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Dissociation in response to methylphenidate on response variability in a group of medication naïve children with ADHD

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Abstract

Increased variability in reaction time (RT) has been proposed as a cardinal feature of attention deficit hyperactivity disorder (ADHD). Increased variability during sustained attention tasks may reflect inefficient fronto-striatal and fronto-parietal circuitry; activity within these circuits is modulated by the catecholamines. A disruption to dopamine signaling is suggested in ADHD that may be ameliorated by methylphenidate (MPH). This study investigated the effects of MPH administration on the variability in RT and error performance on a sustained attention task of a group of 31 medication naïve children with ADHD, compared with 22 non-ADHD, non-medicated, control children. All children performed the fixed-sequence sustained attention to response task (SART) at two time-points: at baseline and after six weeks. The children with ADHD were tested when medication naive at baseline and after six weeks of treatment with MPH and whilst on medication. The medication naïve children with ADHD performed the SART with greater errors of commission and omission when compared with the control group. They demonstrated greater standard deviation of RT and fast moment-to-moment variability. They did not differ significantly from the control group in terms of slow variability in RT. MPH administration resulted in reduced and normalised levels of commission errors and fast, moment-to-moment variability in RT. MPH did not affect the rate of omission errors, standard deviation of RT or slow frequency variability in RT. MPH administration may have a specific effect on those performance components that reflect sustained attention and top–down control rather than arousal.

Keywords: Response time; Methylphenidate; Variability; Dopamine; ADHD

1. Introduction

Children with attention deficit hyperactivity disorder (ADHD) often display difficulties in sustaining attention to tasks (Hood, Baird, Rankin, & Isaacs, 2005; Manly et al., 2001). The literature suggests that fronto-striatal and fronto-parietal brain circuits are critically important for sustaining attention to a task (Graybiel & Saka, 2004; Robertson & Garavan, 2004; Sturm & Willmes, 2001). The difficulties shown by children with ADHD on vigilance-type tasks may reflect altered functioning of the dorsolateral prefrontal cortex, the parietal cortex and the basal ganglia (Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006; Silk et al., 2005; Spalletta et al., 2001; Teicher et al., 2000). Dysfunction within the catecholamine signalling systems, especially that of dopamine, is hypothesised to contribute to these difficulties (Solanto, 2002). ADHD has been associated with altered synaptic levels of dopamine within the striatum and basal ganglia, although the exact physiology remains unclear (Sadile & Viggiano, 2005; Solanto, 1998).

Methylphenidate (MPH) administration is an effective pharmacological treatment in approximately 70% of children with ADHD (Greenhill, Haplerin, & Abikoff, 1999). MPH concen-

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trates maximally in the human striatum (Volkow et al., 1995) and is believed to block the dopamine (DAT) and noradrenaline transporters on the presynaptic nerve terminals (Kuczenski & Segal, 1997; Solanto, 1998). MPH reduces DAT availability in the striatum by an average of 60% in normal healthy adults (Volkow et al., 2002), resulting in increased levels of dopamine in the synaptic cleft available to bind with the dopamine receptors (Rosa-Neto et al., 2005; Volkow et al., 2001, 2002). Dopamine is thought to decrease background firing rates of post-synaptic neurons, resulting in improved signal-to-noise ratios in the target neurons, which may enhance attention (Volkow et al., 2001). In some studies, individuals with ADHD appear to have an increase in DAT binding potential, suggesting an increase in dopamine transporter availability (Cheon et al., 2003; Dougherty et al., 1999; Larisch et al., 2006; Spencer et al., 2005), which is normalised by brief (4 weeks) (Krause, Dresel, Krause, Kung, & Tatsch, 2000) or longer (3 months) periods of treatment with MPH (Vles et al., 2003) although the evidence is not consistent (Jucaite, Fernell, Halldin, Forssberg, & Farde, 2006; van Dyck et al., 2002; Volkow et al., 2006).

The effect of MPH on sustained attention in participants with ADHD has been extensively studied (for a review see (Riccio, Waldrop, Reynolds, & Lowe, 2001). MPH administration normalises performance on the sustained attention subscales of the Test of Everyday Attention for Children (TEACH) (Hood, Baird, Rankin, & Isaacs, 2005). Signal detection is significantly improved with administration of MPH (Fitzpatrick, Klorman, Brumaghim, & Borgstedt, 1992; Klorman, 1991; Tucha et al., 2006). A reduction in errors of commission and omission after MPH administration is a common finding, e.g. (Levy & Hobbes, 1988). MPH helps to maintain stable mean RT over time, whereas in the absence of MPH treatment RT may slow (Fitzpatrick, Klorman, Brumaghim, & Borgstedt, 1992; van der Meere, Shalev, Borger, & Gross-Tsur, 1995). Recently, Rosa-Neto et al. (2005) performed a MPH challenge on a group of adolescents with ADHD. They measured the availability of striatal binding sites for dopamine 2- and 3-type receptors using [^{11}C] raclopride and performance on the Test of Variables of Attention (TOVA), a continuous performance task (CPT). MPH treatment significantly improved performance in terms of commission errors, mean and S.D. of RT, but omission errors were unchanged. Participants with poorest performance at baseline on the TOVA demonstrated the greatest MPH-evoked decrease in [^{11}C] raclopride in the right striatum, suggesting a link between poor attentional control and elevated clearance rates of extracellular dopamine (Rosa-Neto et al., 2005). A reduction in variability of RT is a common effect of MPH treatment (Fitzpatrick, Klorman, Brumaghim, & Borgstedt, 1992), however, it is not always found (Tucha et al., 2006).

Increased variability in RT on cognitive tasks may reflect inefficient prefrontal activation and diminished top–down control of attention (Bellgrove, Hester, & Garavan, 2004; MacDonald, Nyberg, & Bäckman, 2006; Stuss, Murphy, Binns, & Alexander, 2003). Traditionally, variability in RT is measured as the standard deviation of RT. Recently, a time-series analysis of variability in RT was suggested, using a fast Fourier transform (FFT) of the RT data (Castellanos et al., 2005), which provides a measure of the magnitude of changes in RT at different temporal frequencies. MPH did not affect error rates or the interference score of the mean RT (mean RT of incongruent trials—mean RT of congruent trials) on a cognitive interference task (Eriksen Flanker Task) (Scheres et al., 2003). Castellanos et al. (2005) however, reanalysed this RT data using the FFT method and found that mean RT became faster and variability in RT was reduced after MPH administration. In particular, the power (or amount of RT variability) in the frequency band between 0.02 and 0.07 Hz was normalised after MPH administration (Castellanos et al., 2005).

The sustained attention to response task (SART) (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997) measures vigilant attention over a 5 min period. Participants press a button in response to stimuli (digits 1–9) that are presented sequentially and repetitively on a computer screen, except to the no-go digit 3. FFT analysis of the SART RT data has revealed two variability components, a fast frequency measure of moment-to-moment variability in RT and a slow frequency measure of slow changes in RT over the course of the task (Johnson, Kelly, et al., 2007). It has been suggested that increased fast frequency variability reflects poorer top–down control of attention, whilst increased slow frequency variability reflects elements of fluctuating arousal (Johnson, Robertson, et al., 2007).

Given that the fronto-striatal and fronto-parietal areas are involved in sustaining attention and that dopamine may modulate this ability, the present study investigated the effects of MPH on the performance of children with ADHD on the SART. Of particular interest was the influence of MPH on the two forms of response variability (slow and fast).

2. Methods

2.1. Participants

Thirty-one children with ADHD (5 females, 4 left-handers) and 22 control children (5 female, 3 left-handers) participated in the study (see Table 1). The average age of the children with ADHD (mean 9.0 years ± 3.0) did not differ significantly from the average age of the control group (mean 8.7 years ± 1.0). The IQs of the children with ADHD (mean 92.8 ± 17.6), measured at baseline using four subtests (picture completion, vocabulary, information, block design) of the WISC (Wechsler, 1992), were significantly lower than those of the control children (mean 107.5 ± 16.3), [$F(1,53) = 9.592$, $p < 0.003$].

The baseline data from 10 (Johnson, Kelly et al., 2007) and 6 (Johnson, Robertson et al., 2007) children with ADHD were previously published.

Exclusion criteria for participation in the study included known neurological conditions, pervasive developmental disorders or serious head injuries. Control children were also excluded if they had first-degree relatives with ADHD. All children scored above 70 on the Wechsler Intelligence Scale for Children (Wechsler, 1992). Handedness was measured using the Edinburgh Handedness Inventory (Oldfield, 1971).

The children with ADHD were recruited as part of a larger naturalistic pharmacogenetic study. At baseline, the children were newly diagnosed and yet to be treated with any form of stimulant medication. They were then assessed after six weeks while maintained on methylphenidate-based treatments. These children were treated by consultant child and adolescent psychiatrists in the community. Confirmation of clinical diagnoses were made by a trained psychiatrist (EB) using the parent version of the Child and Adolescent Psychiatric Assessment (CAPA) interview (Angold et al., 1995). Additional information regarding symptom pervasiveness was obtained using the child attention-deficit hyperactivity disorder teacher telephone interview (CHATTI) (Holmes et al.,

Table 1
Information on the ADHD and Control children

Group	ADHD	Control
Number	31	22
Gender (male/female)	26/5	17/5
Age (mean, S.D.)	9.0 (3.0)	8.7(1.0)
IQ (mean, S.D.)	92.8(17.6)	107.5(16.3)
Left-handers	4	3
Conner's ADHD index (mean, S.D.)-off medication[a]	77.7 (6.2)	45.5 (4.8)
Conner's ADHD Index (mean, SD) - on medication[a]	59.8 (8.7)	
Conner's inattentive subscale (mean, S.D.)-off medication[a]	76.1 (8.5)	44.3 (4.0)
Conner's Inattentive Subscale (mean, SD)-on medication[a]	59.4 (9.2)	
Conner's Hyperactivity Subscale (mean, S.D.)-off medication[a]	79.1 (11.0)	49.4 (8.4)
Conner's Hyperactivity Subscale (mean, S.D.)-on medication[a]	60.8(11.7)	
No. included in SART FFAUS analysis	24	22
No. included in SART SFAUS analysis	17	21

[a] Conner's Parent Rating Scale.

2004). All children met DSM-IV diagnosis for ADHD (American Psychiatric Association, 1995). Twenty-three (74%) of the ADHD participants had a diagnosis of ADHD Combined type, 7 (23%) participants had a diagnosis of ADHD predominantly Inattentive type and 1 (3%) participant had a diagnosis of ADHD predominantly Hyperactive/Impulsive type. Fifteen (48%) of the children with ADHD met diagnostic criteria for oppositional defiant disorder and 7 (23%) met diagnostic criteria for conduct disorder.

Stimulant type and dose was prescribed at the discretion of the treating consultant psychiatrist within the community. All of the ADHD participants included in this study were treated with MPH-based preparations (Ritalin (17); Concerta (10) or Ritalin LA (4)). Dose was calculated as mg/kg of MPH and varied between participants from 0.18 to 0.82 mg/kg/day (mean 0.51 ± 0.20).

The behaviour of all children was assessed using the short version of the Conners' Parent Rating Scale (Conners, 1997). All children with ADHD scored greater than 65 on the Conners ADHD Index at baseline, whilst all control children scored less than 60.

The control children were recruited from Dublin schools. Consent was obtained from parents of all children and the experimental work was conducted under the approval of local ethical committees in accordance with the Declaration of Helsinki.

2.2. Apparatus and procedure

The children performed the fixed-sequence version of the Sustained Attention to Response Task (Fixed SART) (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997) across two testing sessions, at time baseline and after a period of six weeks. At baseline, the children with ADHD were medication naïve. The second session occurred after the children with ADHD had received 6 weeks of MPH-based preparations and whilst they were on medication.

The SART was presented on a laptop computer to the children. The SART stimuli consisted of a repeating fixed sequence of digits (1–9). A single digit appeared on the screen for 313 ms; a mask was then presented for 125 ms, after which a response cue (a bold cross) appeared for 63 ms, followed by a second mask for 375 ms and a fixation cross for 563 ms. The total inter-stimulus interval (ISI) was 1439 ms (digit onset to digit onset). Participants were instructed to respond, using a button press, to every digit (go-trial) except '3' (no-go trial). They were asked to respond when the response cue appeared on screen 125 ms after the digit was extinguished, or 438 ms from the start of the trial. The response cue was used to limit the impulsive response style of the ADHD children and to reduce any speed/accuracy trade-offs (Bellgrove, Hawi, Kirley, Gill, & Robertson, 2005). Participants performed 225 trials, representing 25 runs of the 1–9 sequence, lasting approximately 5.5 min.

2.3. Data analysis

Errors of commission (responses made on digit 3) and omission (non-responses on every other digit) and the mean and S.D. of the RTs on the go-trials were calculated. The sequence of 225 RTs was also analysed using a fast Fourier transform (FFT), following the methodology of (Johnson, Kelly et al., 2007). Grand average FFT spectra were also calculated per group for descriptive purposes.

2.3.1. Data preparation for FFTs

To calculate the FFTs, the RTs for the digit 3 and RTs of less than 100 ms were linearly interpolated from the immediately preceding and following RTs. For the fast-frequency area under the spectra (FFAUS), individual RT data were detrended, subtracting out any linear components, which were analysed separately.

2.3.2. Derivation of FFT spectra

The RT data were analysed according to Welch's averaged, modified periodogram method. The RT data were analysed over the entire trial (225 data points per individual). The time-series was first divided into seven segments of 75 data points, with an overlap of 50. Each segment was Hamming-windowed and zero-padded to length 450.[1] The FFT was then calculated for each segment. For the full-run analyses, the FFT for each segment was averaged across the seven segments to provide a spectrum per individual. All RT data points were represented in this analysis, due to the 50 data point overlap. Any segments of 75 data points where there were over six errors of omission (not necessarily occurring together) were excluded in the FFT. At least three segments needed to be included per participant, otherwise the participant was excluded. Subsequently, for the FFT analyses, a number of participants were excluded (see Table 1).

The power (variance) in the RT signal was measured by calculating the area under the spectrum (AUS) over a broad band of interest. Information contained within the original RT series remains after the FFT, hence if the power over the entire frequency range is integrated, this will equate to the overall variance in the data. The peak power at a particular point in the spectrum measures consistency and distinctness of a particular periodic RT pattern. Healthy adult control subjects often show a slowing in RT on digit one relative to digits nine and two in preparation for the upcoming no-go response on the SART (Dockree et al., 2004). If this average pattern is consistently reproduced on every 1–9 sequence, a peak in the spectra at 0.0772 Hz is found (reciprocal of 9 digits $\times$ 1.439 s inter-stimulus interval) (see dotted line in Fig. 1). This peak was used as a marker to divide the variability into two components. The fast-frequency area under the spectra (FFAUS) encompassed all sources of variability faster than once per SART cycle (0.0772 Hz) (area under curve to the right of dotted line in Fig. 1). Trial-to-trial or moment-to-moment variability was captured in this calculation. The slow-frequency AUS (SFAUS) encompassed all sources of variability slower than once per SART cycle (area under curve to the left of dotted line in Fig. 1). Variability that occurred over any time period greater than one SART cycle was captured in this calculation. To ensure that all low frequencies were encompassed in the SFAUS, the time series was not divided into segments. Any RT time series where there were greater than seven errors of omission in a row were excluded in the FFT for the SFAUS measure (see Table 1). The data were not detrended in the SFAUS analysis, allowing an analysis of the linear components of the RT variation. In a separate test, the linear component in isolation was analysed by fitting regression lines to the RTs of each participant using a first order polynomial fit (linear). The slope of the regression line was then calculated.

2.4. Statistics

All dependent variables were calculated per participant. The Conner's ADHD Index scores at baseline and at 6 weeks for the children with ADHD

[1] Please refer to Oppenheim, Schafer, & Buck et al. (1999), for an explanation of the steps involved in time-series analysis, including Hamming-windows and zero-padding.

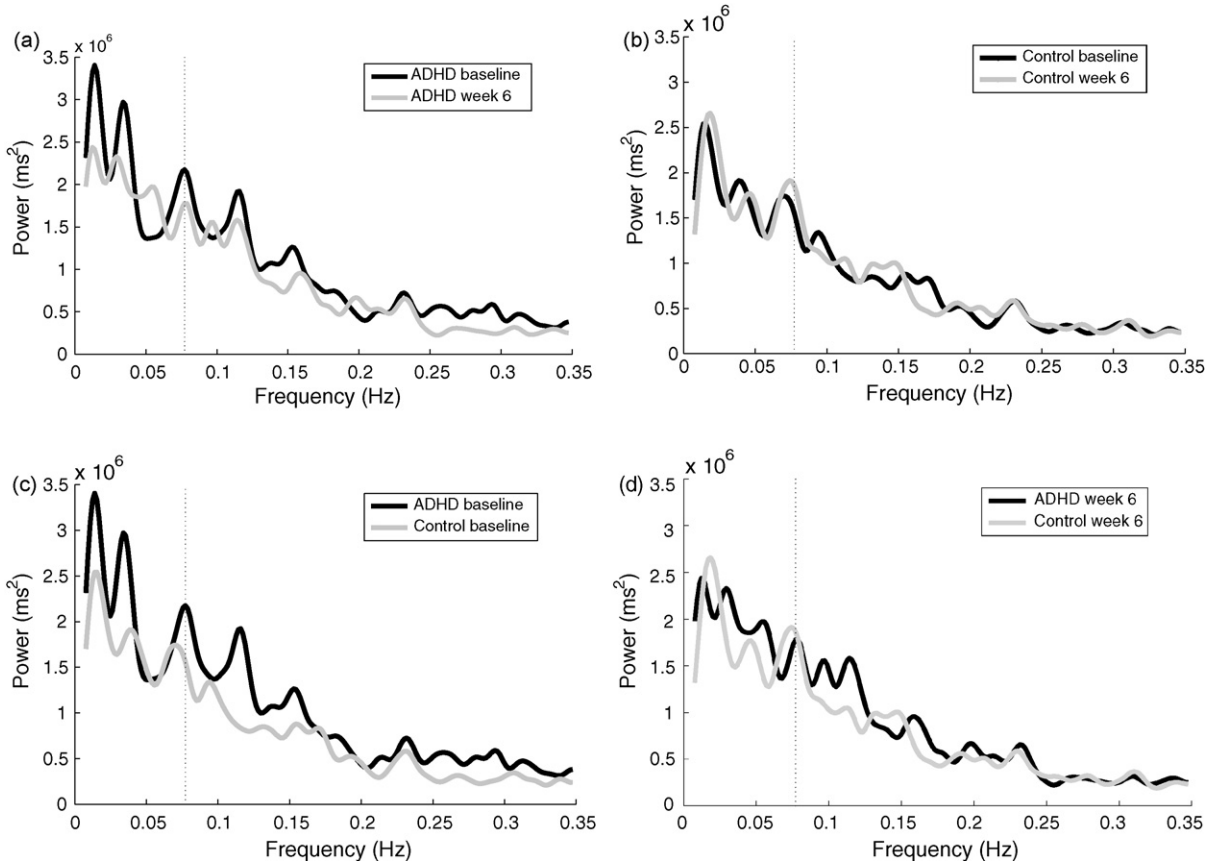

Fig. 1. Grand average of the fast Fourier transform (FFT) of the mean response time (RT) data on the fixed sustained attention to response task (SART) for the children with attention deficit hyperactivity disorder (ADHD) when medication naïve (baseline), after 6 weeks of methylphenidate treatment (week-6) and the control group (baseline and week-6). The *Y*-axis represents the power of periodic changes in RT data. The *X*-axis represents the different temporal frequencies, in Hertz (Hz). The dotted line represents the point at which the slow and fast frequency variability measures were derived. It is at 0.0772 Hz (one SART cycle), the reciprocal of 9 digits × 1.439 s inter-stimulus interval (ISI) of the SART. Grand average spectra were calculated per group using the FFT function in Matlab 7.3.0 (The MathWorks, Natick, Massachusetts).

were compared with a paired samples *t*-test. The Conner's ADHD Index scores of the children with ADHD (medication naïve and on medication) and the control children were compared using one-way ANOVAs. The number of errors of commission and omission, mean RT, S.D. of RT, FFAUS, SFAUS and linear regression of RT were analysed using a Group (ADHD versus Control) by Time (baseline versus week-6) two-way repeated factors ANOVA. The test–retest reliability of the SART dependent measures for the control children was measured using Pearson's product-moment correlation coefficient. The alpha level was set at 0.05 and Bonferroni adjustments were used throughout the analysis.

3. Results

The average FFT spectrum for each group is shown in Fig. 1.

3.1. Conners ADHD index

The Conners ADHD index scores of the children with ADHD when medication naïve (mean 77.7 ± 6.2) were significantly higher than those of the control children (mean 45.5 ± 4.8), $[F(1,53) = 418.681, p < 0.001]$. There was a significant decrease in the Conners ADHD Index scores of the children with ADHD when medicated (mean 59.77 ± 8.7) compared with when the children were medication naïve $[t(1,30) = 10.022, p < 0.001]$. When the children with ADHD were on medication, the Conners ADHD Index scores were still significantly higher than those of the control children, $[F(1,53) = 48.537, p < 0.001]$.

3.2. Commission errors

A significant group main effect and a significant time main effect were further explained by a significant group by time interaction, $[F(1,51) = 16.051, p < 0.001]$, (see Fig. 2). Pairwise comparisons indicated that the reduction in the number of commission errors made by the children with ADHD on medication (mean 6.4, S.D. 3.4) compared with when they were medication naïve (mean 10.2, S.D. 5.3) ($p < 0.001$) was driving the interaction. There was no significant difference in the number of commission errors made by the control children at baseline (mean 5.0, S.D. 3.5) and at week-6 (mean 5.7, S.D. 3.8) ($p > 0.05$), suggesting no practice effects. At baseline, the children with ADHD made significantly more commission errors than the control children ($p < 0.001$): at week-6 there was no significant difference in the number of commission errors made by the children with ADHD and control children ($p > 0.05$).

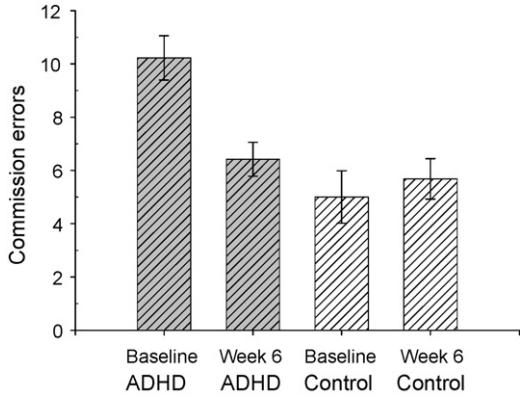

Fig. 2. Mean number of commission errors made on the SART by the children with ADHD when medication naïve (baseline), after 6 weeks of methylphenidate treatment (6-week) and the control group at baseline and at 6 weeks.

3.3. Omission errors

The children with ADHD (mean 23.0 S.D. 19.7) made significantly more omission errors than the control children (mean 7.8, S.D. 9.0), [$F(1,51) = 17.257$, $p < 0.001$] (see Fig. 3). The number of omission errors made by the children with ADHD and the control children did not change between the baseline and week-6 testing sessions, suggesting that MPH did not have a significant effect on the number of omission errors made by the children with ADHD and that there was no practice effect influencing the performance of either group.

3.4. Mean RT

There was no significant difference in mean RT between the children with ADHD and the control children. Both the children with ADHD and the control children performed the SART at a significantly faster mean RT at the week-6 testing session (mean 470 ms, S.D. 110) when compared with the baseline mean RT (mean 504 ms, S.D. 118), [$F(1,51) = 7.119$, $p < 0.010$]. There was no significant interaction.

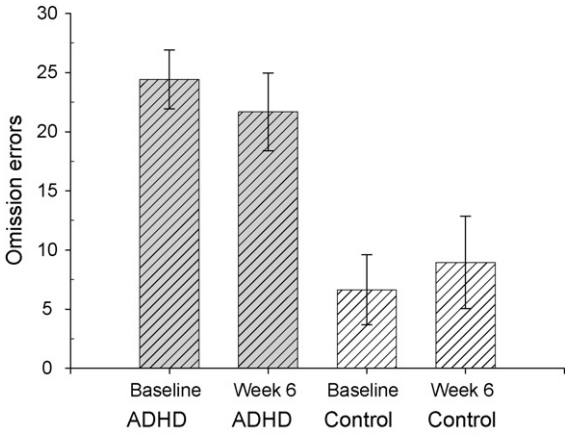

Fig. 3. Mean number of omission errors made on the SART by the children with ADHD when medication naïve (baseline), after 6 weeks of methylphenidate treatment (week-6) and the control group at baseline and at 6 weeks.

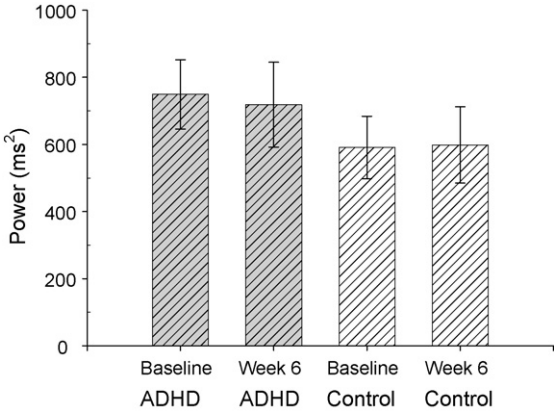

Fig. 4. Mean power of the slow frequency area under the spectra (SFAUS), encompassing all sources of variability slower than once per SART cycle (area under curve to the left of dotted line in Fig. 1), for the children with ADHD when medication naïve (baseline), after 6 weeks of methylphenidate treatment (week-6) and the control group at baseline and at 6 weeks.

3.5. Linear regression of RT

There was no significant difference between the slope of the linear regression lines between the children with ADHD (mean 0.61, S.D. 5.7) and control (mean 1.1, S.D. 5.1) children and the slope of the linear regression line did not change between the two testing sessions, for either group.

3.6. S.D. of RT

The children with ADHD (mean 226, S.D. 66) performed the SART with greater variability in RT than the control children (mean 177, S.D. 49), [$F(1,51) = 10.374$, $p < 0.002$]. There was no significant effect of time and no significant interaction between group and time, suggesting that although the ADHD group was more variable than the control group at both time points, there was no significant change in this global measure of variability for either group at week-6 compared with baseline.

3.7. Slow frequency area under the spectra (SFAUS)

There was no significant difference between the two groups in terms of slow frequency variability and both groups performed the SART with a similar amount of slow frequency variability across the two testing sessions (see Fig. 4). At both the baseline (mean 749 ms^2, S.D. 440) and week-6 (mean 702 ms^2, S.D. 521) testing sessions, the children with ADHD performed the task with a similar amount of slow frequency variability as the control children (baseline: mean 591 ms^2, S.D. 414; 6 weeks: mean 598 ms^2, S.D. 511), ($p > 0.05$).

3.8. Fast frequency area under the spectra (FFAUS)

A significant group main effect was further explained by a significant time by group interaction [$F(1,44) = 3.941$, $p < 0.05$] (see Fig. 5). The children with ADHD performed the SART with a significantly higher degree of fast moment-to-moment variability at baseline (mean 8,55,260 ms^2; S.D. 3,66,125) compared

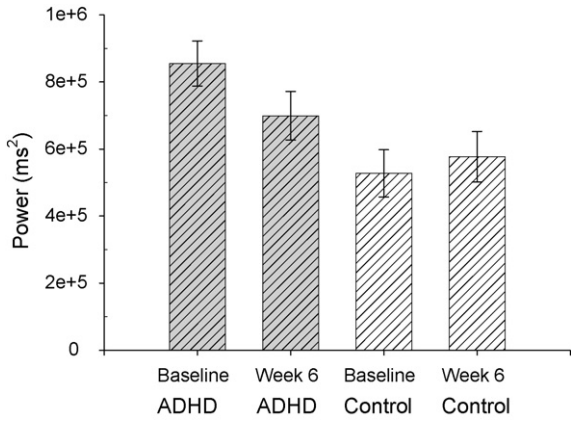

Fig. 5. Mean power of the fast frequency area under the spectra (FFAUS), encompassing all sources of variability faster than once per SART cycle (area under curve to the right of dotted line in Fig. 1), for the children with ADHD when medication naïve (baseline), after 6 weeks of methylphenidate treatment (week-6) and the control group at baseline and at 6 weeks.

with the performance at week-6 when on medication (mean 6,98,939 ms^2; S.D. 3,62,472) ($p < 0.035$). In contrast, there was no difference in performance for the control group between baseline (mean 5,27,465 ms^2; S.D. 2,83,746) and week-6 (mean 5,77,236 ms^2; S.D. 3,45,289) ($p > 0.05$), suggesting no effect of practice. The medication naïve ADHD group was significantly more variable in terms of fast moment-to-moment variability than the control group ($p < 0.002$). There was no significant difference between the two groups when the ADHD group was on medication at week-6 ($p > 0.05$).

3.9. The relationship between MPH dose and change in performance

To investigate whether there was a relationship between dose of MPH and performance of the children with ADHD on the Fixed SART, a change score was calculated for each dependent variable (baseline – week-6) to account for baseline performance. The change scores for each dependent variable and dose of MPH were then analysed with a Pearson correlation coefficient, with adjustments for multiple comparisons. There was a significant relationship between dose of MPH and change in the number of omission errors, $r = .45$, $p < .012$; a larger reduction in omission errors after MPH administration was significantly associated with a higher dose of MPH. No other significant associations were detected between the dependent variables and MPH dose.

3.10. Test–retest reliability of the SART dependent measures

The reliability of the SART dependent measures for the control children are presented in Table 2. The number of commission errors, mean RT, S.D. of RT, SFAUS and FFAUS all showed strong test–retest reliability. There was no significant correlation between the performance of the control children at baseline and at week-6 for the number of omission errors and the linear regression of the mean RT.

4. Discussion

This study investigated the effects of MPH administration on the sustained attention performance of a group of newly diagnosed, medication-naïve children with ADHD, relative to a group of control children. Medication naive children with ADHD demonstrated substantial sustained attention deficits on the SART, relative to the control group, in terms of the number of commission and omission errors, S.D. of RT and fast moment-to-moment variability. The two groups did not differ in terms of the slow frequency variability component. After 6 weeks of treatment with MPH, performance of the children with ADHD significantly improved and indeed normalised with respect to commission error rates and fast moment-to-moment variability in RT. MPH administration did not improve the number of omission errors made or the S.D. of RT. The direct influence of MPH on commission errors and fast moment-to-moment variability, but not on the number of omission errors, suggests that MPH has a specific effect on sustained attention and top–down attentional control but is less effective on those components that reflect, to some degree, arousal mechanisms.

The medication naïve children with ADHD performed the SART with increased commission and omission error rates, increased S.D. of RT and fast moment-to-moment variability in RT, compared with the control group. Being medication naïve, the children with ADHD in this present study are hypothesised to have had overactive dopamine transportation (Cheon et al., 2003) causing a reduction in the availability of dopamine in the synaptic cleft (Solanto, 2002). This could then have decreased the signal-to-noise ratio available to the post-synaptic neurons within the striatum (Volkow et al., 2001), interfering with the transmission of neuronal activity within the fronto-striatal and fronto-parietal circuits, resulting in poorer top–down attentional control over the task.

A differential effect of MPH administration was found on discrete SART measures. Performance on the fast frequency variability in RT and the commission error rate significantly improved with MPH administration. The fast frequency measure reflects moment-to-moment variability in RT and is not contaminated by the low-frequency components of the traditional S.D. of RT measure. We have argued that it reflects top–down attentional control (Johnson, Kelly et al., 2007; Johnson, Robertson et al., 2007). Top–down executive control of attention is achieved through distributed neural networks involving both fronto-striatal and fronto-parietal circuits and especially the prefrontal cortex, with dopamine and noradrenaline acting as key neuromodulators (Bellgrove, Hester, & Garavan, 2004; Graybiel & Saka, 2004; Pardo, Fox, & Raichle, 1991; Sturm et al., 1999). Deficits in sustained attention in ADHD may reflect dysfunction of this executive control system. This system is hypothesised to operate over a relatively fast timeframe, with fluctuations in top–down control occurring over 10–40 s (Parasuraman, Warm, & See, 1998; Pardo, Fox, & Raichle, 1991; Whitehead, 1991). Fast, moment-to-moment variability in RT appears to be a sensitive indicator of dysfunction within this system. One function of MPH administration may be to allow a relative increase in dopamine levels within the synaptic cleft via blockage of

Table 2
Test–retest reliability analysis of SART measures for control children

Dependent variable	Baseline	Week-6	Pearson product-moment correlation coefficient	N
Commission errors	5.0 (S.D. 3.5)	5.7 (S.D. 3.8)	.685 ($p<0.001$)	22
Omission errors	6.6 (S.D. 7.2)	9.0 (S.D. 10.5)	.359 ($p>0.05$)	22
Mean RT	529 (S.D. 112)	499 (S.D. 112)	.578 ($p<0.005$)	22
S.D. of RT	176(S.D.46)	177(S.D.53)	.752 ($p<0.0001$)	22
Linear regression of mean RT	0.8 (S.D. 5.3)	1.3 (S.D. 4.9)	−.060 ($p>0.05$)	22
SFAUS	582 (S.D. 406)	598 (S.D. 511)	.600 ($p<0.004$)	21
FFAUS	527,465 (S.D. 283,746)	577,237 (S.D. 345,289)	.642 ($p<0.001$)	22

the dopamine transporter (Kuczenski & Segal, 1997; Solanto, 1998), improving the transmission of neuronal signals within the fronto-striatal and the fronto-parietal circuits (Alexander & Crutcher, 1990; Paus et al., 1997), via dopaminergic and noradrenergic mechanisms and thus enhancing sustained attention. The modulation of fast, moment-to-moment variability by MPH is also consistent with the cognitive enhancing effects of MPH, via activation of dopamine 1-class receptors particularly within the prefrontal cortex (Arnsten & Dudley, 2005).

Of interest was the finding of no difference in the slow frequency variability between the children with and without ADHD at either the baseline or week-6 sessions. The slow frequency variability in RT failed to change with MPH administration in the children with ADHD. This measure reflects changes in RT over a timeframe longer than 20 s and so may reflect lapses in attentional control, possibly mediated by diminishing arousal levels over the course of the task (Johnson, Kelly et al., 2007). Sub-cortical arousal mechanisms, possibly involving the reticular formation, the locus coeruleus and/or the anterior cingulate (Critchley, Melmed, Featherstone, Mathias, & Dolan, 2002; Nigg, 2005; Paus et al., 1997) may be influencing this slow frequency variability in RT. We have previously found significant differences between children with and without ADHD on the slow frequency variability measure (Johnson, Kelly et al., 2007; Johnson, Robertson et al., 2007). In these studies, the average age of the children with ADHD (mean 10.7, S.D. 2.1) and control children (mean 11.1, S.D. 1.8) was substantially older than in the current study (mean 8.7 years; S.D. 1.0).[2] The average SFAUS of the control children in this current study (mean 595; S.D. 460) was considerably higher than those recorded from control children in the older age groups (e.g. mean 378; S.D. 229) in (Johnson, Robertson et al., 2007). The ability to maintain a consistent RT over longer timeframes, as measured by the SFAUS, may be a skill that is refined by control participants throughout childhood, but which might be developmentally delayed in children with ADHD. This hypothesised delay may be related to the development of the arousal system in childhood. This is the subject of further investigation.

[2] In Johnson, Kelly et al. (2007) study the mean age of the impaired ADHD group was 10.8 (S.D. 2.0; $n=24$) and the control group mean age was 11.3 (S.D. 1.7; $n=29$). In Johnson, Robertson et al. (2007) study, the mean age of the ADHD group was 10.5 (S.D. 2.4; $n=23$) and the control group was 11.1 (S.D. 1.9; $n=18$).

It is important to note that the point at which we divided the frequency spectra (0.0772 Hz) into fast, moment-to-moment variability (FFAUS) and the slow change in RT (SFAUS) was chosen in accordance with the timing of the SART, which involves a repeating sequence of nine stimuli and inter-stimulus interval of 1.439 s. This makes it difficult to directly compare these results with those of Castellanos et al. (2005), where the administration of methylphenidate resulted in a normalisation of variability in RT in the frequency band between 0.02 and 0.07 Hz (Castellanos et al., 2005). The inter-stimulus interval of the Eriksen Flanker task, used in the Castellanos et al. (2005) paper, was a slow 3 s. It is possible that the 0.05 Hz frequency, the most common oscillation of the ADHD group, might be considered "fast" with the slow presentation rate of stimuli. If so, the reduction in power at this frequency, in response to methylphenidate, would concur with the results in the present experiment.

Diminished arousal might also be influencing the omission error performance, whereby on the SART an omission error is the absence of an ongoing, primed response. The children with ADHD made significantly more omission errors than the control children, both when medication naïve and when on MPH. At the doses given to the children with ADHD in this study, MPH did not significantly reduce the high omission error rate. In addition, this was the only measure to show some sensitivity to the dose level. Rosa-Neto et al. (2005) in their study using the TOVA, also found no significant effect of MPH on the number of omission errors. They used a standard dose of 0.30 mg/kg. It may be that in order for the omission error rate to significantly improve, higher levels of MPH are needed. If the omission error rate is reflecting the functioning of the sub-cortical arousal systems, greater levels of catecholamine modulation may be needed before an effect is seen in ADHD, especially if these systems are under indirect dopaminergic or direct noradrenergic control. In any case, the data suggest that the omission error measure is less susceptible to MPH modulation than the fast-frequency variability and commission error measures.

MPH administration had no effect on the S.D. of RT. In many previous sustained attention experiments, the S.D. of RT decreased with MPH administration (e.g. (Fitzpatrick, Klorman, Brumaghim, & Borgstedt, 1992; Rosa-Neto et al., 2005)) although this finding is not conclusive (Tucha et al., 2006). There was a trend towards a decrease in the S.D. of RT with MPH administration in this study; the absence of an effect of MPH on the slow frequency variability measure will have outweighed the effect of a reduction in fast, moment-to-

moment variability, whilst the use of a response cue in the SART may have helped stabilise overall response variability to some degree.

A decrease in RT associated with MPH treatment has been noted previously (e.g. (Winsberg, Javitt, & Silipo, 1997)). In the present study, both groups reacted significantly more quickly to the SART stimuli in 6-week. This suggests that MPH was not having an effect on mean RT in this response-cued task, over and above the influence of practice. It should be noted that the mean RT measure was the only measure associated with the SART that was influenced by practice in the control group. The high test–retest reliability of the SART measures supports the candidacy of the SART as a measure of sustained attention in endophenotype studies and in future longitudinal medication studies.

This study has a number of limitations. First, due to the naturalistic focus of the pharmacogenetic study, there was no untreated ADHD group to act as a control for the treated ADHD group. Second, the average IQ of the control children was significantly greater than that of the ADHD group. Due to the potential statistical violations of the assumptions of ANOVA, in particular caused by multicollinearity between IQ and group, we did not use IQ as a covariate in the analyses. Third, the dosages (range: 0.18–0.82 mg/kg/day; mean 0.51 ± 0.20) that were determined by the treating clinician to achieve symptom reduction may have been inadequate to achieve robust cognitive enhancement in the children with ADHD. Konrad, Günther, Hanisch, & Herpertz-Dahlmann (2004) reported an improvement in total errors and S.D. of RT on a sustained attention task as the dose of MPH increased, from place 0.25 to 0.50 mg/kg/day. Although the maximum dose of the Konrad study was similar to the mean dose of this study, we cannot discount the possibility that higher dosages of MPH would have led to improvements in omission errors. Nevertheless, the current study found a robust influence of MPH on aspects of sustained attention and top–down attentional control.

There are a number of lines of further research stemming from this work. First, it is of interest to investigate the role of genotype on the response to medication and performance on this task. For example, allelic variation in the DAT1 gene has been linked to sustained attention deficits (Bellgrove, Hawi, Kirley, Gill et al. 2005), response time variability (Bellgrove, Hawi, Kirley, Fitzgerland et al. 2005) and separately to the clinical response achieved by MPH (Bellgrove, Hawi, Kirley, Fitzgerland et al. 2005). Examining the relationship between genetic and neuropsychological predictors of stimulant response would be of considerable further interest. Second, the same study could be performed with atomoxetine, a noradrenergic reuptake inhibitor, to investigate if altering noradrenergic transmission affects the slow frequency (and indeed the fast frequency) variability. In a similar manner, it would be fascinating to investigate the effect of a selective dopaminergic drug on the fast and slow forms of variability. Third, it would be interesting to conduct a study in which dose is at the control of the experimenter so that a dose-response curve for sustained attention, as measured by the SART, could be plotted. This would have the advantage of elucidating the optimal dosage of MPH required for enhancement/normalisation of sustained attention in children with ADHD. The development stages of top–down cortical control of executive attention and the arousal system in control and children with ADHD should be further researched. Finally, it would be interesting to investigate how the variation in fast and slow frequency measures relates to the hypothesised overactive default-mode network in children with ADHD, as proposed by Sonuga-Barke & Castellanos (2007).

In conclusion, the medication naïve children with ADHD performed below control levels on every measure of the SART, with the exception of mean RT and the slow frequency measure of variability. Performance on the SART improved significantly with MPH treatment for only the commission error rate and the fast, moment-to-moment variability in RT. These measures may reflect fluctuation in the moment-to-moment, top–down control of executive attention, which may be more conducive to catecholaminergic manipulation than the omission error and slow frequency variability measures.

Disclosure/Conflict of interest

The authors declare that over the past two years FMcN has received consultant fees from Eli Lilly and Jansen-Cilag and has been on the Speaker's Bureau for Eli Lilly and Jansen-Cilag. There are no other disclosures to make or conflicts of interest to declare.

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