication had on intra-individual response variability, or distributional skew, as measured by deviation from the mode. As expected, deviation from the mode was reliably reduced under active medication. As evident in Figure 2, children displayed fewer abnormally slow responses when medicated which caused an overall reduction in the positive skew of their distributions. In addition and consistent with previous research indicating that variability in responding is particularly prominent in children with ADHD (see Leth-Steensen et al., 2000), medication had a large effect on deviation from the mode ($d = .89$). In fact, the medication effect size on deviation from the mode was more than four times the effect size of medication on mode RT. Given that distributional skew in children with ADHD is thought to result from abnormally long responses or lapses in attention

(see Leth-Steensen et al., 2000), our results suggest that MPH is particularly effective at reducing lapses in attention, relative to speeding general motor processing, at least in ADHD.

Although research on the effect of MPH on lapses in attention as assessed by intra-individual variability is limited, the effectiveness of MPH in improving sustained attention in children with ADHD is supported by a wealth of research (see reviews by Brown, Borden, Wynne, Schlessner, & Clingerman, 1986; Losier et al., 1996; Riccio et al., 2001). However, these studies have primarily focused on performance (e.g., target hits, omission errors, and reaction time) during versions of the Continuous Performance Task (CPT; Rosvold, Mirsky, Sarason, Bransome, & Beck 1956). Our data provides initial evidence that MPH also specifically reduces lapses in attention during a simple discrimination task as indicated by a significant reduction in the positive skew of intra-individual response distributions.

Consistent with the interpretation of skew as reflecting lapses in attention, data from the current sample, which also completed an A-X CPT each day of the summer research camp, demonstrates that deviation from the mode is significantly and positively correlated with target misses on a CPT paradigm under placebo conditions, $r = .40, p < .007$. Misses are typically thought to measure lapses in sustained attention (Riccio et al., 2001). Thus, this relationship provides further evidence that greater deviations from the mode are indicative of *lapses* in attention. Although these results provide initial evidence of convergent validity, future work will need to investigate whether and how deviation from the mode is associated with other measures of inattention.

Interestingly, although the means were in the expected direction, we did not find significant differences between the low and high dose of MPH on mode RT and deviation from the mode, but such differences were observed for mean RT and standard deviation of RT. The reason for the discrepancy is not clear, but the pattern of effects suggests that the high dose is exerting a stronger effect on motor speed compared to lapses in attention, with only deviation from the mode reflecting the latter process. More generally, the findings with mode and deviation from the mode are consistent with the broader literature demonstrating a lack of dose effects across multiple higher-order cognitive processes such as inhibitory control and focused attention (see review by Pietrzak, Mollica, Maruff, & Snyder, 2006). In addition, our results suggest that a relatively low dose of MPH may be effective at speeding responses and improving lapses in attention. This finding is consistent with evidence that even lower doses of MPH can have a substantial impact on children and adolescents' behavior and performance in the classroom or laboratory settings (Evans et al., 2001; Gorman, Klorman, Thatcher, & Borgstedt, 2006). Conversely, it is also notable that no child received a high dose that was greater than 90 mg. Although this upper limit was important for safety, it limited the separation of low and high doses for heavier children. Thus, further work is needed to better elucidate the dose-response function for MPH effects on RT parameters. Given the above discussion, such work should consider doses lower than the 0.3 mg/kg dosing provided in the present study.

We chose to use mode RT and deviation from the mode as measures of speed and skew, respectively, following the previous argument that the two measures were distinct from one another (Hausknecht et al., 2005; Sabol et al. 2003). As noted earlier, correlational analyses in the current study provided evidence that mode RT and deviation from the mode measure distinct processes. Furthermore, the two medication effects were not significantly correlated with one another once two outliers were removed. The lack of a relationship between the two medication effects suggests that the effect of MPH on deviation from the mode was not simply due to a speeding up of overall RT values. Rather, these correlations suggest that MPH works to decrease the peak and reduce the skew of RT distributions and that these two effects reflect dissociable processes.

Although our findings clearly demonstrate that MPH is effective at speeding responses and reducing distributional skew, questions remain as to whether other treatments for ADHD, such as behavioral interventions, can reduce children's speed and variability in responding. There is strong empirical support for the effectiveness of behavioral therapy as well as the combination of behavioral therapy and stimulant medication in the treatment of ADHD (American Academy of Pediatrics, 2001). Specifically, contingencies, in the form of reinforcement and response cost, which are central in behavioral treatments of ADHD (Pelham & Waschbusch, 1999) have been clearly shown to improve the functioning of children with ADHD across home and school settings (Pelham & Fabiano, in press; Pelham et al., 1998). In addition, research has demonstrated that incentives can improve some neurocognitive processes including response speed (measured by mean RT) and behavioral inhibition (see review by Luman, Oosterlaan, & Sergeant, 2005) as well as working memory (Shiels et al., 2008). Although no published studies have examined the effects of such behavioral techniques on intra-individual speed and variability, we are currently testing whether incentives improve response speed and skew.

Results from the current study extend the current literature on intra-individual RT measures and clearly indicate that MPH, the first-line pharmacotherapy for ADHD, is effective at speeding responses *and* reducing positive distributional skew in children. However, this study is not without limitations. Like many samples of ADHD children, ours was predominately boys with combined subtype and marked comorbidity with other disruptive behavior disorders (see Table 1). This limits the generalizability of the results and leaves open several potential moderators of stimulant effects on RT parameters.

Beyond characteristics of the sample, characteristics of the task should also receive further attention. Specifically, future research studies should examine the effects of task type and event rate on RT distribution characteristics given the hypothesized role of these factors in ADHD (Scheres, Oosterlaan, & Sergeant, 2001). For example, previous research has demonstrated that slow trial rates tend to elicit slow and variable responding (Scheres et al., 2001) whereas fast trials rates may contribute to impulsive response styles (see Hervey et al., 2006). Although we did not observe a speed-accuracy trade-off in the current study, it is possible that this would emerge in tasks with faster trial rates. In addition, it may be important to use simple discrimination tasks, such as those used in the current study and by Leth-Steensen et al. (2000), rather than tasks that require inhibition, as they may shift children's response distributions. For example, recall that Epstein et al. (2006) used the Connors CPT, during which children respond 90% of the time but inhibit responses to targets (10%), to compare children taking stimulants to those who were not taking medication at the time of testing. In that study, the leading edge of the distribution was slower, not faster, among children who were medicated. The authors suggested that the result reflected a beneficial effect of medication on impulsive responding. Although the study by Epstein was not a controlled medication study, the data suggest that the addition of task demands, such as inhibition, may influence the size and even the direction of medication effects on RT. This may also complicate the interpretation of "go trials" on the frequently used stop signal paradigm, as several studies indicate that participants change response strategies when the stop signal is introduced, frequently trading speed for inhibitory success (see review by Verbruggen & Logan, 2008). Thus, we echo the call of Tannock (1998) and others to use measures that most simply and directly assess the processes of interest.

In summary, our data contribute to the growing literature on intra-individual RT distribution characteristics in ADHD. This literature is relevant to both etiology and intervention. Regarding etiology, leading theories of ADHD have shifted the emphasis from single neurocognitive deficits to either multi-process models (e.g., Sonuga-Barke, 2005) or to more general, regulatory processes (e.g., Douglas, 1999; Sergeant et al., 1999). As proposed by

Douglas, the large tail in the RT distribution of children with ADHD reflects lapses in attention that result from problems in these regulatory processes. The present study builds on this perspective, demonstrating that response variability is improved by a leading pharmacotherapy, and this effect is dissociable from the stimulant enhancement of overall motor speed. This study, like others in this area, focused on a single task in a laboratory setting. Importantly, there is evidence that children with ADHD display behavioral variability outside of the laboratory including notable symptom, mood, and arousal fluctuations (e.g., Guevremont & Barkely, 1992; Shea & Fisher, 1996). In addition, recent research has demonstrated that children with ADHD display significantly greater variability in attentive behavior in clinical settings, such as the classroom, compared to their peers (Kofler, Rapport, and Alderson, 2008). It will be exciting to examine whether individual differences in treatment effects on laboratory measures of intra-individual variability predict improvement in real-world settings.

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A.

B.

C.

D.

Figure 1. Mean Reaction Time (Panel A), Standard Deviation of Reaction Time (Panel B), Mode Reaction Time (Panel C), and Deviation from the Mode (Panel D) for each of the medication conditions.

9-year old male *11-year old male* **Figure 2.**

Reaction time distributions for representative participants. Data are presented for a 9 year-old male (upper) and an 11 year-old male (lower) under Placebo (left), Low MPH (middle), and High MPH (right) conditions.

Table 1

Participant characteristics

Age, mean (SD)	10.5 (1.1)
Gender (male:female)	39:10
WISC Full Scale IQ, mean (SD)	104 (14)
WJ Test of Achievement, mean (SD)	
Letter-Word Identification	104 (10)
Calculation	106 (13)
Spelling	105 (13)
DBD rating scale	
Hyp/Imp, mean (SD)	
Parent report	14.1 (5.9)
Teacher report	11.6 (7.5)
Inattentive, mean (SD)	
Parent report	17.0 (5.6)
Teacher report	13.7 (6.7)
CBCL, t-score mean (SD)	
Attention Problems	68.1 (7.8)
Externalizing Problems	61.2 (8.7)
Internalizing Problems	58.0 (9.5)

Note. The observed range of estimated IQ scores on the WISC was 77-135. The observed ranges on the WJ subtests were as follows; Reading: 87-126, Math: 75-147, Spelling: 82-137. The values on the DBD represent the total score of the items (rated 0-3) within each subtype domain on the rating scale. The observed ranges were as follows; Parent-rated hyperactivity/impulsivity: 1-27, Teacher-rated hyperactivity/impulsivity: 0-27, Parent-rated inattention: 2-27, Teacher-rated inattention: 1-27.