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ORIGINAL INVESTIGATION

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Effects of methylphenidate on spatial working memory and planning in healthy young adults

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Abstract Previous studies of the effects of the psychomotor stimulant, methylphenidate, have concentrated on vigilance and reaction time tasks. In this study, the effects of methylphenidate on more complex aspects of cognition were studied using tasks from the CANTAB battery and related tests which have been shown to be sensitive to frontal lobe dysfunction. Twenty-eight young healthy men participated in a counterbalanced, double-blind, placebo-controlled study of the effects of methylphenidate. Cognitive assessment included tests of spatial working memory, planning, verbal fluency, attentional set-shifting and sustained attention. Methylphenidate had significant effects on performance of the tests of spatial working memory and planning but not on the attentional and fluency tests. When the drug was taken on the first test session, performance on the spatial tests was enhanced by the drug compared to placebo. However, when the drug was taken second, performance accuracy was impaired whereas response latencies were decreased. These results are consistent with a hypothesis that methylphenidate influences performance in two conflicting ways; enhancing executive aspects of spatial function on novel tasks but impairing previously established performance. This pattern of effects is discussed within the framework of dual, interacting arousal mechanisms.

Key words Psychomotor stimulant · Dopamine · Cognition

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Introduction

A growing body of evidence has implicated dopaminergic systems in cognitive performance. Studies both of experimental animals (e.g. Goldman-Rakic 1992) and human patients and volunteers (Clark et al. 1986; Lange et al. 1992) have converged to suggest a crucial role for dopamine (DA) in “executive” function; that is those control processes which coordinate and optimise cognitive performance (Shallice 1982; Baddeley 1986; Robbins 1996). Spatial delayed response, a test sensitive to frontal lobe damage and widely used to assess working memory in experimental animals, has been found to be impaired following 6-hydroxydopamine (6-OHDA) lesions of the dorsolateral prefrontal cortex (Brozoski et al. 1979). These deficits were reversed by administration of dopamine agonists such as L-dopa and apomorphine. Roberts et al. (1994) confirmed that DA depletions from the prefrontal cortex impaired delayed response performance in marmosets, but found a different pattern of effects in an attentional set-shifting task which appeared to depend on distinct and interacting effects on performance of striatal and cortical mechanisms.

Evidence from neurological patients also suggests that DA systems play an important role in cognition. Patients with Parkinson's disease, a disorder characterised by striatal DA depletion, show pronounced performance impairments on neuropsychological tests (e.g. Brown and Marsden 1988; Owen et al. 1992, 1995a), particularly on tests of executive function. Further, Lange et al. (1992) studied the effects of L-dopa withdrawal on the performance of patients with Parkinson's disease and found that this withdrawal selectively impaired performance on tests from the CANTAB battery that are sensitive to frontal lobe dysfunction with prominent executive components, including spatial working memory and planning.

These performance impairments following L-dopa withdrawal are compatible with the subtle enhancement

of working memory function following administration of a DA agonist in human volunteers which has recently been described by Luciana et al. (1992). The D₂ receptor agonist, bromocriptine, facilitated working memory performance and this facilitation was not secondary to non-specific activating or arousing effects of the drug. Nonetheless, it is clear that such activating and arousing effects of dopaminergic drugs may be vital to a full description of their cognitive effects. Perhaps the most widely studied indirect DA agonist, in humans and animals, is amphetamine, although this drug also affects noradrenergic mechanisms. The main behavioural effects of amphetamine and related psychomotor stimulants are that they enhance response output, leading to hyperactivity and stereotyped responding in experimental animals (Lyon and Robbins 1975; Ridley et al. 1988) and comparable effects in human subjects (Randrup and Munkvad 1967; Robbins and Sahakian 1979; Naylor et al. 1985; Clark et al. 1986).

In this study we tested the effects of methylphenidate, a psychostimulant related to amphetamine (Scheel-Kruger 1971), on several aspects of cognitive function, with particular emphasis on spatial working memory and planning. In a study of the subjective effects of the two drugs, Heishman and Henningfield (1991) found that amphetamine and methylphenidate produced a very similar pattern of effects. However, methylphenidate is not a drug of abuse and carries a lower risk of side effects than amphetamine (BMA 1992). Acute effects of a single dose include agitation, increased heart rate and headache, all of which reverse as the drug is metabolised. Methylphenidate (Ritalin) has been used clinically for many years as a treatment for attention deficit disorder and hyperactivity in children (e.g. Conners and Eisenberg 1963; Knights 1974).

Despite its clinical use, studies of methylphenidate in normal volunteers have to date largely focused on its effects on vigilance and reaction time tasks (Koelega, 1993), rather than other aspects of cognitive performance. The present study used the CANTAB neuropsychological battery and related tests to provide a comprehensive assessment of the effects of methylphenidate. This battery included a number of tests examining spatial memory and its executive control, including a self-ordered search test of spatial working memory, a test of spatial span and a test of spatial sequence generation. In addition, we included two specific tests of planning based on the Tower of London task (Shallice 1982), which differed in their demands on spatial imagery and movement sequencing. All of these tests have been used previously in the neuropsychological assessment of patients with frontal lobe excisions (Owen et al. 1990, 1995b), and Parkinson's disease (Morris et al. 1988; Owen et al. 1992, 1995a). Moreover, recent functional activation studies have revealed that these tests engage specific neural networks, including overlapping foci within the prefrontal

cortex (Baker et al. 1996; Owen et al. 1996). Several of them have also been used in earlier studies of the effects of psychoactive drugs such as diazepam and clonidine in normal volunteers (e.g. Coull et al. 1995a, b). Finally we also included several non-spatial tests of executive function, including verbal fluency, attentional set shifting and a test of sustained attention.

Materials and methods

Subjects

Twenty-eight healthy male volunteers were recruited by advertisement in the local community. A full medical history was taken prior to testing by a consultant psychiatrist (K.M.) and subjects with any history of psychiatric or biochemical illness were excluded. Subjects were asked to abstain from excessive alcohol intake on the evenings before test sessions or excessive caffeine intake on the mornings of test sessions. Subjects were assessed by the psychiatrist prior to going home. Informed consent was given by all subjects and the study was approved by the University Research Ethics Committee. The mean age of the subjects was 21.25 years (SD 1.84) and the mean NART-IQ was 119.0 (SD 4.0).

Procedure

Each subject was tested on two occasions; half received methylphenidate on the first and placebo (odourless garlic tablets, chosen because they almost exactly resembled the methylphenidate tablets in appearance) on the second, the other half received placebo first and drug second. The first eight subjects took 20 mg methylphenidate (2 × 10 mg tablets) and the others took 40 mg (4 × 10 mg). These two different doses were used in order to allow dose-dependent effects to be assessed. In fact, preliminary analysis of the results indicated no differences between the effects of these two doses and so, in the interests of clarity, subsequent analyses were performed irrespective of dose. Peak plasma concentration of methylphenidate is reached approximately 2 h after ingestion and the half life of the drug in plasma is 1–2 h (Gilman et al. 1980). Cognitive testing was therefore started 90 min after ingestion of the drug to maximise drug levels during the test session. Pulse rate and blood pressure were monitored at 30-min intervals throughout. All test sessions were in the morning, with ingestion of the drug at approximately 10 a.m. The two test sessions for each subject were separated by between 1 and 2 weeks.

Visual analogue scales

Before ingesting the drug or placebo, subjects were asked to rate themselves for feelings of "alertness", "anxiety", "tiredness" and "restlessness". These ratings were repeated just prior to the testing, 90 min after ingestion. Subjects were asked to place a cross on a 100 mm line marked "VERY" at one end and "NOT AT ALL" at the other for each of the categories.

Cognitive tests

On both sessions, subjects were given the same tests in the same order (the order in which they are described below): Subjects were given the verbal fluency test (Benton 1968) which is traditional

neuropsychological test sensitive to frontal lobe dysfunction. This test requires subjects firstly to generate as many words as they can starting with the letter "F" in 1 min. This is repeated for the letters "A" then "S" and then subjects are asked to generate as many exemplars as they can from the semantic category "ANIMALS" in 90 s. The other tests were taken from the CANTAB battery and its derivatives and have been described in detail elsewhere (e.g. Sahakian et al. 1988; Lange et al. 1992; Robbins et al. 1994; Owen et al. 1995a). Only brief details are given here.

The spatial span task is a test of spatial short term memory capacity based on Corsi's block tapping task (Milner 1971). Subjects watch a series of white boxes in a spatial array change colour before being asked to reproduce this sequence. The length of the sequences presented increases steadily up to a maximum of nine. In this study, all subjects had a spatial span of seven or more and therefore all subjects attempted at least up to three eight-box sequences. Thus it was possible to derive a sensitive measure of performance as the total errors made up to and including the eight box stage.

The spatial working memory test is a self-ordered search task which requires subjects to search through a spatial array of coloured boxes for "tokens". In this test, both between- and within-search errors can be defined (see Owen et al. 1990) but for the purposes of this investigation, these were combined as a total errors score. A measure of strategy can also be derived (Owen et al. 1990), the lower this "strategy score", the more efficiently the subject was performing the task.

The Tower of London task is an explicit test of planning, adapted from a task developed by Shallice and McCarthy (Shallice 1982) and described in detail by Owen et al. (1990) and Robbins et al. (1992). Two sets of three coloured balls are presented, arranged in three hanging pockets. Subjects have to move the balls in one of these arrangements according to specified rules, to match the other, goal, arrangement. Problems can be solved in a certain minimum number of moves (two, three, four or five moves) and subjects are told to work out the solution prior to moving any balls. Each problem has a corresponding yoked motor control task to allow independent measurement of thinking and movement time.

Subjects also performed a more recent version of the Tower of London task which reduces the motor demands placed on subjects (Owen et al. 1995a for details). Again two patterns of coloured balls are presented but subjects are asked to *work out*, using the same rules as in the previous test but without actually moving the balls, the minimum number of moves it would take to achieve the goal arrangement. The two main measures of performance are of accuracy (percentage correct) and the latency to correct solutions.

The attentional set shifting task, also known as the ID/ED paradigm, consists of a series of stages which have been extensively described elsewhere (see Owen et al. 1993 and Elliott et al. 1995). Subjects perform under two sets of conditions. In both conditions subjects are firstly trained on a series of visual discriminations and reversals with stimuli which varied along two dimensions, one relevant and one irrelevant. The critical stage of the test is the extra-dimensional shift stage, where the two conditions diverge; in one, termed "perseveration", stimuli vary along the previously *relevant* dimension and a novel dimension and subjects have to switch attention to the novel dimension, in the other, termed "learned irrelevance" stimuli vary along the previously *irrelevant* dimension and a novel dimension and subjects have to switch attention to the previously irrelevant dimension.

Subjects also performed a test of sequence generation devised by Owen et al. (1995a) in which subjects are presented with four red squares on the screen. Subjects are told that there are 24 different sequences in which each box is touched once and only once and are asked to produce as many of these sequences as possible in 24 attempts. After 24 attempts (regardless of the number of novel sequences), the first part of the test ends. In the next stage, subjects are presented with the same array of boxes, with one box highlighted by a white surround. They are asked to generate six sequences beginning with the highlighted box. This is repeated for each of the four boxes. After this stage, which teaches the subjects a strategy

to help perform the task, they are presented with four un-highlighted boxes as in the first stage, and asked to generate all 24 sequences.

Finally, the Rapid Visual Information Processing test (RVIP), adapted by Sahakian et al. (1989) from that of Wesnes and Warburton (1984) was used to assess sustained attention capacity. In this test, which is sensitive to frontal lobe damage (Coulter 1994), subjects are presented with a white box in the centre of the screen in which digits between two and nine flash one at a time in a pseudo-random order at the rate of 100 digits per minute. Subjects are asked to monitor the digits for three specified sequences of three digits and to press a response button when any of these sequences is detected. After a 1-min practice period, the test period runs for 6 min continuously.

Experimental design and data analysis

This study followed a within-subjects placebo-controlled counter-balanced crossover design as used previously (e.g. Coull et al. 1995a). Such a crossover design is advocated in drug studies where the number of subjects is small (Cochran and Cox 1957). The within-subjects placebo-controlled design, where performance of each subject is measured twice, once following administration of drug, the other following placebo, has been widely used in pharmacological studies (Hills and Armitage 1979). The data were analysed using the Statistical Package for Social Scientists (SPSS: Nie et al. 1970). The groups that had taken drug first or placebo first were matched in terms of age, NART-IQ or initial ratings on visual analogue scales. Repeated measures MANOVAs were performed with drug condition (drug or placebo) and, if applicable, level of difficulty as within-subject factors and session order (which had two levels; drug first, placebo second or placebo first, drug second; D/P or P/D) as the between-subjects variable. When significant interactions were found, these were investigated further using analysis of simple main effects (Winer 1971, p. 545).

In cross-over designs, the index of variation commonly used is not the standard error of the means but the standard error of the difference of the means (SED), which is used when one is interested in the *relationship* between variables rather than the variables themselves. The SED will therefore be used in the figures. The SED is calculated using the formula provided in Cochran and Cox (1957, p. 131):

$$SED = \sqrt{(2 \times MSe)/n}$$

MSe = mean square for the error, or residual, term

n = number of observations made

Crossover designs have the potential problem that practice may confound the interpretation of drug effects. However, between-subject effects on only the first session allow the assessment of drug effects unconfounded by practice and thus these effects were also separately analysed with ANOVA. For these analyses, the standard error of the mean was used as the most suitable index of between-subject variability.

Results

Effects of drug dose

There were no significant differences in the effects of 20 mg and 40 mg methylphenidate on the main measures used, including the subjective and physiological measures. For examples, see Table 1. There were only eight subjects in the 20 mg group of this between-subjects comparison, but the finding does suggest that *clear* dose-dependent effects were not observed.

Since there were no effects of drug dose, subsequent analyses are presented collapsed over drug dose.

Table 1 Mean values of performance variables for subjects taking 20 mg and 40 mg methylphenidate. No differences were significant at 0.05 level

	20 mg session 1	20 mg session 2	40 mg session 1	40 mg session 2
Pulse	8.8	12.0	9.3	12.3
Tiredness	-1.9	-1.9	-1.6	-2.1
Spatial working memory: errors	4.3	5.7	4.7	5.0
Tower of London: % correct	85.9	88.0	85.6	88.6
New Tower of London: % correct	93.2	88.2	95.1	87.1
RVIP: latency/ms	436	419	433	412

Separate analyses are presented for between subject comparisons on session 1 and for the full within-subjects crossover design.

Effects on the first test session only

Between-subject comparisons of methylphenidate and placebo on session 1 only enabled the effects of the drug on performance unconfounded by practice to be determined ($n = 14$ for both groups). The only significant effect seen in this analysis was on the new Tower of London test, where there was a significant drug \times difficulty level interaction [$F(3,78) = 4.34$, $P < 0.01$] due to a significant facilitatory effect of drug on four move problems. Subjects on methylphenidate solved more of the four move problems correctly than those on placebo (92.9% compared to 73.2%).

Within-subjects crossover design

Physiological measures

The three measures were systolic blood pressure, diastolic blood pressure and pulse rate and Table 2 shows

the mean maximum change in these variables (i.e. the difference between the maximum or minimum value reached and the initial value). For both blood pressure measures, there was a significant main effect of drug [$F(1,26) = 53.0$, $P < 0.001$ for systolic and $F(1,26) = 20.2$, $P < 0.001$ for diastolic]. Methylphenidate increased blood pressure equivalently whether the drug was taken on the first or the second session. For pulse rate, there was again a significant main effect of drug [$F(1,26) = 39.4$, $P < 0.01$] due to an increase in pulse when the subjects had taken methylphenidate.

Visual analogue scales

Subjects rated their feelings of anxiety, restlessness, alertness and tiredness before taking the drug or placebo and just before neuropsychological testing. Only the latter two measures showed any significant changes as shown in Table 2. For subjective alertness, there was a significant main effect of drug [$F(1,26) = 6.5$, $P < 0.05$] due to subjects becoming more alert after taking methylphenidate than after taking placebo. For the tiredness rating, there was also a significant main effect of drug [$F(1,26) = 13.4$, $P < 0.001$] with the drug acting to reduce subjective tiredness.

Cognitive tests

Verbal fluency

The mean numbers of words generated in the letter fluency subtest are shown in Table 2. Repeated measures MANOVA showed a significant session order \times drug interaction [$F(1,26) = 12.8$, $P < 0.01$] but this was simply due to a practice effect; both groups of subjects generated more items in the second session, regardless of drug condition. The mean number of items generated on the category subtest are shown in Table 3. Repeated measures MANOVA showed a significant session order \times drug interaction [$F(1,26) = 6.1$, $P < 0.01$] but again this reflected simply a practice effect with performance improving across sessions.

Table 2 Physiological measures and subjective variables taken from visual analogue scales. The values given are for the maximum change during test sessions. SEDs for the within-subjects analysis are given in the penultimate column

	Drug session 1	Drug session 2	Placebo session 1	Placebo session 2	SED	
Pulse rate	9.1	12.2	-1.4	1.4	1.2	**
Systolic BP	7.4	6.7	-2.0	-1.3	1.3	**
Diastolic BP	6.7	6.3	-0.6	1.4	1.3	**
Anxiety	-1.2	0.4	0.1	-0.7	0.5	
Alertness	0.9	1.3	0.4	-0.2	0.4	*
Restlessness	0.9	0.9	0.1	-0.1	0.4	
Tiredness	-1.7	-2.0	0.1	0.0	0.8	**

*Main effect of drug significant at 0.05 level

**Main effect of drug significant at 0.001 level

Table 3 Mean values of performance variables for subjects taking methylphenidate or placebo on the first or second test sessions. The appropriate SED for comparisons between the means is given in the penultimate right-hand column

	Drug session 1	Drug session 2	Placebo session 1	Placebo session 2	SED
Letter fluency	64.4	67.9	62.6	69.3	1.5
Category fluency	36.0	38.4	35.0	37.5	1.2
Strategy	24.8	25.7	26.4	24.1	0.8
Tower of London: movement time/ms	1163	1137	1177	1195	32
New Tower: latency correct/ms	14331	11753	13703	11442	780
Attentional set shifting: mean perseverative errors	1.6	2.2	1.5	2.0	0.1
RVIP: % correct	43.3	54.4	44.0	53.1	3.2
RVIP: latency/ms	434	415	476	460	15**

** Main effect of drug significant at 0.001 level

Spatial span

Mean errors on the spatial span task are shown in Fig. 1a. Repeated measures MANOVA showed a significant main effect of session order [$F(1,26) = 4.9$, $P < 0.05$] with the P/D subjects making more errors than the D/P subjects. There was also a significant session order \times drug interaction [$F(1,26) = 4.87$, $P < 0.05$]. This was due to subjects on placebo making fewer errors if placebo was taken on the second session than if it was taken on the first [$F(1,50) = 9.7$, $P < 0.01$] and to P/D subjects making more errors on placebo than on drug [$F(1,26) = 5.0$, $P < 0.05$]. As Fig. 1a shows, this may correspond to a relative enhancement of performance by methylphenidate in the first session. An alternative explanation is that the D/P and P/D groups show overall performance differences with the P/D group performing worse, and that the drug enhances their performance on the second session. However, there is no reason to suppose that there may be systematic performance differences between the two groups and therefore this explanation seems unlikely.

Spatial working memory

Total errors for the more difficult six and eight box problems are shown in Fig. 1b. Repeated measures MANOVA showed a significant main effect of session order [$F(1,26) = 4.4$, $P < 0.05$] due to P/D subjects making more errors than D/P subjects. There was also a session order \times drug interaction [$F(1,26) = 7.45$, $P < 0.01$]. This was due to subjects on placebo making fewer errors if placebo was taken on the second session than if it was taken on the first [$F(1,45) = 8.4$, $P < 0.01$] and to P/D subjects making more errors on placebo than on drug [$F(1,26) = 5.0$, $P < 0.05$]. As

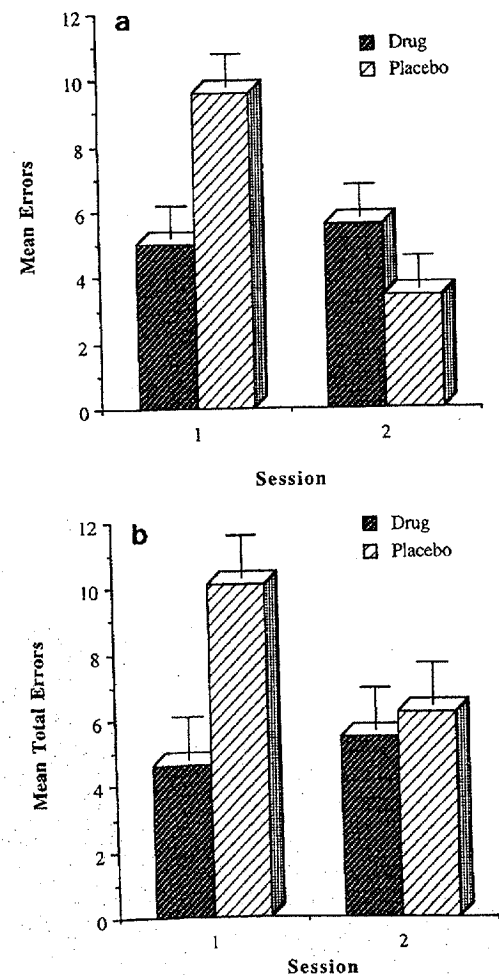


Fig. 1a, b Performance of subjects having taken drug or placebo in session 1 or session 2 on the spatial span task (a) and the most difficult six and eight box problems of the spatial working memory task (b)

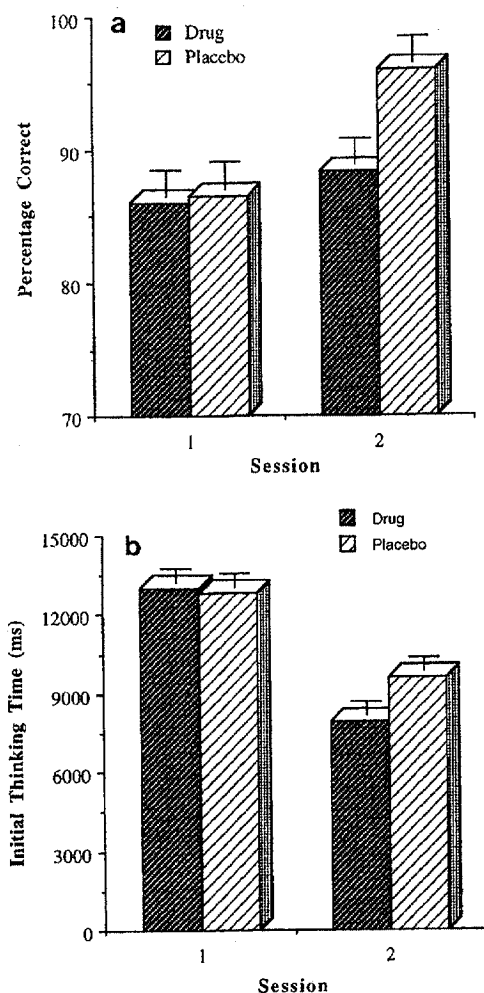


Fig. 2a, b Performance of subjects having taken drug or placebo in session 1 or session 2 on the Tower of London task. a Accuracy of performance in terms of percentage correct on the more difficult four and five move problems. b Time taken to think about the problems prior to the first move

Fig. 1b shows, this corresponds to a relative enhancement of performance by methylphenidate in the first session, as for the spatial span task above. There were no significant effects on the strategy scores (see Table 3).

Tower of London test (old version)

Performance accuracy. The accuracy measure used here was the percentage of perfect solutions at the most difficult four and five move levels as shown in Fig. 2a. MANOVA showed no significant main effects but a significant session order \times drug interaction [$F(1,26) = 4.89, P < 0.05$]. This was due to a significant effect of drug for the D/P group [$F(1,46) = 6.83, P < 0.01$] and a significant effect of session order in the placebo condition [$F(1,26) = 4.24, P < 0.05$]. This corresponds to

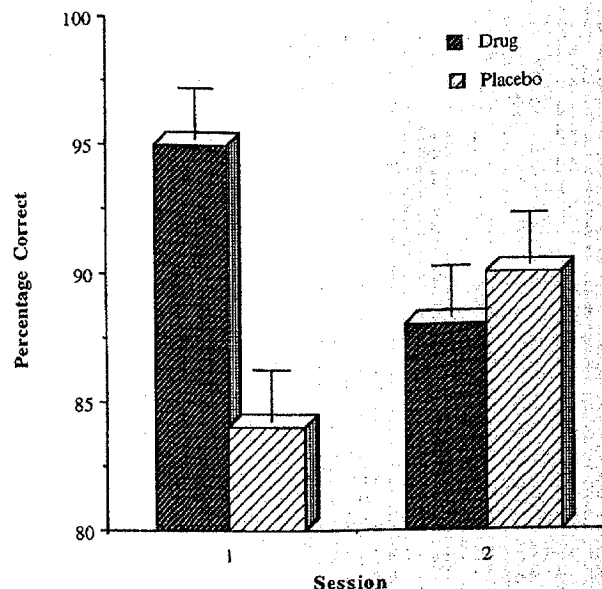


Fig. 3 Accuracy of performance of subjects having taken drug or placebo in session 1 or session 2 on the four and five move problems of the one-touch version of the Tower of London task

methylphenidate causing a relative impairment of performance on the second session.

Planning/thinking times. There were no effects of methylphenidate on the times taken to move the balls in the yoked control condition (data not shown). However, for the corrected thinking latencies (prior to the first move), there were significant effects as shown in Fig. 2b. Repeated measures MANOVA showed a significant session order \times drug interaction [$F(1,14) = 14.18, P < 0.01$]. This was due to subjects who took the drug second spending less time thinking than those who took it first [$F(1,46) = 11.4, P < 0.01$] and also to subjects who took placebo first and drug second spending less time thinking on drug than placebo [$F(1,26) = 6.8, P < 0.05$]. Thus methylphenidate reduced planning latencies in the second session.

Tower of London (new version)

For the most difficult four and five move problems, percentages solved correctly are shown in Fig. 3. Repeated measures MANOVA showed a significant main effect of session order [$F(1,26) = 5.4, P < 0.05$]. Subjects who took drug first and placebo second were more accurate than those who took placebo first and drug second. As Fig. 3 shows, this effect is mainly due to *enhancement* of performance by the drug when taken in the first session, in contrast to the *impairment* on the second session shown in the alternate version of the task (Fig. 2a). As discussed above, this was the only analysis where a significant between subjects effect on the first session only was seen, with subjects on drug

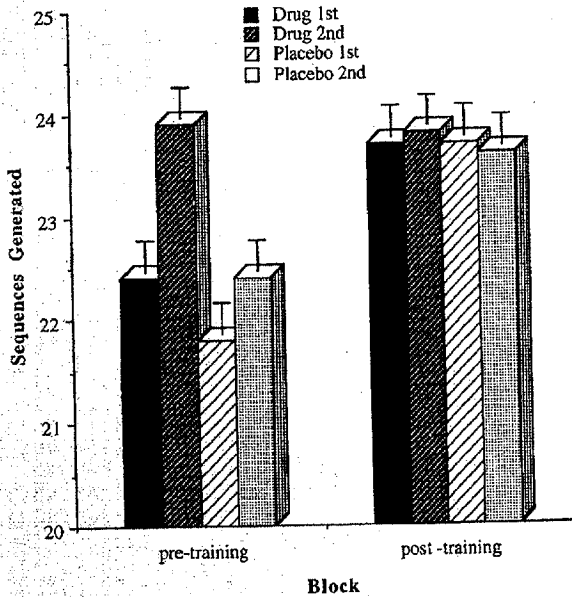


Fig. 4 Performance of subjects on the spatial sequencing task, expressed as the number of sequences generated out of a possible 24

showing enhanced performance compared to subjects on placebo.

Planning latencies are shown in Table 3. Repeated measures MANOVA showed a significant session order \times drug interaction [$F(1,14) = 8.9, P < 0.01$]. However, simple effects analysis showed this to be simply a practice effect, with both groups performing more quickly on the second session.

Attentional set-shifting task

Errors at the extra-dimensional shift stage under the two conditions are shown in Table 3. A three-way analysis of the errors at the extra-dimensional shift stage showed that there was a significant main effect of condition, with more errors being made on the perseveration condition. Methylphenidate had no effect on this set-shifting task.

Sequence generation task

The mean number of sequences generated at the pre-training and post-training attempts out of a possible 24 are shown in Fig. 4. Three-way repeated measures MANOVA showed a significant main effect of training [$F(1,26) = 3.2, P < 0.01$], due to both more sequences being generated in the post-training block, and also a significant main effect of drug [$F(1,26) = 12.2, P < 0.01$], with subjects generating more sequences on drug than placebo. There was also a significant session order \times

drug interaction [$F(1,26) = 6.9, P < 0.05$]. Simple effects analysis showed that this was due to subjects who took drug second generating more sequences on the drug than those who took it first [$F(1,52) = 5.3, P < 0.05$] and to subjects who took placebo first and drug second generating more sequences on drug than on placebo [$F(1,26) = 14.6, P < 0.01$]. Thus, methylphenidate facilitated sequence generation and, as Fig. 4 clearly shows, particularly on the second session and in the pre-training block.

RVIP task

The percentages of sequences detected are shown in Table 3. The number of false positive responses made was minimal and did not differ between groups. Therefore, since response bias was not a significant factor, it was possible to study sequences detected directly. MANOVA showed a session order \times drug interaction [$F(1,26) = 25.7, P < 0.001$]. However, this was due to a significant effect of drug in both groups, the D/P subjects detecting more sequences on placebo and the P/D subjects detecting more on drug, which is simply a practice effect. Latencies to detect the sequences were also measured and are shown in Table 2. MANOVA showed a significant main effect of drug [$F(1,26) = 14.9, P < 0.001$] with subjects responding more quickly on drug than on placebo.

Discussion

This study revealed a number of novel effects of methylphenidate on different aspects of cognitive performance particularly on tasks with a spatial component. These effects included both impairment and facilitation, depending on the familiarity and precise requirements of the task. We also observed the expected speeding of responding in the RVIP test of sustained attention and physiological and subjective effects consistent with previously reported effects of psychomotor stimulants (Koelega 1993; Camp-Bruno and Herting 1994).

Methylphenidate produced relative improvements in accuracy of performance on several of the spatial tasks (spatial span, spatial working memory, new Tower of London), though on the first session of the crossover design. On the new Tower of London task, this facilitation was also evident using the simpler but less powerful between-subject analysis of first session performance. By contrast, there were no significant effects on non-spatial tests also sensitive to frontal lobe dysfunction such as verbal fluency and attentional set-shifting. For the RVIP test of sustained attention, there were no effects on performance accuracy. The facilitation on the spatial tasks thus seems unlikely to have

resulted simply from global effects on arousal. This is further confirmed by the lack of variation of the physiological and subjective measures under the drug across the two sessions. For similar reasons, the relative impairment of performance on the second session in the old Tower of London task cannot be attributed solely to detrimental effects of elevated arousal. A full explanation of the cognitive effects of methylphenidate must account for this very different pattern of performance on the two planning tests.

One hypothesis that explains this pattern of results is that methylphenidate has dual, potentially conflicting, effects on performance. Firstly, it facilitates cognitive performance in relatively novel situations and secondly, it increases the speed of performance such that subjects respond before they have fully processed the information. This detrimental effect of impulsivity can be seen from the effects on planning latencies in the old Tower task, subjects taking drug second being significantly quicker on drug than placebo. We postulate that the facilitation effect predominates when the task is unfamiliar, hence the enhancement of performance in the first session. However, when the task is familiar, the impulsivity is predominant, hence the performance decrement in the second session. This explanation alone, though, does not account for the differences between the different versions of the Tower of London task. A further factor which must also be taken into consideration when formulating a theoretical account of these effects is the exact requirements of individual tasks. The old Tower of London task, where performance impairment was found, is particularly sensitive to premature (impulsive) responding as subjects can begin to move the balls in the array before having fully planned the solution, in contrast to the new Tower where subjects have to arrive at solutions to the problems with a single response (Owen et al. 1995a). In both tasks, subjects are explicitly encouraged to work out the answer before making any response and in both, the solution involves a series of stages of the form "move ball A to position X". In the old version of the planning task, each of these stages corresponds to a move of the final solution and there is therefore a response appropriate to each stage; in the new version, on the other hand, there is not a response corresponding to each stage but a single final response. Thus a subject performing the old Tower has to inhibit the stage by stage responses until the entire solution has been generated and an impulsive subject may fail to inhibit this responding.

This hypothesis is compatible with the rejection by Robbins (1984) and Clark et al. (1986) of a unitary concept of arousal. Robbins and Everitt (1987) suggested an alternative account which considers roles for putative "upper" and "lower" arousal mechanisms, as originally proposed by Broadbent (1971) to account for effects of drugs and other stressors on cognitive function. The upper mechanism monitors performance

under circumstances where activation of the lower mechanism is sub- or supra-optimal and serves to inhibit the detrimental effects of under- or over-arousal. Robbins and Everitt (1987) postulate that the lower mechanism may be modulated by striatal DA transmission while the upper mechanisms may depend on the dorsal noradrenergic bundle (DNAB). The present results can readily be accommodated by this hypothesis, taking into account the possible effects of methylphenidate on cortical noradrenergic as well as cortical and subcortical dopaminergic mechanisms.

By increasing striatal DA levels, methylphenidate would activate the lower mechanism, increasing responsiveness and distractibility and thereby potentially disrupting the performance of complex tasks. The upper mechanism must inhibit these disruptive effects for accurate performance and the results of this study suggest that this mechanism operates effectively in the first, but not the second, session. This is compatible with the postulated role of the DNAB which projects from the locus coeruleus, a structure which has shown to be activated by novel situations (Aston-Jones et al. 1991). In the first session, the locus coeruleus fires in response to the novel stimuli, activating the DNAB such that the upper arousal mechanism inhibits the disruptive effects of methylphenidate on the lower mechanism. On the second session, the stimuli are no longer novel and consequently the upper arousal mechanism is less effective and the supra-optimal activity induced by methylphenidate in the lower mechanism therefore becomes disruptive; response latencies decrease and performance accuracy is impaired. Thus the concept of dual arousal mechanisms can explain why methylphenidate may impair performance in the second session but not the first.

However, this account does not clearly address the reasons why methylphenidate may actually *enhance* performance accuracy in the first session on spatial tasks with executive components sensitive to frontal lobe dysfunction. There is increasing evidence that the dopaminergic system may be involved in spatial working memory processes dependent on an intact prefrontal cortex. Sawaguchi and Goldman-Rakic (1994) found that local injections of D₁ antagonists into the primate prefrontal cortex impaired performance on a spatial delayed response task. Subtle enhancement of executive function following administration of a DA agonist in human volunteers has also been described by Luciana et al. (1992), who found that the D₂ receptor agonist, bromocriptine, facilitated working memory performance.

Thus the enhancement of performance may be due to an effect of increased DA transmission to the prefrontal cortex. However, methylphenidate also releases noradrenaline, which is known to be important in the function of the prefrontal cortex (Thomas et al. 1992), a region where high densities of noradrenergic α_2 receptors have been reported (Goldman-Rakic et al. 1990).

Clonidine is an α_2 -agonist which acts presynaptically at low doses, reducing coeruleo-cortical activity and postsynaptically at higher doses, enhancing postsynaptic noradrenergic function (Arnsten and Goldman-Rakic 1985; Arnsten et al. 1988; Arnsten and Cai 1994). At low doses it impairs performance on tasks sensitive to frontal dysfunction in non-human primates (Arnsten and Goldman-Rakic 1985). At higher doses in man, Coull et al. (1995a) found some significant improvements in performance of CANTAB tests sensitive to frontal lobe dysfunction. Improvements in aspects of executive performance have also been found following administration of the α_2 -antagonist, idazoxan, which elevates functional noradrenaline levels (Smith et al. 1992). Thus, there is evidence to suggest that noradrenaline also plays a role in frontal lobe function. The enhancement of executive performance by methylphenidate may therefore depend on either dopaminergic or noradrenergic influences within the prefrontal cortex or, indeed, a combination of the two. On the first session, this enhancement combines with the effect of novelty to inhibit adequately the distractibility and impulsivity associated with supra-optimal activity in the striatal DA systems, but when the stimuli are familiar on the second session, the enhancement of prefrontal function is insufficient to compensate for the hyperactivity in the striatal systems.

This study therefore extends the existing literature on the effects of methylphenidate by establishing a consistent pattern of effects on spatial working memory and planning function. A different pattern of performance is, however, seen in the spatial sequence generation task. Subjects in both sessions under both drug conditions showed near perfect performance in the post-training state. In the pre-training stage, however, methylphenidate enhanced performance in the second session only, with subjects who took the drug second performing at post-training levels in the pre-training stage. This is a very different pattern to that seen in the other tasks. One possible explanation is that hyper-activation of the lower arousal system on the second session, as discussed above *facilitates* performance of this task. It is certainly possible that rapid disinhibited performance may be beneficial, since the longer subjects take over the task the more time they have to forget the sequences already generated. However, an alternative explanation, involving a qualitatively different performance effect from those described above, may be more plausible. This task has several components; at the initial pre-training stage, it is a strategic task which presumably relies on executive function. The training stage then *explicitly* teaches subjects an appropriate strategy so the post-training stage can be seen as a test of ability to acquire and use a strategy or of procedural learning. If the whole task is presented again after a time interval, subjects may be able to retrieve and use the strategy learned originally on session 1. The results presented in this

study suggest that methylphenidate administered just prior to the second session enhanced the retrieval of the strategy implicitly and explicitly learned in the first. Subjects who took placebo second did not retrieve this strategy and responded as though the test were unfamiliar. This is in accord with the finding of Evans et al. (1986) that methylphenidate enhanced retrieval but not acquisition processes in learning in hyperactive children.

In conclusion, this study demonstrated a consistent pattern of effects of methylphenidate on performance of tests of spatial working memory and planning. The drug enhanced cognitive performance but also increased response output (i.e. speeded response latencies), as predicted by previous studies. These dual effects tended to exert opposing influences on performance, their interactions with the novelty and precise requirements of individual tasks determining whether enhancement or impairment was observed. These findings suggest that the modulatory influence of catecholaminergic transmission on cognitive performance is complex, probably involving a delicate balance between mutually inhibitory prefrontal cortical and striatal systems.

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