

Methylphenidate improves working memory and set-shifting in AD/HD: relationships to baseline memory capacity

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Objective: Catecholamine stimulant drugs are highly efficacious treatments for attention deficit/hyperactivity disorders (AD/HD). Catecholamine modulation in humans influences performance of numerous cognitive tasks, including tests of attention and working memory (WM). Clear delineation of the effects of methylphenidate upon such cognitive functions in AD/HD would enhance understanding of the effects of drug treatment. **Method:** Here we present a double-blind, placebo-controlled study of the cognitive effects of an acute dose of methylphenidate (c. .5 mg/kg) in 14 boys aged 10.86 (± 1.19) years meeting criteria for DSM-IV AD/HD. Current behaviour was ascertained using Conners' teacher and parent self-report questionnaires and IQ was tested using sub-tests from WISC-III-UK. Tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) were selected to assess visuo-spatial recognition memory, spatial WM, planning, visual-search and attentional-set shifting. **Results:** Methylphenidate improved spatial WM, attentional-set shifting and visual-search task performance. Correlational analyses suggested possible relationships between WM capacity and spatial WM performance improvement. Also, poor performance on the attentional-set shifting task on placebo was associated with increased errors on the spatial WM task on placebo. **Conclusions:** Methylphenidate may selectively improve both underlying cognitive difficulties in tasks dependent on intact fronto-striatal structures, and clinical symptoms of AD/HD. Pre-treatment measures may have some predictive value in determining individual differences in drug response. **Keywords:** ADD/ADHD, cognition, executive function, methylphenidate, visuo-spatial functioning, working memory.

Children with attention deficit/hyperactivity disorder (AD/HD) present with both behavioural and cognitive problems (DSM-IV, Pennington & Ozonoff, 1996). The current pharmacological treatments of choice (catecholaminergic stimulant medications) are known to ameliorate the cardinal clinical signs of AD/HD symptomatology (Barkley, DuPaul, & Costello, 1993; MTA Cooperative Group, 1999), but less is known about the effects of treatment upon cognitive processes. It has been suggested that catecholaminergic stimulant medications can both enhance and impair certain cognitive functions in children with AD/HD, including those sensitive to fronto-striatal damage. Whilst evidence for the former claim is widespread (e.g., Rapport & Kelly, 1991; Douglas, Barr, O'Neill, & Britton, 1986; Kempton et al., 1999; Berman, Douglas, & Barr, 1999; Barnett et al., 2001; Tannock, Ickowicz, & Schachar, 1995), evidence for the latter claim is limited (Dyme, Sahakian, Golinko, & Rabe, 1982; Tannock & Schachar, 1992).

Stimulants such as methylphenidate act to increase the synaptic concentration of the monoamines dopamine and noradrenaline by blocking their reuptake (Seeman & Madras, 1998; Volkow et al., 2001). Systemic administration of dopamine or noradrenaline agents in normal volunteers can modulate performance on various cognitive tests, including those designed to assess executive functions. For example, α_2 -noradrenergic receptor agon-

ists can modulate performance of tasks of spatial WM, sustained and selective attention, with no effect on attentional-set shifting (Coull, Middleton, Robbins, & Sahakian, 1995a,b; Jäkälä et al., 1999; Rogers et al., 1999). Of particular interest for the present single-dose study are the results of Jäkälä et al. (1999) which support the notion of lower doses impairing spatial WM performance by acting pre-synaptically to reduce coeruleo-cortical activity and higher doses having greater action at post-synaptic (and post-junctional) receptors (Charney & Heninger, 1986; Arnsten, 1997), to enhance or disrupt performance. Such effects have been modelled as 'inverted-U' functions. In such schemas, increasing activity within a drug system is associated with improving performance, up to an 'optimum level' beyond which increasing activity is associated with decreasing performance (Robbins & Sahakian, 1979; Zahrt, Taylor, Mathew, & Arnsten, 1997). The relationship between dopamine and spatial WM performance has also been described in terms of the 'inverted-U' function, based on administration of dopamine-D1 receptor agents or amphetamines in animals (Arnsten, 1997), or L-dopa in patients with Parkinson's disease (Cools, Stefanova, Barker, Robbins, & Owen, 2002). One prediction from 'inverted-U' descriptions of catecholamine function is that baseline levels of performance on WM tasks may have some predictive value for the performance

effects of drug administration. Here we present a double-blind, placebo-controlled trial of a single dose of methylphenidate in treated children with AD/HD withdrawn from medication for at least 16 hours prior to each session. Each child was given a series of cognitive tests, including core tests taken from CANTAB (www.camcog.co.uk), in addition to baseline performance measurements of WM capacity.

Converging evidence from neuropsychological, neuroimaging and psychopharmacological studies highlight fronto-striatal systems of the brain as the major targets for the modulatory effects of catecholamine agents on cognitive performance (Grasby et al., 1993; Mattay et al., 1996; Mehta et al., 2000b; Mehta, Sahakian, & Robbins, 2001). Interpretation of neuroimaging data in AD/HD has been limited by changing definitions of hyperactivity, but nonetheless appear to implicate dysfunctional fronto-striatal and cerebellar brain systems (Giedd, Blumenthal, Molloy, & Castellanos, 2001). Few studies have examined the influence of catecholamine stimulant medication of brain activity patterns in children with AD/HD using neuroimaging techniques. Lou and colleagues (Lou, Henriksen, & Bruhn, 1984; Lou, Henriksen, Bruhn, Borner, & Nielsen, 1989), using SPECT, showed that methylphenidate increased striatal blood flow in a group of hyperactive children and adolescents. Using functional magnetic resonance imaging (fMRI), Vaidya et al. (1998) showed increased BOLD signal in frontal regions during a stimulus-controlled sustained attention task in both children with AD/HD and healthy aged-matched controls. Striatal activity was, however, differentially affected by methylphenidate, with healthy children showing decreased activity from baseline and hyperactive children showing increased activity from their lower baseline.

In the present study, we have selected a series of cognitive tasks known to be sensitive to fronto-striatal damage, and differentially sensitive to various catecholamine manipulations in healthy adults. Some of the tests have previously been used to examine performance in separate groups of treated and untreated children with AD/HD (Kempton et al., 1999; Barnett et al., 2001). Kempton et al. (1999) tested a group of 15 treated, and 15 stimulant medication naïve children with AD/HD using CANTAB. The untreated children showed impaired self-ordered spatial WM, planning (Tower of London), attentional-set shifting, delayed matching-to-sample and spatial recognition memory performance and reduced spatial memory spans. Only spatial recognition memory was impaired in the medicated group. These findings are in keeping with previous reports of impaired cognitive flexibility and spatial working memory in children with ADHD using classical tests (Chelune, Ferguson, Koon, & Dickey, 1986; Gorenstein, Mammato, & Sandy, 1989; Seidman, Biederman, Faraone, Weber, & Ouellette, 1997; Karatekin &

Asarnow, 1998). Barnett et al. (2001) replicated the spatial WM findings of Kempton et al. (1999) in a larger group of children. These between-group studies suggest that methylphenidate may improve performance on tests measuring aspects of executive function when compared to placebo in children with AD/HD. These include spatial (working) memory, cognitive planning, and tests of attentional function (e.g., sustained attention, attentional-set shifting). Both of these studies (Kempton et al., 1999; Barnett et al., 2001) acknowledged the importance of similar research conducted *within* groups where each patient acts as their own control.

The aim of the present study was, therefore, to test the following hypotheses in a placebo-controlled design: (1) that methylphenidate would improve performance on tests of spatial WM, attention-set shifting and cognitive planning and (2) that the improved WM performance would depend partly upon baseline WM capacity. Since the catecholamines are assumed to play a central role in modulating WM performance and WM has a putative importance in cognitive theories of AD/HD (see Denney & Rapport, 2001; Barkley, 1997), the relationship between WM performance and performance on other tasks was also examined.

Materials and methods

Participants and procedures

Fourteen male children meeting criteria for DSM-IV AD/HD (aged 9years 3months to 13years 8months) were carefully selected from referrals to psychiatric services in Cambridge over a two and a half year period so as to exclude those with comorbid disorders and the inattentive sub-type of AD/HD. Certain comorbid disorders are known to present with cognitive problems, and the effects of stimulant medication on these are as yet unclear. Therefore by excluding comorbidities, we sought to identify the neuropsychological characteristics of methylphenidate in a specific manner in this study (see discussion). Diagnosis was made by one of two child psychiatrists on clinical grounds within a multidisciplinary 'hyperactivity clinic' also including a psychologist and community nurse. Fourteen age-matched control children were also recruited (see below). The study was approved by the Cambridge Local Research Ethics Committee and written informed consent was given by one parent for all children. Conners' Parent and Teacher Rating Scales – Revised: Short Form (CPTRS-R:S) (Conners, 1997) were completed by parents and teachers of children with AD/HD to provide an assessment of problem behaviours whilst off medication around the time of the study (see Table 1). It should be noted that the children were treated at the time of recruitment, and this is probably reflected in the lower scores given by teachers as they rarely saw the children off medication. The high scores on the Conners' ratings scales, particularly for the parents, confirmed the clinical diagnosis of the study cohort: the children were rated as problematic, particularly in

Table 1 Parent and teacher ratings from the Conners' short-form questionnaires for the 14 children diagnosed with AD/HD

	Parent ratings		Teacher ratings	
	Mean percentile score	No. above cut-off ^a	Mean percentile score	No. above cut-off ^a
ADHD index	97.62 (2.73)	13	88.15 (18.71)	10
Cognitive problems	96.02 (4.00)	10	75.04 (20.99)	3
Hyperactivity	98.62 (1.65)	14	89.74 (14.56)	9
Oppositional	95.92 (5.13)	11	86.51 (13.32)	6

Percentile score values are means (SD in parentheses).

^a Cut-off percentile for each child is equivalent to a standard *T*-score of 65 (or 93¹/₃ percentile).

terms of the ADHD index (indicates high risk of ADHD) and hyperactive behaviour.

Children with AD/HD were all stabilised on methylphenidate prior to the study. They were asked to come off treatment for the purpose of the study visits. Thus, all children were stimulant-free for at least 16 hours (approximately 4 half-lives; Gualtieri et al., 1982) prior to each study visit. A double-blind, placebo-controlled, counter-balanced, cross-over design was used to assess possible effects of oral methylphenidate on cognitive function, such that seven children received methylphenidate on the first session and placebo on the second (D/P group), presented in identical capsules; and the other seven children received placebo then methylphenidate (P/D group). The dose of methylphenidate chosen was .5 mg/kg (to the nearest 5 mg) as has been suggested for use in single-dose studies on the basis of previous investigations (Rapport & Kelly, 1991). The mean dose administered was 18.21 mg (SD = 5.75 mg). There was no difference in terms of age as a function of session-order group [$F(1,12) = .28, p = .61$]. Intelligence quotient was ascertained using a short-form dyad of the Weschler Intelligence Scale for Children (WISC-III-UK) (Weschler, 1992) comprising the block design and vocabulary sub-tests. This short-form correlates highly with the full-scale score ($r = .91$; Sattler, 1988). There was no significant difference in IQ between patients in the D/P and P/D groups [$F(1,12) = .30, p = .60$]. Mean age and IQ scores are summarised in Table 2. Children were also administered the digit span sub-test as a measure of baseline verbal WM capacity.

In order to maximise levels of methylphenidate during the experiment, cognitive testing was commenced approximately 1½ hours after capsule ingestion and lasted for about 1 hour (Gualtieri et al., 1982). For each participant, administration of drug or placebo was always at the same time of day and the two visits of the cross-over design were separated by between 1 and 4 weeks, and both conducted at the patient's own home.

Table 2 Age and IQ scores for the two groups of children diagnosed with AD/HD

	D/P group	P/D group
Number of subjects	7	7
Age	10.70 (.85)	11.04 (1.51)
WISC pro-rated IQ	94.57 (9.82)	97.57 (10.77)

Values shown are means with standard deviations in parentheses.

Representative sample of children from the local community

The aim of the present study was to examine the effects of methylphenidate on cognitive function in children diagnosed with AD/HD. However, it is important to know the level of performance in a 'representative' sample of normal children from the local community of similar age and IQ. Luciana and Nelson (1998) demonstrated the reliability of CANTAB in groups of children aged 4–8 years. We tested 14 male children aged 8 years 10 months – 13 years 7 months [mean age, 11.58 (1.01); mean WISC-III IQ, 105.2 (15.08)] using the same tests as the patients received, given in the same order on two occasions separated by between 1 and 4 weeks, recruited by writing to local schools. While slightly higher in the representative sample, the mean IQ score is in the same range as patients (i.e., average). In addition, the digit span test was performed better than in patients for this sample, but only in terms of total forward span score [AD/HD = 8.43 (2.06), representative sample 10.35 (2.10); $F(1,26) = 6.01, p < .025$]. There was no statistical difference for the maximum forward span reached [AD/HD = 6.93 (1.07), representative sample 7.57 (1.09); $F(1,26) = 2.48, p = .13$]. Direct statistical comparison of the representative sample to patients on drug or placebo, on either session 1 alone or over both sessions, was not made due to the low statistical power of the former and the assumptions the latter requires regarding equivalence of practice effects in patients and controls. In addition, while each child had no known psychiatric history, no formal assessment of ADHD symptomatology was conducted. For the reader's benefit, the scores for representative children are, therefore, displayed in the appendix, with the exception of errors on the attentional-set shifting task, which are shown in Table 4 for clarity.

Cognitive tests

On the first session, the tests were preceded by a motor screening task designed to familiarise children with the computer and procedures. The following tests were taken from the CANTAB. Only brief descriptions are presented here, but the reader is referred to fuller descriptions if required.

Pattern and spatial recognition memory tests (Sahakian et al., 1988). These tests are separated into presentation and discrimination phases. During the presentation phase the participant was shown a

series of 12 abstract patterns or, for the spatial task, a series of 5 squares in different locations. In the discrimination phase participants were presented with each pattern or location, paired with a novel pattern or location. Recognition memory was tested using a forced choice discrimination between targets and distractors. The pattern recognition task comprised 2 sets of 12 stimuli and the spatial recognition task comprised 4 sets of 5 locations. Different stimuli were used for each session.

Self-ordered spatial WM (Owen, Downes, Sahakian, Polkey, & Robbins, 1990). For this test participants were initially presented with three coloured boxes on the screen and instructed to search through them for blue tokens. The tokens were hidden, one at a time, behind the coloured boxes. Once a token had been found, participants placed it in a column on the right-hand side of the screen by touching it. Participants were told that once a token had been found behind a particular box, that box would not be used again to hide a token. Participants performed three further problems with 3 boxes and then four problems with each of 4, 6 and 8 boxes. The number of hidden tokens in each problem equalled the number of boxes. Two types of search error were possible in this task. Participants could return to a box in which they had previously found a token (between-search error) or return to a box they had previously searched within the same trial (within-search error). A strategy score was calculated by summing the number of times a search commenced with a different box. Thus deviations from ordered, repetitive searches led to a higher score reflecting poorer use of strategy. This strategy is known to be beneficial to performance (Owen et al., 1990).

Tower of London (Owen et al., 1990). This task is a computerised version of the Tower of London test designed by Shallice (1982), in which each participant has to move coloured balls on the computer screen from an initial arrangement pattern on the bottom half of the screen to one corresponding to the goal arrangement pattern shown on the top half of the screen.

Following example problems requiring a minimum of one and two moves, participants attempted 2 two-move, 2 three-move and 4 four-move problems. Children were told not to initiate solutions until they were sure of the moves that they wanted to make. Following these problems, participants performed a yoked motor control segment for which they were required to simply follow, with the balls in the lower arrangement, the moves 'played out' by the computer in the arrangement on the top half of the screen. These moves matched those performed by participants for the preceding problems. A second set of problems (a motor control segment) were then given to participants comprising 4 four-move and 4 five-move problems. The principal measures were: the number of problems solved in the minimum number of moves, the average number of moves made in solving problems at each level, the initial thinking times (the time taken to initiate solutions minus the time taken to initiate movement on the motor control sections) and the subsequent thinking times (the time taken to complete solutions minus the time taken to complete the motor control problems).

Attentional-set shifting test (ID/ED) (Downes et al., 1989). There are nine stages in this task during each of which the participant is required to learn a visual discrimination to a criterion of six consecutive correct responses. First, the participant has to learn a simple visual discrimination (SD) followed by a reversal of this discrimination (SDR). For example, the SD may be between two same-coloured shapes. In the third stage an irrelevant dimension (e.g., lines) is introduced (initially spatially separate from the shapes and subsequently overlying the shapes), and participants must learn that the new dimension is irrelevant and then reverse the learned discrimination [compound discrimination (C_D then CD) and reversal (CDR) respectively]. In the sixth stage new exemplars are introduced and the relevant dimension is the same as in the CD and CDR stages (e.g., shapes). This is termed an intra-dimensional shift (IDS) and is followed by a reversal of the learned discrimination [intra-dimensional reversal (IDR)]. The eighth stage of this test again involves the introduction of new exemplars, but this time participants must shift their attention to the previously irrelevant dimension [an extra-dimensional shift (EDS)] and finally reverse this rule [extra-dimensional reversal (EDR)]. For example, participants would be required to respond to lines instead of shapes. The EDS stage is akin to a category shift in the Wisconsin Card Sort Test (Grant & Berg, 1948; Milner, 1964). The main performance measures of interest for this task are the number of stages passed, the number of errors at the intra-dimensional and extra-dimensional shift stages and the latencies per choice at these stages. Parallel versions were used across the test sessions.

Matching-to-sample visual search (Downes et al., 1989). For this task, participants were required to (1) inhibit response movement until a decision was made, and (2) to search for target stimuli in the presence of variable numbers of distractors. A central red box surrounded by eight white boxes was displayed on the computer screen. Once the participant depressed a switch-pad, a complex visual pattern ('target') appeared in the red box, followed by 1, 2, 4 or 8 choice patterns in the surrounding white boxes, one of which was identical to the target. The participants' task was to keep the pad depressed and search for the choice stimulus that matched the target, and then to release the switch-pad and touch it. For each response auditory and visual feedback was given. After four practice trials, 48 test trials (12 of each choice condition) were presented in a random order. The main measures from this task were the percentage of correct responses and the choice latencies. Experience from previous studies has demonstrated that the latency between releasing the pad and touching a choice pattern (termed movement time) might not reflect the true movement time since participants may release the pad and then hesitate before making a final decision. Therefore this measure was not used in the analysis. Different stimuli were used for each session.

Statistical analysis

Data analyses were performed using SPSS 9.0 (SPSS Inc., 1999), using parametric or non-parametric tests as

appropriate. For parametric analyses, drug (drug or placebo) was used as a within-subjects factor and group (D/P or P/D) as a between-subjects factor with an additional within-subjects factor of level or difficulty if appropriate. For significant drug effects, observed power is quoted. An additional precautionary analysis was performed on the data on session 1 of the cross-over design which, despite having lower statistical power, is unconfounded by any practice or carry-over effects.

Results

Effects of methylphenidate in children with AD/HD on the first test session only

For the between-subjects comparisons on the first test session only, unconfounded by practice, there were no significant differences between performance of participants when on methylphenidate compared to placebo.

Within-subjects analysis for the first and second session

Pattern recognition. There was no effect of methylphenidate on the performance accuracy of this task [$F(1,12) = .13, p = .13$], see Table 3. There was, however, a main effect of group [$F(1,12) = 6.69, p = .024$] with those in the D/P group recognising fewer patterns than those in the P/D group [drug: 85.12% correct; placebo: 92.86% correct]. There was no drug \times group interaction [$F(1,12) = .13, p = .72$]. For the response latencies (see Table 3) there was no main effect of drug [$F(1,12) < 1, p = .95$], or group [$F(1,12) = 3.61, p = .082$], and no interaction [$F(1,12) = .93, p = .36$].

Table 3 Performance measures for children with AD/HD having taken methylphenidate or placebo

Performance measure	Drug	Placebo	SED
Pattern recognition			
Percentage correct	88.39	89.58	2.31
Response latency (ms)	2195	2185	50.0
Spatial recognition			
Percentage correct	68.21	70.00	3.29
Response latency (ms)	2138	2115	117
Spatial working memory			
Between search errors	41.3	47.4	1.10*
Strategy score	36.0	36.4	.60
Tower of London			
Minimum move solutions	6.79	7.21	.34
Initial thinking time (ms)	4206	2175	672*
Subsequent thinking time (ms)	596	495	172†
Visual Search			
Percentage correct	94.0	91.1	1.03*
Response latency (ms)	2673	2910	270
Attentional-set shifting			
Stages passed	8.29	7.14	.35*

SED = standard error of the difference of the means for the children with AD/HD.

* Main effect of drug, $p < .05$.

† Interaction effect of drug, see text for details.

Spatial recognition. In terms of accuracy there were no significant effects of drug [$F(1,12) = .15, p = .71$], or session order group [$F(1,12) = 2.30, p = .16$], and no interaction [$F(1,12) = .01, p = .94$]. There were also no differences for the latencies to the correct choices [drug: $F(1,12) = .02, p = .90$; group: $F(1,12) = .07$; interaction: $F(1,12) = .16, p = .69$]. Mean scores and latencies are shown in Table 3.

Self-ordered spatial WM. For the between-search errors (see Table 3) there was a main effect of drug [$F(1,12) = 5.25, p = .041$; power = .53], with those on drug making fewer errors than those on placebo. There was also, as expected, a main effect of difficulty [$F(1.37, 16.47) = 90.98, p < .01$]. There were no other significant main or interaction effects for the between-search errors, although there was a strong tendency for a session order group \times drug interaction [$F(1,12) = 4.32, p = .06$] due to those in the P/D group making fewer errors on drug [$F(1,6) = 21.08, p = .004$]. In the light of the *main effect* of drug, this can be interpreted as reflecting a greater contribution to the main effect of drug on session 2 compared with session 1 [session 1: drug errors = 48.56, placebo errors = 45.71; session 2: drug errors = 34.00, placebo errors = 49.14].

For within-search errors (see Figure 1) it was not possible to perform repeated-measures analysis across the three difficulty levels (due to the extreme heterogeneity of variance) and therefore the data were collapsed across this factor. For the total number of within-search errors there was a main effect of drug [$F(1,12) = 5.08, p = .044$] with participants making fewer errors on drug. There was no main effect of group [$F(1,12) = 3.37, p = .10$] and no interaction [$F(1,12) = 2.49, p = .14$]. For the strategy scores there was no main effect of drug [$F(1,12) = .45, p = .51$], or session order group [$F(1,12) = .07, p = .80$] and no interaction [$F(1,12) = 1.38, p = .26$].

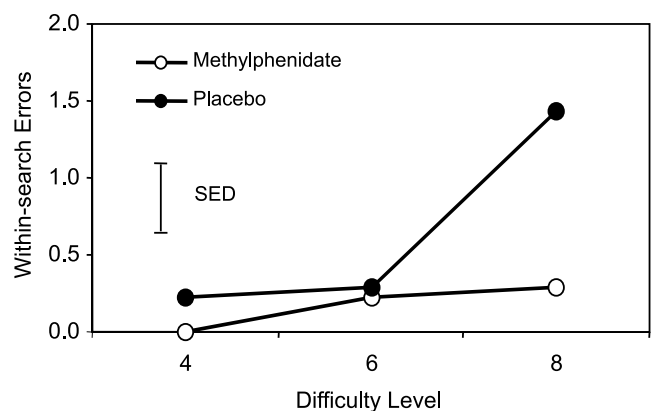


Figure 1 Mean within-search errors on the self-ordered spatial working memory task across the three difficulty levels for subjects with AD/HD having taken .5 mg/kg methylphenidate or placebo. The SED is used to represent the within-subject variability for the main effect of drug

The use of strategy, as with adults, was associated with performance on both drug [$r = .63, p = .016$] and placebo [$r = .66, p = .011$], with those using a better strategy making fewer errors. In summary, therefore, those on drug performed better than those on placebo on this task, in terms of errors, but not strategy usage.

Tower of London. There was no difference between those on drug and those on placebo in terms of minimum move solutions [$F(1,12) = .81, p = .39$], see Table 3. For this measure there was also no effect of session order group [$F(1,12) = .25, p = .39$] and no group \times drug interaction [$F(1,12) = 2.24, p = .16$]. For the mean number of moves (depicted in Figure 2) it was not possible to analyse all the levels of difficulty together in a single repeated-measures ANOVA model. This was due to little (or no) variance in the data for the 2-move problems. Separate (non-parametric) analysis of the mean moves to complete the 2-move problems showed no significant difference between participants when on drug and when on placebo [$z = -1.00, p = .32$]. For the 3-, 4- and 5-move problems there were no main effects of either group [$F(1,12) = 2.07, p = .18$] or drug [$F(1,12) = .22$], although there was a significant group \times drug interaction [$F(1,12) = 4.91, p = .047$; power = .51]. This was due to participants on drug on session 1 making *more* moves than those on drug on session 2 [$F(1,12) = 6.64, p < .05$] and those in the D/P group tending to make *more* moves on drug [$F(1,6) = 5.42, p = .06$], see Figure 2. There was, as expected, a main effect of difficulty [$F(2,24) = 147.9, p < .01$], but no interactions with the difficulty factor.

For the initial thinking times, unlike the mean moves, it was possible to analyse all the difficulty

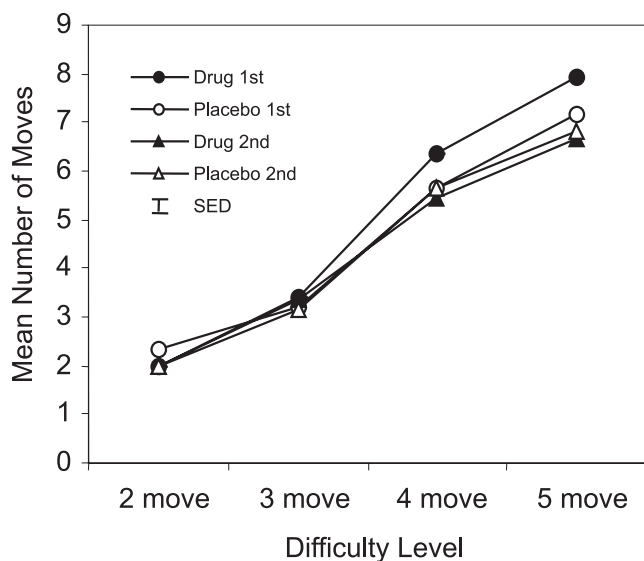


Figure 2 The mean number of moves made by subjects with AD/HD on either methylphenidate or placebo, for both sessions of the cross-over design, on each level of the Tower of London task. SED is used to represent the within-subject variability

levels in one repeated-measures ANOVA model. For this variable there was a main effect of drug [$F(1,12) = 17.46, p = .01$; power = .97], with participants on drug being significantly *slower* to initiate problem solutions. There were no other main effects or interactions for this measure. The initiation latency data (collapsed across the difficulty levels) are shown in Table 3.

For the subsequent thinking times there was a main effect of difficulty [$F(1.58, 19.00) = 10.94, p < .01$] with participants generally showing longer subsequent thinking times for the more difficult problems. There were no interactions with the difficulty factor. There was also no main effect of group [$F(1,12) = 1.68, p = .22$], or drug [$F(1,12) = .69, p = .42$], although the group \times drug interaction was significant [$F(1,12) = 5.53, p = .037$]. This was due to participants on drug on session 1 evidencing longer latencies than participants on drug on session 2 [$F(1,12) = 4.45, p < .05$], and participants in the D/P group being slower on drug [$F(1,6) = 5.98, p = .05$], see Figure 3.

Therefore, in summary, participants on drug, on session 1 were less accurate in their solutions (mean moves) and showed longer thinking times once solutions had been initiated. In addition, participants on drug, regardless of session, were slower in initiating problem solutions.

Matching-to-sample visual search. The percentage correct measure for this task was analysed non-parametrically: those on placebo made fewer correct choices compared with those on drug [$z = -1.96, p = .0499$]; see Table 3

For the latency measure [\log_{10} transformed for analysis], participants on methylphenidate did not differ from when they were on placebo [$F(1,12) = 1.34, p = .27$]. There was, as expected, a main effect of difficulty [$F(3,36) = 99.17, p < .01$], with

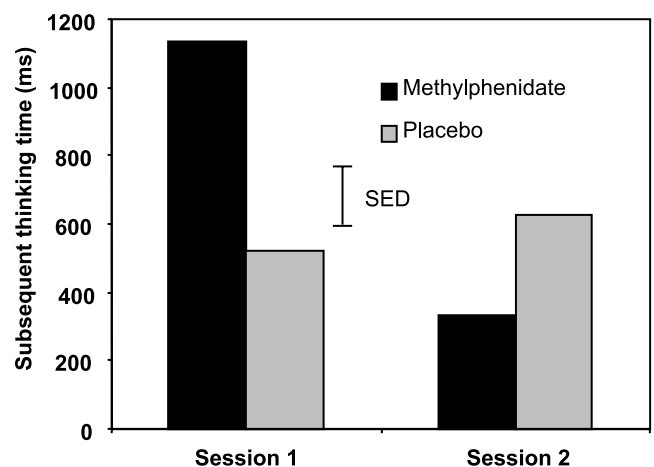


Figure 3 The mean subsequent thinking times on the Tower of London task for children with AD/HD on drug (black bars) or placebo (grey bars). Error bars represent SEM

participants taking longer to respond on trials with more choices. There were no significant interaction effects for the latency measure. The mean response times (collapsed across difficulty levels for clarity) are shown in Table 3.

Attentional-set shifting task. The number of stages reached on this task was analysed non-parametrically. Using a Wilcoxon signed-rank, matched-sample test revealed a significant effect of drug [$z = -2.03, p = .04$], with participants on drug successfully passing significantly more stages than those on placebo (see Table 3). The number of participants successfully passing each stage on either drug or placebo is depicted in Figure 4. Of those participants who attempted the ID shift stage on both drug and placebo there was no difference in pass rate (drug: 11/12, placebo: 11/12). However, for those participants who attempted the ED shift

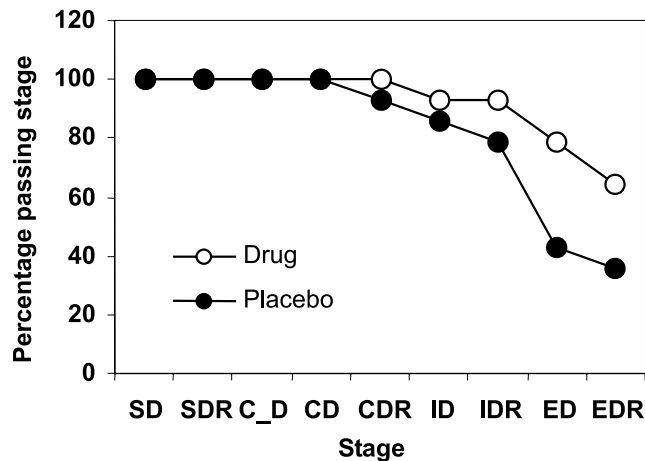


Figure 4 Performance on the attentional-set shifting paradigm, assessed in terms of proportion of subjects reaching each stage of the test. SD, simple discrimination; SDR, simple reversal; C-D, compound discrimination, spatially discontinuous elements; CD, compound discrimination; CDR, compound discrimination reversal; ID, intra-dimensional shift; IDR, intra-dimensional shift reversal; ED, extra-dimensional shift; EDR, extra-dimensional shift reversal

stage on both drug and placebo a significantly higher proportion passed whilst on drug [drug: 10/10, placebo: 6/10; $p = .006$].

The number of errors made at each stage (for those who attempted each stage) is shown in Table 4. Two sets of analyses were performed on the error data. In order to determine if participants on drug or placebo differed in performance of the task up to the ID stage, the summed errors up to this stage were compared using repeated-measures ANOVA. There were no differences between those on drug or placebo [$F(1,11) = .23, p = .64$] or between those in the D/P group or in the P/D group [$F(1,11) = 1.91, p = .19$] and there was also no interaction [$F(1,11) = .53, p = .53$]. The second analysis tested whether there was a difference between the ED-shift stage compared with the ID-shift stage for those children who attempted both stages on drug and placebo. The similarity in errors between the drug and placebo performance apparent in Table 4 was confirmed using statistical analysis [drug: $F(1,8) = 2.59, p = .15$; drug \times shift: $F(1,8) = .82, p = .39$]. In summary, in terms of stages passed, those on placebo demonstrated a specific deficit at the ED-shift stage when compared with those on drug.

Correlational analysis. In order to examine possible associations between baseline neuropsychological/demographic measures and the performance changes on drug compared with placebo, Pearson's product moment correlation coefficient, r , or Spearman's rank-order correlation coefficient, r_s , was used as appropriate. Prompted by the results of previous studies (Kimberg, D'Esposito, & Farah, 1997; Mehta et al., 2000b), baseline digit span scores were correlated with the change in the errors on the self-ordered spatial WM task. There was a significant correlation between baseline forward and backward digit-span and the improvement on the WM task (placebo - drug) [forwards $r_s = .58, p = .03$; backwards $r_s = .77, p = .001$]. Children with AD/HD who had lower baseline digit-spans improved the least on methylphenidate on the spatial WM task (the correlation with backwards digit span is shown in Figure 5).

Table 4 Mean errors committed at each stage of the attentional-set shifting paradigm by subjects with AD/HD on methylphenidate or placebo, or controls

	Stage								
	SD	SDR	C_D	CD	CDR	ID	IDR	ED	EDR
Drug	1(.36)	2.57(.92)	2.57(.83)	.29(.16)	1.36(.36)	2.21(1.49)	1.77(.46)	9.15(2.71)	4.55(2.40)
<i>n</i>	14	14	14	14	14	14	14	13	11
Placebo	1.21(.60)	1.78(.43)	1.50(.50)	2.57(1.70)	4.00(2.05)	4.75(2.40)	2.27(.90)	10.91(3.42)	5.33(3.03)
<i>n</i>	14	14	14	14	13	12	11	11	6
Control	1.78(.51)	1.29(.24)	1.07(.43)	.21(.16)	1.57(.25)	2.64(1.74)	2.54(.88)	11.23(3.20)	2.00(1.00)
<i>n</i>	14	14	14	14	14	14	13	13	10

Values shown are mean errors with SEMs in parentheses. See Figure 5 for key to abbreviations.

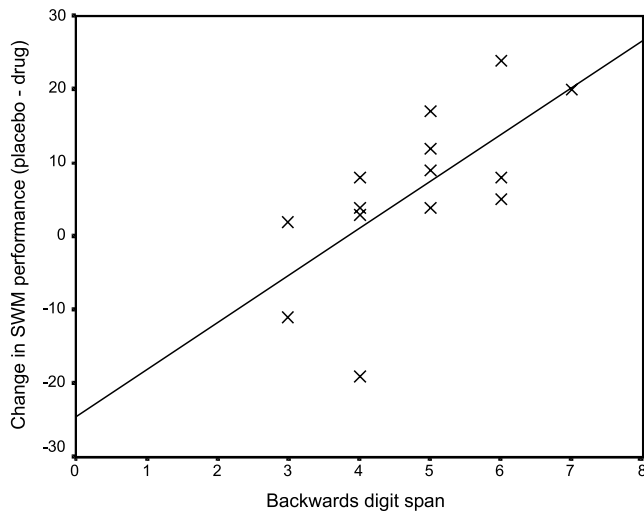


Figure 5 Scatter plot of baseline digit-span scores and change in between-search errors (drug versus placebo) on the spatial working memory task for children with AD/HD with a fitted regression line

Additionally, correlational analyses were performed to examine possible associations between all cognitive measure change scores (placebo - drug), and baseline age, WISC IQ, digit spans and Conners' ratings scale scores. Because of the large number of correlations being performed, a restricted significance threshold of $p = .01$ was used to represent a significant association between variables. None of the correlations reached statistical significance at $p = .01$ or at $p = .05$.

A third set of correlational analyses was also performed in order to examine possible relationships between the WM task performance and other cognitive measures on either drug or placebo. These comparisons were planned *a priori* on the basis of the putative importance of WM function in understanding the psychopathology of AD/HD (e.g., Barkley, 1997; Denney & Rapport, 2001). For participants on placebo there was a significant correlation between the between-search errors on the spatial WM task and two measures from the attentional-set shifting task: errors at the ED-shift stage ($r = .66$, $p = .026$) and the number of stages reached ($z = -.67$, $p = .009$). Participants who performed poorly on the spatial WM task on placebo also performed poorly on the attentional-set shifting task, particularly at the ED-shift stage. No other comparisons were significant.

Discussion

The main findings of this study were: (1) that methylphenidate improved performance on tasks of WM, visual search and attentional-set shifting, (2) that the improved WM performance correlates with measures of baseline WM capacity, (3) that the impaired attentional-set shifting ability in children on

placebo may depend, in part, upon their impaired WM ability and (4) the effects were observed in children diagnosed only with AD/HD with no comorbid disorders. In addition, matching-to-sample visual search task deficits were ameliorated by methylphenidate, providing a cognitive analogue for the behavioural phenomenon of distractibility (DSM-IV). It is unlikely that the poor performance on placebo reflected a speed-accuracy trade-off, as participants on placebo were, if anything, slower to make responses on the visual search task.

The pattern of executive function tasks that demonstrated improvements after methylphenidate is consistent with a hypothesis of catecholaminergic modulation of cognitive processes subserved by neural networks including the prefrontal cortex (Robbins, 2000), even though it is difficult to generalise from the results of a single dose of methylphenidate. However, the self-ordered spatial WM and attentional-set shifting tasks are both impaired following frontal lobe damage (Owen, Roberts, Polkey, Sahakian, & Robbins, 1991; Owen et al., 1990; Owen, Morris, Sahakian, Polkey, & Robbins, 1996b), activate defined neural networks, including regions of the prefrontal cortex (Owen, Evans, & Petrides, 1996a; Rogers, Andrews, Grasby, Brooks, & Robbins, 2000) and are sensitive to catecholaminergic manipulations in normal humans (Elliott et al., 1997; Jäkälä et al., 1999; Rogers et al., 1999; Mehta, Sahakian, McKenna, & Robbins, 1999). We have also shown that an adult with AD/HD similarly benefited from an acute dose of methylphenidate (.5 mg/kg) on the same WM test (Mehta, Calloway, & Sahakian, 2000). Children on methylphenidate also made fewer within-search errors than when on placebo on the self-ordered spatial WM test, a measure previously only shown to be sensitive to frontal lobe damage (Owen et al., 1990).

Not all tasks of spatial (working) memory were improved by methylphenidate. For example, performance on the spatial recognition memory task, which is sensitive to frontal lobe damage (Owen, Sahakian, Semple, Polkey, & Robbins, 1995) was unaffected by methylphenidate in this study - a finding consistent with the lack of difference in performance of the same task between a group of treated and untreated children with AD/HD (Kempton et al., 1999). Such differences across working memory tasks may reflect differential load on certain processes across tasks (e.g., encoding, rehearsal, motor planning), although further work is needed to clarify this speculation (D'Esposito & Postle, 1999). An important difference between the present study and that of Kempton et al. (1999) is that children in the latter study were unable to develop efficient and systematic strategies to assist performance. All groups of children in the present study did, however, show adult-like relationships between strategy and error scores on the spatial WM task (Owen et al., 1990). The age of children tested may be an

important factor in the differences between these two studies as the children tested by Kempton et al. (1999) were approximately 2.5 years younger than the participants of the present study. However, age does not seem to account for the findings *within* this study – that is, age did not correlate with any of the performance changes.

Age may also be an important factor in interpreting performance of the attention-set shifting test (Luciana & Nelson, 1998). This task was improved in children on methylphenidate compared with placebo. Specifically, a higher proportion of children passed the crucial extra-dimensional shift stage on drug. Impaired performance on the same task in a group of unmedicated children with AD/HD in the study by Kempton et al. (1999) was not limited to the ED-shift stage and therefore it is unclear whether methylphenidate may improve cognitive flexibility in a younger group of children.

The specific drug-induced improvement in attentional-set shifting seen here does not support the notion that methylphenidate at a moderate dose of approximately .5 mg/kg can impair cognitive flexibility (Dyme et al., 1982). However, the use of a range of cognitive tasks has allowed specification of the attention-set shifting task deficits to a greater degree than previous studies have examined. For some participants (including, at least, controls) the reversal stages of the task and stages prior to the ED-shift stage are very easy compared with the ED-shift stage (Luciana et al., 1998) and may often be accomplished after just one error. For the ED-shift stage it is usually necessary to integrate information from a number of trials in order to identify both the relevant dimension and the correct exemplar within that dimension. This calls for the availability of resources such as focused attention and WM more than previous stages of the task. Thus, impairments in processes other than set-shifting could account for some of the difficulties on the attentional-set shifting task experienced by children with AD/HD when on placebo. Indeed, errors at the ED-shift stage were correlated with between-search errors on the spatial WM task, on placebo, when participants evidenced difficulties with both tests.

Taken together, the results from the present study suggest that some of the cognitive deficits seen in AD/HD may arise because of a dysfunctional catecholamine system. Methylphenidate may compensate for AD/HD-related dysfunction in certain brain areas, including fronto-striatal systems (Giedd et al., 2001). However, an important preliminary finding from the present study is that methylphenidate may also induce deficits in a planning task sensitive to fronto-striatal damage. One explanation for this pattern of results is that different tasks require different levels of catecholamines for their optimum performance (Zahrt et al., 1997). In other words, the administration of methylphenidate, while optimising the performance of some tasks, could be detrimental

to the performance of other tasks. Individual differences at baseline cognitive testing may provide clues regarding which participants might benefit the most from stimulant treatment. Indeed, individual differences at baseline were related to the drug response on the self-ordered spatial WM task – the participants with higher baseline digit-spans demonstrated the greatest improvement on the spatial WM task in terms of between-search errors. The influence of baseline levels of activity upon the behavioural response to stimulant medication has long been recognised (Robbins & Sahakian, 1979; Solanto, 1984), and there is accumulating evidence that certain cognitive measures may be predictive of drug-induced changes in certain performance measures (Buitelaar, Van der Gaag, Swaab-Barneveld, & Kuisperet, 1995; Kimberg et al., 1997; Mehta et al., 2000b). Improved self-ordered spatial WM performance in a group of normal adult volunteers given 40 mg methylphenidate was also related to baseline WM capacity (Mehta et al., 2000b), but unlike the children with AD/HD, adults with a lower baseline memory capacity evidenced the greatest improvements. Thus, a dynamic model where an optimum range of drug modulation exists may account for these findings. Proposed sigmoidal functions of catecholamine relationships with performance (Servan-Schreiber, Printz, & Cohen, 1990) would therefore lead one to hypothesise a hypodopaminergic state in neural systems recruited during WM performance in childhood AD/HD, which is normalised following methylphenidate (Mehta et al., 2001).

This hypothesis is supported by the known pharmacological action of methylphenidate, which is believed to block the dopamine transporter, thereby reducing the rapid reuptake of synaptic dopamine. It has been proposed (Grace, 2001; Seeman & Madras, 1998) that methylphenidate increases tonic levels of extracellular dopamine, but diminishes relative phasic increases. Thus, we can speculate from the results of this and previous studies (e.g., Solanto, 1986) that methylphenidate may either normalise low tonic levels of dopamine in AD/HD, or block elevated levels of dopamine transporters (Dougherty et al., 1999).

There are a number of issues that may limit the interpretation of the findings in the present study. The results presented were for a small group of children with AD/HD, and all of them had previously been successfully treated with methylphenidate. Therefore some of the effects observed may be partly due to long-term effects of stimulant treatment or transient 'rebound' effects of methylphenidate withdrawal. Although little is known about the long-term effects of treatment with stimulant drugs (but see Gillberg et al., 1997), it is reassuring that placebo performance of children on, for example, the spatial WM tasks is similar to that seen in medication naïve patients (Kempton et al., 1999). 'Rebound' from acute withdrawal of medication has been previously

observed with dextroamphetamine (Porrino, Rapoport, Behar, Ismond, & Bunney, 1983). In a study with children taking methylphenidate there were no significant 'rebound' effects observed (using behavioural rating scales) (Johnston, Pelham, Hoza, & Sturges, 1988). Placebo-controlled trials in medication naïve patients would be required to clarify this issue for cognitive measures. Nonetheless, this study has demonstrated that acute withdrawal from methylphenidate may contribute to worsening of performance in specific tasks of executive function in the short term.

In addition, there was a suggestion that children on methylphenidate may also perform worse on the Tower of London task, but only when it was novel to them. This effect may represent differential practice across the groups of children, since no practice effects were detected in the representative sample. Nonetheless, our findings contrast with those of Elliott et al. (1997) who observed *enhanced* performance in normal adults on the same version of the Tower of London task when it was novel to them (in addition to impaired performance on another version when it was familiar to them). Furthermore, there was some evidence for 'impulsive' responding on session 1 contributing to the observed performance deficits, since, although the initial thinking times were longer on methylphenidate compared with placebo, the subsequent thinking times were also lengthened. Thus, participants on drug spent more time 'thinking' once solutions were initiated on session 1.

It could be argued that the results of the present study were due to generalized or global effects of stimulant medication on cognitive behaviour, allowing the children to concentrate on performing the tasks. This explanation seems unlikely because it does not fully account for the pattern of results observed. First, general improvements in behaviour would probably have resulted in more global improvements in task performance, whereas enhancements were limited to only certain tasks, including those improved by methylphenidate in normal adult volunteers. In addition, symptom severity was not predictive of the behavioural changes observed. Indeed, such a behavioural account would not have predicted the impairments seen on the Tower of London task in children with AD/HD when on methylphenidate.

The present study was limited to 14 boys aged 9½–13½ and therefore it remains to be seen whether the findings reported here extend to girls and children of different ages. In addition, future studies should address whether the effects of methylphenidate on cognitive function differ for the inattentive subtype of DSM-IV AD/HD (Nigg, Blaskey, Huang-Pollock, & Rappley, 2002) and AD/HD children with significant comorbid diagnoses.

The results of this study have provided support for the hypothesis that methylphenidate modulates the

performance of tasks dependent on intact frontostriatal structures, thereby ameliorating frontostriatal dysfunction in AD/HD (Shue & Douglas, 1992). Preliminary evidence was also provided suggesting that these effects may be detrimental as well as beneficial to the functioning of such systems, depending on the cognitive tasks employed. These results have potential implications for the understanding of the catecholamine systems in AD/HD and may provide insights into underlying differences in these systems from normal volunteers. If confirmed in a larger sample size, the findings may also have relevance for clinical practice. Baseline assessments of cognitive function may aid treatment choice, and 'cognitive monitoring' may be advisable during treatment and at times of medication withdrawal.

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Appendix

Performance of a group of control children across 2 test sessions

Measure	Session 1	Session 2
Pattern recognition		
Percentage correct	89.58 (2.26)	88.69 (2.88)
Response latency (ms)	2179 (117)	2014 (140)
Spatial recognition		
Percentage correct	70.40 (4.01)	78.21 (3.62)*
Response latency (ms)	2138 (162)	2115 (220)
Spatial working memory		
Between-search errors	33.1 (5.81)	29.36 (5.07)
Within-search errors	1.29 (.46)	64 (.23)
Strategy score	35.7 (1.63)	32.86 (1.63)*
Tower of London		
Minimum move solutions	6.57 (.48)	7.78 (.42)
Initial thinking time (ms)	2702 (285)	3173 (571)
Subsequent thinking time (ms)	976 (137)	498 (135)*
Moves (2-move problems)	2.00 (0)	2.07 (.07)
Moves (3-move problems)	3.43 (.13)	3.25 (.09)
Moves (4-move problems)	5.89 (.26)	5.57 (.20)
Moves (5-move problems)	7.27 (.34)	6.88 (.37)
Visual Search		
Percentage correct	95.8 (.79)	94.8 (1.09)
Response latency (ms)	2509 (230)	2320 (187)
Attentional-set shifting		
Stages passed	8.29 (.34)	8.43 (.37)

Values shown are mean errors with SEMs in parentheses.

*A significant practice effect revealed by repeated-measures ANOVA, $p < .05$.

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