Psychopharmacology (2004) 176: 331–342
DOI 10.1007/s00213-004-1899-2

ORIGINAL INVESTIGATION

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Impaired set-shifting and dissociable effects on tests of spatial working memory following the dopamine D_2 receptor antagonist sulpiride in human volunteers

Received: 12 November 2003 / Accepted: 29 March 2004 / Published online: 28 April 2004

Abstract *Rationale:* Dopamine (DA) D_2 receptor antagonists have been shown to produce similar impairments to those seen in Parkinson's disease. These include working memory and set-shifting deficits. Theories of DA function have predicted that distraction or impaired switching may be important determinants of such deficits. *Objectives:* In order to test these hypotheses, we have followed up our previous findings with more refined tests (1) that allow measurement of spatial working memory (SWM) and distraction, (2) that allow separation of executive and mnemonic components of SWM and (3) that allow isolation of set-shifting from learning deficits. *Methods:* Thirty-six young healthy male volunteers were tested on two occasions after oral administration of either 400 mg sulpiride or placebo. All participants performed the delayed response task. Sixteen participants received task-irrelevant distractors during this task, and were also given a self-ordered SWM test. The remaining participants were given delayed response tasks with task-relevant distractors, and tests of attentional and task set-shifting. *Results:* Sulpiride impaired performance of the delayed-response task both without distraction and with task-relevant distraction. By contrast, the drug protected against deficits from task-irrelevant distraction seen in the placebo group. Task set-switching was also impaired by sulpiride, with participants being slower to respond on switch trials compared with non-switch trials. There was also a trend for attentional set-shifting to be impaired following sulpiride. In contrast, self-ordered SWM performance was enhanced by sulpiride on the second test session only. *Conclusions:* These results support models of central DA function that postulate a role in switching behaviour, and in certain aspects of working memory.

Keywords Dopamine · D_2 receptor · Working memory · Set-shifting · Attention

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Introduction

Intact dopaminergic neurotransmission is important for optimal cognitive functioning within the prefrontal cortex (PFC) and striatum (e.g. Brozoski et al. 1979; Roberts et al. 1994; Dias et al. 1996; Arnsten 1998; Collins et al. 2000; Mehta et al. 2000; Crofts et al. 2001). For example, systemic administration of DA D_2 agents in monkeys appears to modulate SWM performance (Arnsten et al. 1995), while administration of specific DA D_1, but not D_2, receptor agents, directly into the PFC modulates performance on similar tasks (Sawaguchi and Goldman-Rakic 1991; Williams and Goldman-Rakic 1995). In humans, systemic administration of the DA D_2 receptor agonist, bromocriptine, or the DA receptor antagonist, haloperidol, has been shown to enhance or impair performance, respectively, on a delayed-response working memory task (Luciana et al. 1992; Luciana and Collins 1997). However, other studies have not been able to clearly replicate these findings (Kimberg et al. 1997; Müller et al. 1998). Differences in baseline levels of performance, dose of administered drugs, and specific task requirements have been suggested to account for differences among these

studies (Kimberg et al. 1997; Luciana and Collins 1997; Mehta et al. 2001).

In our previous study (Mehta et al. 1999), we demonstrated cognitive deficits following the DA D_2/D_3 (subsequently referred to as D_2) receptor antagonist sulpiride using two tasks of short-term spatial memory. The first task was a spatial recognition task taken from the CANTAB suite of tests. Although performance of this task was impaired, and an analogous non-spatial version was unaffected by sulpiride, the effects were limited to response latency and not accuracy. We have used a more refined spatial memory task in the present study, allowing a dissociation of the effects of sulpiride on maintenance in working memory from those on distraction. If distraction augments the effects of sulpiride on SWM this would imply that the drug is influencing an executive attention mechanism, rather than maintenance processes per se. The second spatial memory task impaired in our previous study (Mehta et al. 1999) required SWM, and included a defined strategic component. Although performance was impaired by sulpiride, this was limited to the first session of the crossover design used in the study. This task has affinities to the SWM task from CANTAB, which allows segregation of executive and mnemonic aspects of performance (Robbins 1996). The CANTAB task requires searching through an array of boxes for hidden tokens and benefits from a defined search strategy (Owen et al. 1990), mediated by a neural network which includes the prefrontal cortex (Owen et al. 1996; Bor et al. 2003). We have recently demonstrated that sulpiride 400 mg does *not* affect performance of this task when the maximum search array is eight boxes (Mehta et al. in preparation). However, participants recruited in these studies typically have spatial memory spans of around seven (Mehta et al. 1999, 2001), possibly limiting the sensitivity of the working memory test. We have therefore refined this test to include an additional level of difficulty with an array of 12 elements. Recently, it has been suggested that the effects of sulpiride may be less apparent in the prefrontal cortex than the striatum (Mehta et al. 2003), and that the implementation of strategy may override suppression of striatal dopamine release in some situations (Phillips et al. 2004).

The specific hypotheses tested with respect to SWM in this study were that (1) sulpiride impairs SWM as tested by the delayed response task, and (2) the effects of sulpiride would be limited during tasks requiring executive attention, via, for example, resisting distraction, or implementing strategy.

In addition to impairments in certain spatial memory tests, we previously demonstrated impaired attentional set-shifting following sulpiride 400 mg, particularly when the tests were novel to subjects (Mehta et al. 1999). The attentional set-shifting task used is sensitive to frontal lobe damage (Owen et al. 1991; Pantelis et al. 1999), and activates discrete regions of the anterior frontal lobes in healthy volunteers (Rogers et al. 2000). The same task is also sensitive to Parkinson's disease (Downes et al. 1989; Owen et al. 1992), where the major neuropathology is degeneration of the nigro-striatal dopaminergic neurones; although the dependence of the deficit on DA in Parkinson's disease is unclear (Downes et al. 1989; Lange et al. 1992; Swainson et al. 2000). The attentional set-shifting task is conceptualised as a staged discrimination-learning paradigm and as such, it confounds learning and set-shifting (Swainson et al. 2000). However, switching cognitive behaviour (i.e. reorienting sensory/internal resources to behaviourally relevant targets), at the stimulus, attentional, or task level has been postulated to involve DA neurotransmission (Redgrave et al. 1999; Suri 2002). Therefore, to minimise confounding effects of new learning, we have employed a task set-switching paradigm, which requires switching between well-established stimulus-response mappings (Rogers and Monsell 1995; Cools et al. 2001b). The task set-switching paradigm is more specific for measuring switching abilities than the attentional set-shifting paradigm, because switches are externally cued, thus reducing possible confounding effects of working memory load (Rogers and Monsell 1995). Importantly, patients with Parkinson's disease are impaired in switching between two tasks (Cools et al. 2001b), and dopaminergic medication remediates this impairment (Cools et al. 2001a). Thus, by comparison to subsequent studies in Parkinson's disease, it is unclear if our original results with sulpiride on attentional set-shifting (Mehta et al. 1999) reflect learning, working memory or shifting deficits. In order to isolate the shifting mechanism, we used a similar task set-switching paradigm to that of Cools et al. (2001a,b).

We have tested the hypotheses regarding SWM and set-shifting using sulpiride (400 mg). This dose of sulpiride was chosen because we have previously shown it can produce a distinct profile of cognitive deficits in normal volunteers (Mehta et al. 1999). A single dose was used here, because a lower dose of sulpiride (200 mg) was less effective in our previous study and possible side-effects limited the use of higher doses in healthy volunteers. Moreover, a recent PET study (Mehta et al. 2003) revealed that sulpiride 400 mg dramatically increases regional cerebral blood flow in the striatum. Therefore, this dose appears to produce distinctive neuropsychological and neurophysiological effects.

Materials and methods

Participants

Thirty-six healthy volunteers were recruited by advertisement. All volunteers were medically screened, with those evidencing current or past psychiatric, neurological or cardiac problems being excluded. Evidence of past, or current substance abuse, or alcoholism also served as exclusion criteria. All participants gave written informed consent and the study was approved by the Cambridge University Psychology Research Ethics Committee.

Participants were separated into two cohorts (see below and Table 1) of 16 and 20 members. The use of two

cohorts ensured that the length of the task battery was not unnecessarily long, thus minimising possible effects of fatigue on performance. Each participant was randomised into one of two groups in a double-blind crossover design study. Nineteen participants (13M:6F) received sulpiride 400 mg orally on the first occasion, and placebo (lactose) on the second, both presented in identical capsules (D/P group). Seventeen participants (13M:4F) received placebo then sulpiride (P/D group). One-way ANOVA revealed no differences between the two groups in terms of age [35.94, SE 2.97 years (D/P) and 35.00, SE 2.97 (P/D); $F(1,34)=0.05$, $P=0.82$] or NART-predicted verbal IQ (Nelson and Willison 1991) [116.9, SE 4.86 (D/P) and 117.5, SE 3.56 (P/D); $F(1,34)=0.17$, $P=0.69$]. Plasma level of sulpiride 400 mg peak at around 3 h after ingestion (half-life 12 ±2 h), and prolactin increases to peak levels after about 1 h, which then decline slowly (Wiesel et al. 1982; von Bahr et al. 1991). As with our previous study (Mehta et al. 1999), cognitive testing was therefore started 90 min after capsule ingestion to maximise drug levels during the experiment. For each participant both visits were at the same time of day and the test sessions were separated by 1–4 weeks.

Cognitive tests

With the exception of the visual analogue scales, all tasks were presented on a Datalux computer fitted with a touch-sensitive screen for responses where appropriate. Not all participants performed all tests. The delayed-response task without distraction was performed by all participants. Sixteen participants (cohort 1) also performed the same test with "simple" distraction, as well as reaction time and self-ordered SWM tests. The remaining twenty participants (cohort 2) performed the delayed-response task with "complex" distraction, and tasks of attentional-shifting and task set-switching. The tests given to participants in each cohort are summarised in Table 1. There was no difference between the two cohorts of participants in terms of age, or NART predicted IQ. However, it should be noted that all female volunteers ($n=10$) were in cohort 2; thus where appropriate, possible effects of cohort and gender were examined.

Visual analogue scales

Prior to drug administration, participants were asked to rate themselves on a 100 mm line in terms of 16 scales including Alert-Drowsy, Troubled-Tranquil and Happy-Sad (Bond and Lader 1974). Administration of the scales was repeated just prior to cognitive testing.

Delayed-response task

This test was based on the spatial delayed-response tasks previously used with both monkeys and humans (e.g. Sawaguchi and Goldman-Rakic 1991; Luciana et al. 1992). Initially, a fixation-cross was displayed in the centre of the screen shortly followed by a target (a white, filled circle) in a pseudo-random location elsewhere on the screen. It was the location of this target that was to be remembered. After 150 ms (too short an interval to permit a successful saccade to the targets, on average), the entire screen went blank. The central fixation-cross was also removed to prevent participants remembering the target location relative to this. Participants were then cued by a beep to touch the screen exactly where they saw the target circle. In order to test visuo-perceptual abilities, a control condition was included in which there was no delay. Participants were instructed to touch the screen, exactly where they saw the target, immediately after it appeared on the computer screen. Following three practice trials, eight test trials were administered with no delay. Sixteen trials utilising an 8-s delay period were then presented.

Delayed-response task with distraction (simple and complex)

This test was similar to the delayed-response task, with the exception that visual distractor(s) were presented during

Table 1 A summary of tasks and their variants given to the two cohorts in this study. *n.s.* not significant

Task/measure	Cohort 1 ($n=16$)	Cohort 2 ($n=20$)	Effects
Visual analogue scales	✓	✓	n.s.
Delayed response task			
0 s delay	✓	✓	n.s.
8 s delay (no distraction)	✓	✓	[a]
8 s delay simple distraction	✓	–	n.s.
8 s delay complex distraction	–	✓	[a]
12 s delay complex distraction	–	✓	[a]
Reaction time			
Simple	✓	–	n.s.
Choice	✓	–	n.s.
Self-ordered SWM	✓	–	[b]
Attentional set-shifting (ID/ED)	–	✓	[b]
Task set-switching	–	✓	[a]

[a]Tasks/measures impaired by administration of sulpiride 400 mg

[b]Interaction effects with sulpiride 400 mg (see text for details)

the delay period. For "simple" distraction, a distractor appeared on the screen for 2 s, 2.5 s after the target disappeared. It is termed "simple" here, as participants are not required to make any responses in relation to the distractor, i.e. the distractors were task-irrelevant. In one set of 16 trials, the location of the distractor was "predictable" (i.e. it was always presented in the same location) and in the other condition (16 trials) the location of the distractor was "unpredictable" (i.e. it was presented in a pseudo-random location on each trial). The average distance of distractors from the targets did not differ between the two conditions. Participants were instructed not to remember the location of the distractors. Initial pilot investigations showed that the use of a distractor identical to the target sometimes led to confusion about which of the target and distractor locations was to be remembered and, therefore, the distractor was a white filled diamond. As with the no distractor condition, following the 8-s delay, participants were cued to touch the location of the target stimulus with one finger by a computer beep.

During "complex" distraction participants were presented with either one or four unpredictable distractors during the delay period. The distractors in this task were single letters from A to H, the same size as the target circles. We have termed these trials "complex" distraction here because, unlike the "simple" conditions, participants were asked to read the distractors aloud, but told that there was no need to remember them, i.e. the distractors were task-relevant. Letters were chosen to ensure participants "reoriented" to the distractors (this could not be tested in the "simple" distractor condition). Single distractors appeared, as in the simple condition, after 2.5 s and the multiple distractors were evenly spaced throughout the delay period. Two blocks of 32 trials were presented; for one block participants were given an 8-s delay period and the other a 12-s delay.

Reaction time

The simple and choice reaction time test (Sahakian et al. 1993) required participants to hold down a response-pad whilst looking at a white circle situated alone in the middle of a computer screen (simple), or alternatively at five white circles in a circular arrangement around the screen (choice). When a yellow dot briefly appeared in a white circle, participants were to release the response-pad as quickly as possible and touch the circle where the dot appeared. Following training, participants performed the test until ten correct trials were recorded. This test did not have a mnemonic component and was included as a simple attentional control for the delayed-response task.

Self-ordered spatial working memory

This working memory task was modified from (Owen et al. 1990). Participants were initially presented with three coloured boxes on the screen and instructed to search through them for blue tokens, which were hidden, one at a time, behind the coloured boxes. Once a token had been found, participants placed them 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 three boxes and then four problems with four boxes, four problems with six boxes, two problems with eight boxes and two additional problems with 12 boxes. Two type 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). The use of a strategy known to be beneficial to performance was also recorded (Owen et al. 1990).

Attentional set-shifting (3D-IDED)

This test of attentional set-shifting is based on the version available in the CANTAB battery (Downes et al. 1989). The version used in this study incorporates an additional dimension, making a total of three, and has been described in detail elsewhere (Mehta et al. 1999; Rogers et al. 1999); hence only a brief description will be given here. There are eight stages 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) and then maintain performance with new exemplars and the introduction of two irrelevant dimensions [compound discrimination (CD)]. Then participants are required to again reverse the learned discrimination (CDR). In the fifth stage, new exemplars are again introduced and the relevant dimension is the same as in the CD and CDR stages. This is termed an intra-dimensional shift (IDS) and is followed by a reversal of the learned discrimination (IDR). The seventh stage of this test again involves the introduction of new exemplars, but this time participants must shift their attention to one of the previously irrelevant dimensions [an extra-dimensional shift (EDS)] and finally reverse this rule [extra-dimensional reversal (EDR)]. The two irrelevant dimensions are randomly associated with the relevant dimension. The EDS stage is akin to a category shift in the Wisconsin Card Sort Test (Grant and 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.

Task set-switching (Cools et al. 2001b)

On each trial, participants were shown a stimulus comprising two adjacent characters on a computer screen. The background colour of the stimulus window determined the task to be performed; participants were required

to either make a button press to indicate a letter, or a number. The letters were sampled randomly from the set {G, K, M, P, R, A, E, U}, digits from the set {2, 3, 4, 5, 6, 7, 8, 9}. For the letter task, one stimulus was always a letter and similarly for the number task and for both tasks the target stimulus was randomly presented as the left or right of the stimulus pair. Participants were required to switch between letter and digit tasks on every second trial. In addition individual trials were crosstalk or no-crosstalk conditions. In the no-crosstalk condition, the stimulus consisted of attributes, which were only associated with the relevant task. The irrelevant character was a neutral, non-alphanumeric character chosen randomly from the set {?, *, %, #}. It was presumed that filtering of irrelevant information was not necessary to perform well in the no-crosstalk conditions. In the crosstalk condition, the irrelevant character was a neutral character, but only on 33% of the trials. On 67% of the trials, the irrelevant character was associated with the competing, irrelevant (letter or digit) task. Thus, in this case the stimulus contained both a letter and a digit. Therefore, for these trials filtering of irrelevant information was needed to perform well. Participants are instructed to respond as quickly as they can without making too many mistakes. A card with a green and a red colour-pallet with the words "letter" and "number" was placed beneath the computer screen to help the participants remember the colour-task associations

Initially, participants were given training on a series of no-crosstalk trials comprising two 24-trial blocks of digit-identification and two 24-trial blocks of number-identification tasks (alternating twice). After each block the mean response latency and number of errors for that block were shown on the computer screen. Following training, the test consisted of the two experimental conditions, crosstalk and no-crosstalk. The sequence of the crosstalk and no-crosstalk conditions was counterbalanced within the two groups. Each experimental condition, comprising four blocks of 40 trials, was preceded by a practice session of two blocks of 40 trials. The mapping of the colour green and red with the letter-identification and the digit-identification tasks was also counterbalanced within the two groups. The stimulus pairs remained on the screen until a button press response was made and the response-stimulus interval was 1000 ms.

Statistical analyses

Measures from the scales and cognitive tasks were analysed using parametric, or non-parametric tests as appropriate. Parametric analyses were conducted using repeated-measures ANOVAs, with appropriate within-subjects and between-subjects factors. Significant interactions were explored using analysis of simple effects (Winer 1971). Non-parametric Wilcoxon signed-ranks matched pairs tests were used to analyse related measures (e.g. drug and placebo scores). Mann–Whitney *U* was used to analyse unrelated measures.

Pearson's product moment correlation coefficient, *r*, was used to test possible relationships between "baseline" performance (placebo performance was used in this study) and the effect of sulpiride (drug-placebo). In examining this baseline-dependent effect the so-called "a(a–b)" effect was controlled for as suggested by Myrtek and Foerster (1986) and tested using a *t*-test.

When error bars are shown in the figures they are the standard error of the mean. More appropriate for within-subjects designs is the standard error of the difference of the means (i.e. the error on the "drug effect"), which is defined as $\sqrt{(2\times MSe/n)}$, where Mse is the residual term and n is the number of observations (Cochran and Cox 1957). The SED is shown in the figure or given in the figure legend.

Results

Results for tasks given to all participants

Visual analogue scales

The scales for one participant were incomplete and therefore the results presented in Table 2 and the analyses are for 35 participants. The 16 visual analogue scales were collapsed into two factors, alertness and tranquillity as described by Herbert et al. (1976). There were no effects of sulpiride on the ratings of factor 1 or 2 [$F(1,33)=2.85$, $P=0.10$; $F(1,33)=0.06$, $P=0.81$, respectively], although participants in general reported feeling less alert over time [$F(1,33)=15.47$, $P<0.001$].

Table 2 Scores on two factors of the visual analogue scales before and 90 min after sulpiride 400 mg or placebo. Values are the average scores (range 0–100) across nine items for factor 1 and seven items for factor 2 with standard errors in parentheses. *SED* standard error of the difference of the means

Scale	Sulpiride		Placebo		SED
	Before	After	Before	After	
Factor 1 (Alertness)	66.1 (3.0)	62.6 (3.2)	71.1 (2.9)	65.2 (3.0)	1.16**
Factor 2 (Tranquillity)	69.7 (2.7)	68.2 (2.9)	69.1 (3.0)	69.6 (2.6)	0.96

Main effect of time, **$P<0.01$

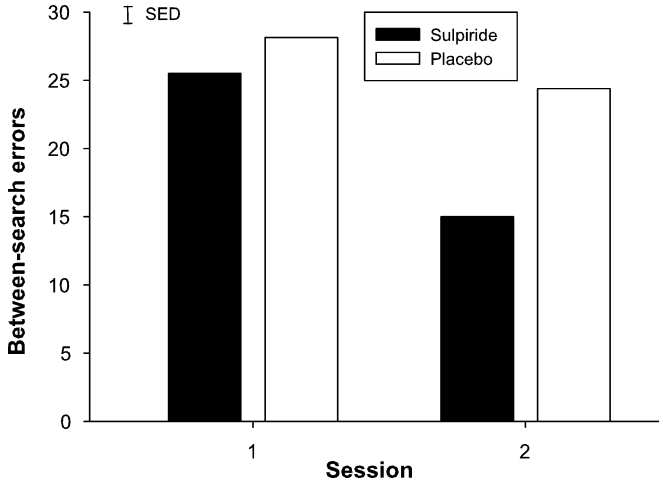

Fig. 2 Mean between-search errors for 6, 8 and 12 box problems on the modified self-ordered SWM task (n=16). Those on drug performed better on the second session (P<0.01). SED=1.28 errors

Delayed-response task without distraction

For this task, analysis was conducted using repeated-measures ANOVA with drug and delay as within-subjects factors and order (D/P or P/D) and cohort as between-subjects factors. For the error measure (see Fig. 1a) there was a main effect of drug [F(1,31)=9.19, P=0.005] and a main effect of delay [F(1,31)=44.4, P<0.001]. Participants performed worse on the 8 s delay trials and worse overall on sulpiride. However, there was no interaction between drug and delay [F(1,31)=0.86, P=0.36] and no other significant main or interaction effects.

There was no significant main effect of sulpiride on response latency for this task [F(1,31)=0.91, P=0.76], although there was, as expected, a main effect of delay [F(1,31)=57.9, P<0.001]; see Fig. 1b. In addition, there was a significant interaction between cohort and delay [F(1,31)=18.5, P<0.001], due to those in the first study (n=16) evidencing a smaller effect of delay than those in the second study (n=19) (mean differences 102 and 421 ms, respectively).

Therefore, sulpiride 400 mg impaired the delayed response task without distraction in terms of performance accuracy.

Delayed response with distraction

For those in cohort 1 who were given the task with simple distraction (a single white diamond during delay period) there was no effect of drug on response error [F(1,14)=0.65, P=0.43], or response latency [F(1,14)=0.14, P=0.71]; see Fig. 1. There was, however, a significant interaction between drug and order for response latencies [F(1,14)=8.44, P=0.012], due to practice for both groups (session 1 and session 2 scores: D/P, 1095 and 940 ms; P/D, 1036 and 896 ms). No other main or interaction effects were statistically significant. Importantly, a separate analysis of the effects of distraction versus no distraction

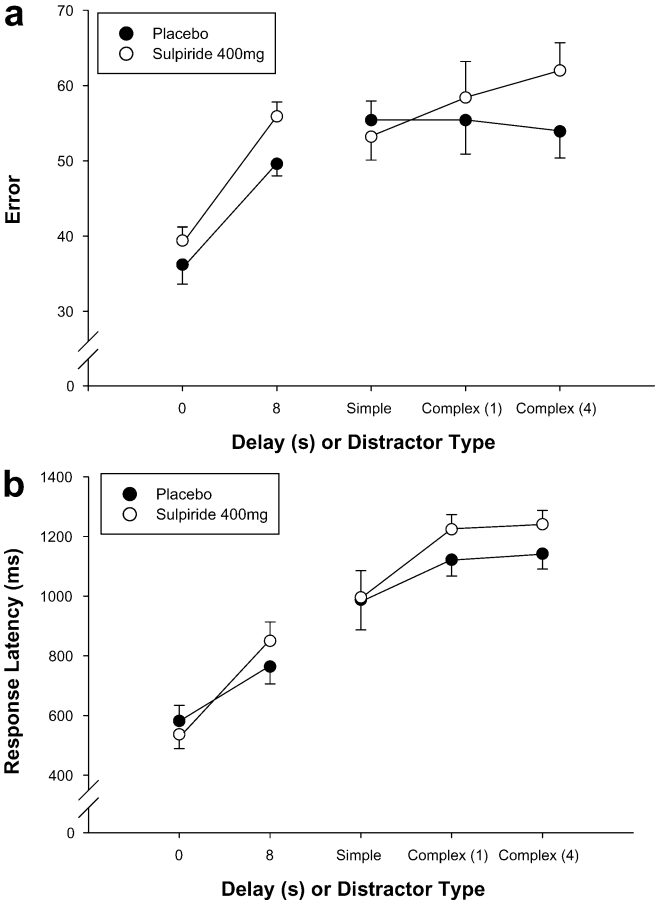

Fig. 1 Mean **a** error scores and **b** response latencies for participants across both study cohorts completing the delayed-response task without distraction (n=35), the delayed-response task with simple distraction (n=16) and complex distraction (n=19). For the task without distraction (n=35) there was a main effect of drug for error scores (P<0.01). No significant difference was observed across study cohorts, except for a cohort×delay for latency (see text for details). Error scores for cohort 1: (drug, 0 s and 8 s; placebo, 0 s and 8 s) 36.3, 57.1; 33.3, 47.6 and cohort 2: 42.5, 54.7; 39.1, 51.6. Response latencies for cohort 1: 488 ms, 961 ms; placebo, 558 ms, 928 ms and cohort 2: 579 ms, 756 ms; 596 ms, 623 ms. For complex distraction (n=19) there was a main effect of drug on error scores (P<0.05) and response latency (P<0.01). Numbers in parentheses indicate the number of distractors. SED for delay error=1.19, for delay latency=21.9. SED for simple distraction error=1.87, for complex distraction error=2.48, for simple distraction latency=38 ms, for complex distraction latency=10 ms

revealed an interaction between drug and distraction for response error [F(1,15)=4.50, P=0.05], due to distraction impairing performance on placebo, but *not* on drug [F(1,15)=12.28, P<0.01 and F(1,15)=0.73, P=0.41, respectively; placebo error mean scores for no distraction and distraction: 47.6, SEM 2.6 and 55.4, SEM 2.6; drug error mean scores: 57.1, SEM 4.7 and 53.2, SEM 3.1]. Therefore, while distraction worsened performance on placebo, 400 mg sulpiride did not significantly alter the performance of the delayed response task with simple distraction.

For the analysis of the task with complex distraction (one or four letters, given to cohort 2) there were no clear effects of delay (8 or 12 s) and therefore, for reasons of

clarity, the results are presented collapsed across delays. Sulpiride significantly increased the response error [$F(1,17)=5.05$, $P=0.038$] as shown in Fig. 1a. It interesting to note that increasing distraction (from 1 to 4 letters) did not appear to worsen performance in the placebo group (see Fig. 1a), suggesting that distraction per se leads to increased errors in those on placebo (see above). There were no other main or interaction effects, except for a delay×distractor interaction [$F(1,17)=4.81$, $P=0.042$]; however, post hoc tests did not elucidate this interaction further. Response latencies were longer after sulpiride compared with placebo [$F(1,17)=8.89$, $P=0.008$]. There were no other main or interaction effects for response latencies.

In summary, sulpiride impaired performance on the delayed-response task either without distraction, or with complex (task-relevant) distraction in terms of response error for both tasks and also in terms of response latency for the latter task. However, sulpiride *protected* against deficits caused by minimal levels of distraction.

Results for other tests given to cohort 1 only

Reaction time

There was no main effect of sulpiride on the reaction time measurements [$F(1,14)=0.47$, $P=0.51$] and no significant interaction effects with group or task (simple versus choice). As expected, participants had slower choice reaction time compared with simple reaction time [$F(1,14)=17.23$, $P=0.001$]: average simple reaction time was 352 and 344 ms on drug and placebo, respectively, and choice reaction time 366 and 361 ms (SED=5.9 ms).

Self-ordered spatial working memory

There was a tendency for those on drug to make *fewer* between-search errors than those on placebo [$F(1,14)=3.84$, $P=0.07$]. However, there was also a significant interaction between drug and order [$F(1,14)=5.36$, $P=0.036$], due to participants making significantly fewer errors on drug on the second session [$F(1,14)=8.49$, $P=0.023$]. This effect is illustrated in Fig. 2. As expected, participants made more between-search errors as difficulty increased [$F(2,28)=26.18$, $P<0.001$]; data not shown. In addition, there was a three-way interaction between drug, order and difficulty level [$F(2,28)=10.52$, $P<0.001$]. This reflected the greater contribution of the most difficult (12 box) problems to the improved performance on drug on the second session [$F(1,14)=15.86$, $P<0.01$], with those on drug making, on average 22.9 errors on session 1 and 10.25 errors on session 2. The apparent improved performance by drug on the second session remained significant even after controlling for NART IQ and age to exclude a possible group effect. There was no effect of sulpiride or order for within-search errors [$F(1,14)=2.46$, $P=0.14$; $F(1,14)=0.73$, $P=0.41$], although there was a trend toward a significant drug×order interaction [$F(1,14)=3.85$, $P=0.07$], but this simply reflected practice across both groups (see Table 3). There were no significant effects for the strategy score ($F<1.85$); see Table 3.

Results for other tests given to cohort 2 only

Attentional set-shifting (3D-IDED)

The mean number of stages reached did not differ for those on drug or placebo ($z=0.42$, $P=0.42$). However, all stages of this task were completed by 17 participants on drug and 15 on placebo, and therefore the other performance measures were only analysed for those 15 who completed the task under both condition (8 D/P, 7 P/D). For this sub-group there was no difference in the number of errors made up to (but excluding) the intra-dimensional shift stage [$F(1,13)=0.09$, $P=0.77$). There was also no effect of order [$F(1,13)=0.62$] and no drug×order interaction [$F(1,13)=3.31$] for the same measure. For the

Table 3 Performance of participants on sulpiride 400 mg or placebo on the self-ordered SWM and 3D-IDED tasks on sessions 1 and 2 of the crossover design. SED values are shown for values analysed parametrically and non-parametrically for completeness

	Drug 1st	Placebo 1st	Drug 2nd	Placebo 2nd	SED
Self-ordered SWM					
Within-search errors	1.13	3.00	0.88	0.75	0.45[a]
Strategy score	28.6	30.4	27.9	28.9	0.72
3D-IDED					
Errors up to IDS	5.0	6.6	2.8	3.4	0.74
ID-stage errors	1.8	2.9	2.3	2.1	0.33
ED-stage errors	8.5	8.1	5.9	3.9	1.18
Latency (up to IDS)	2713	2825	1978	2076	59.6[b]
Latency (ID-stage)	2155	2234	1831	2091	
Latency (ED-stage)	2109	2980	1819	1868	
Task set-switching					
Errors (switch trials)	0.038	0.024	0.067	0.017	0.01
Errors (non-switch)	0.014	0.008	0.021	0.011	
Latency (switch)	1595	1156	1109	1162	42[c]
Latency (non-switch)	937	898	1100	762	

[a]Trend towards practice effect, $P<0.10$

[b]Two-way interaction between drug and stage, $P<0.05$. All latency values were analysed parametrically: SED value shown is therefore for drug×order×stage

[c]Main effect of drug, $P<0.05$; see text for interaction effects

crucial ID and ED stages, errors across the discrimination and reversal stages were summed, due to the low numbers of errors made, as in our previous study (Mehta et al. 1999). Mean errors are shown in Table 3. Total errors for the ID-stage were not normally distributed and, therefore, were analysed non-parametrically, which did not reveal a drug effect (z=−0.82, P=0.41). For the ED-stage there was no main effect of drug [F(1,13)=0.49, P=0.50], although there was a strong trend for a drug×order interaction [F(1,13)=4.24, P=0.06], due to those in the D/P group tending to make more errors on drug on the first session [F(1,7)=3.61, P<0.10]; see Table 3. For response latencies, parametric analysis was suitable and revealed interaction effects between drug and order [F(1,13)=20.5, P=0.001], and drug and stage (stages up to ID-stage, ID-stage and ED-stage) [F(2,26)=3.64, P=0.04], but no main effect of drug [F(1,13)=0.44, P=0.52]. The former significant interaction effect represented practice, whereas the latter represented a speeding of responses on sulpiride for the ED-stage [F(1,13)=6.08, P=0.028], but not for the stages leading up to the ID-stage or the ID-stage itself (F<1).

In summary, sulpiride only affected the ED-stage of this test. Participants tended to make more errors at this stage of the test, but only on the first test session, and also responded significantly faster at this stage, across both sessions.

Task set-switching

For this task, errors and response latencies were the main measures analysed. Nineteen participants were included in the analysis as the data for one participant were incomplete due to a computer error. The proportions of errors made were very low and were not suitable for parametric analysis, even after transformation. Using non-parametric analysis we did not find a main effect of switch (z=−0.73, P=0.46), or an effect of drug on either the switch trials (z=−0.45, P=0.65), or the non-switch trials (z=0.31, P=0.75); see Table 3. For response latencies, using parametric analysis, we found a main effect of drug [F(1,16)=4.79, P=0.04] and switch [F(1,16)=17.9, P=0.001], an interaction between switch and order [F(1,16)=6.37, P=0.023], and an interaction between switch, order and drug [F(1,16)=4.47, P=0.05]. No other main or interaction effects were significant. Participants were, as expected, slower to respond on switch trials, and also slower following drug, but these effects did not interact [F(1,16)=0.002, P=0.97]; see Table 3. Importantly, those in the D/P group showed a specific slowing of responses on drug during switch trials [F(1,8)=12.6, P=0.008], an effect not present in the P/D group [F(1,8)=1.18, P=0.31]. This is interpreted as an impairment in switch trials following sulpiride, but only on the first session. Indeed, analysis of first session only performance confirmed this finding [drug×switch F(1,16)=6.54, P=0.02, due to the drug tending to slow switch trials, F(1,16)=4.09, P=0.06, but not non-switch trials, F(1,16)<1)], which is illustrated in Fig. 3. There was no effect of drug on errors for the first session (switch: U=37, P=0.80; non-switch: U=33, P=0.55).

In summary, sulpiride slowed response latencies on this task, an effect that was more prominent during switch trials on drug, but on session 1 only.

Effects of gender

The second cohort included ten female volunteers. There were no clear differences in the effects of sulpiride between male and female volunteers.

Effects of baseline performance

Using Pearson's product moment correlation coefficient revealed significant relationships between "baseline" performance and the effects of sulpiride for the self-ordered SWM task (r=−0.59, P=0.017, n=16), and the delayed response task without distraction (r=−0.36, P=0.035, n=35), but not for the delayed response task with "simple" distraction (r=−0.33, P=0.22, n=16) or complex distraction (r=0.03, P=0.91, n=19), or for reaction times on the task set-switching test (r=0.05, P=0.86). After controlling for the so-called a(a–b) effect (i.e. the fact that placebo scores are used in both arms of the correlation, see Materials and methods) only the delayed response task without distraction showed "baseline-dependent" changes in performance following sulpiride [t(33)=3.57, P<0.01]. Thus, those participants who performed well on placebo (relative to the other subjects) became worse on drug, and those who performed less well on placebo were unchanged or improved by the drug.

Discussion

We have shown a number of novel effects of systemic administration of the DA D_2/D_3 receptor antagonist

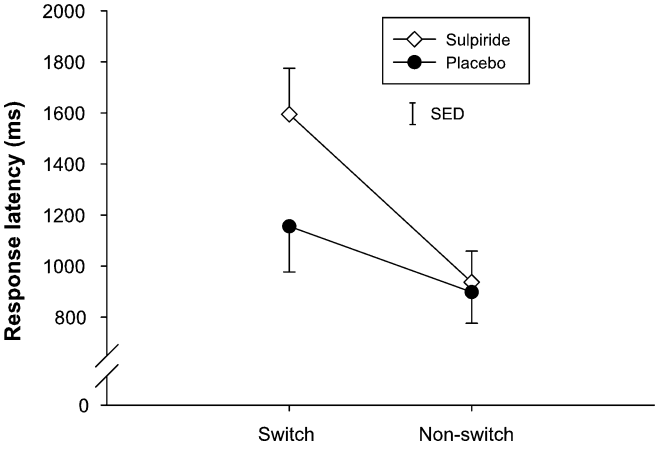

Fig. 3 Mean response latencies for the task set-switching paradigm for those who received sulpiride 400 mg (n=9) or placebo (n=9) on session 1 of the crossover design. SED=83 ms

sulpiride, in normal volunteers. The drug impaired performance on the delayed-response task, without distraction in a baseline-dependent fashion, and also under certain conditions of distraction. In addition, we demonstrated, for the first time, a robust impairment in task set-switching, but only when the task was novel to participants. Surprisingly, sulpiride protected against minimal levels of distraction on the delayed-response task and *enhanced* performance on another, more complex working memory task, but only when it was familiar to participants.

The possibility that these effects resulted from a global effect of sulpiride, due to changes in, for example, mood, arousal or response preparation, seems unlikely (e.g. Brown and Robbins 1991; Weingartner et al. 1992; Luciana and Collins 1997; Tucker et al. 1999): there was no evidence for mood changes on the visual analogue scales and the *shorter* response times on the ED stages of the attentional set-shifting task, compared with slowing on other tasks, do not fit with a global change in performance. Dissociable effects of sulpiride on task set-switching and self-ordered SWM also suggest that the findings from this study cannot easily be accounted for by a global drug effect.

The specific lengthening of switch-costs on the task set-switching paradigm following sulpiride (and the similar trend seen for the attentional set-shifting test) is in keeping with earlier suggestions that DA activity is important for the flexibility of behaviour utilising available sensory information (Cools 1980), and extends our previous finding of impaired attentional set-shifting following sulpiride (Mehta et al. 1999). However, in this study, the impairment in task set-switching was more robust statistically than for the attentional set-shifting task. This may be due to the nature of the task set-switching paradigm, in which participants continually "re-engage" well-learned response mappings, rather than learning a new attentional set. Indeed, patients with Parkinson's disease are also impaired at both switching tasks (Owen et al. 1992; Cools et al. 2001b), although medication only ameliorates task set-switching (Cools et al. 2001a, 2003) and re-engagement of a previously learned attentional set is specifically impaired following 6-OHDA lesions of the caudate nucleus in monkeys (Collins et al. 2000). Therefore, it appears that sulpiride administration was particularly effective at impairing the flexibility of behavioural selections on switching trials. This conclusion is in keeping with the significant slowing of response latencies across all trials by sulpiride, although switching trials on the first session were particularly affected. This session effect arose from the switch-cost being less on the second session compared with the first, and therefore, making the task less sensitive to the effects of sulpiride on the second session. We can speculate that reduced prefrontal cortical activation seen after practice or during learning (Raichle et al. 1994; Fletcher et al. 2001) may mediate this effect, with sulpiride acting in the striatum to influence cortico-striatal or midbrain-striatal connectivity (Honey et al. 2003), or via sulpiride acting directly in the prefrontal cortex (Cools et al. 2003; Mehta et al. 2003).

Through our findings, we have also extended considerably our understanding of the effects of DA receptor antagonists on human SWM. First, sulpiride is a more selective DA D_2 receptor antagonist than haloperidol (Kuroki et al. 1999; Strange 2001), which has been more commonly used in previous investigations (Luciana and Collins 1997; McCartan et al. 2001). Second, we have utilised tasks with varying degrees of intervening distraction allowing examination of possible executive attentional strategies which may be used in the successful performance of the spatial delayed-response task (Arnsten and Contant 1992; di Pellegrino and Wise 1993). The results were in keeping with our hypotheses that sulpiride would impair delayed-response performance, and that added distraction may limit such an impairment. Sulpiride impaired performance (reduced accuracy) of the delayed-response task without distraction, but *not* with added "simple", task-irrelevant distraction; sulpiride again impaired performance (lenghened latency and reduced accuracy) with task-relevant (or "complex") distraction. Thus, the effects of sulpiride were *not* unitary with respect to the levels of distraction used in this study. Specifically, sulpiride appeared "protective" against minor levels of, task-irrelevant, distraction. This striking pattern of results runs counter to what would be expected of D_1 receptor antagonists acting in the PFC, where an increased susceptibility to attentional disruption might be expected, according to recent hypotheses on the role of D_1 receptors in the "stabilisation of representations" (Durstewitz et al. 2000). These results also cannot easily be described by the effects of DA D_2 receptor modulation of neuronal activity in the prefrontal cortex of monkeys associated with memory-guided responses (Wang et al. 2004), where sulpiride might be expected to impair *all* conditions of our delayed-response task. However, the present data are consistent with other findings of *reduced* distractibility following DA depletion of the caudate nucleus in monkeys (Crofts et al. 2001), coupled with impaired delayed response performance (Collins et al. 2000). By reducing susceptibility to task-irrelevant distraction, sulpiride may be acting to increase attentional focussing. Thus, in conditions of minor, task-irrelevant distraction, those subjects on sulpiride, unlike those on placebo, were unaffected by the distraction, whereas with greater degrees of distraction caused by task-relevant cues, the impairment seen without distraction was reinstated. This interpretation, together with the impairments on the switching paradigms, is consistent with the aforementioned effects of DA depletion in the caudate nucleus using a distractor probe test within an attentional set paradigm leading to reduced distractibility, but impaired attentional set-shifting (Crofts et al. 2001), strongly suggesting that the effects of sulpiride on impairing the delayed-response and switching tasks are due to a common action in the striatum, rather than different actions in different brain regions.

In this study, we have shown "baseline-dependent" effects of sulpiride as described previously for other drugs (Kimberg et al. 1997, 2001; Mehta et al. 2000). However, our findings contrast with the predictions from a simple

inverted-U shaped function, where too little or too much DA can impair performance (Zahrt et al. 1997; Goldman-Rakic et al. 2001). In this study, those participants with better spatial delayed response performance accuracy scores were unchanged or impaired by sulpiride, and those with worse baseline ability were *improved*. Current theories are based on dopamine D_1 receptor function in the prefrontal cortex, and thus may not so easily translate to dopamine D_2 receptors, either in the striatum or prefrontal cortex.

The switching and delayed-response impairments seen here show a general similarity to impairments in patients with mild Parkinson's disease (Owen et al. 1992; Postle et al. 1997; Cools et al. 2001a,b), strengthening the conclusions of our previous study that the striatum may be the major site of action mediating the effects of sulpiride in normal volunteers (Mehta et al. 1999), recently confirmed using functional neuroimaging (Mehta et al. 2003). Studies in experimental animals, patients with Parkinson's disease, and now human volunteers (Collins et al. 2000; Swainson et al. 2000; Cools et al. 2001a; Crofts et al. 2001; Mehta et al. 2003) indicate that the caudate nucleus, in particular, may the specific site of dopaminergic modulation of these cognitive functions.

The lack of effect of sulpiride on impairing the self-ordered SWM task on session 1 was in keeping with our hypothesis that the effects of sulpiride may be limited in tasks with a strategic component. It was, however, surprising that there was an apparent *enhancement* in self-ordered SWM performance in participants on sulpiride, particularly on session 2, when the task was familiar to them. Such an effect is not unprecedented—sulpiride has previously been shown to enhance planning performance, but only when the task was familiar to volunteers, or after defined training (Mehta et al. 1999, 2003), and methylphenidate (an indirect catecholamine agonist) has been shown to *impair* performance on a similar planning task when the task was familiar to volunteers (Elliott et al. 1997). However, L-dopa withdrawal impaired performance on the same working memory task in patients with Parkinson's disease (Lange et al. 1992) and methylphenidate improved working memory performance in normal volunteers (Elliott et al. 1997; Mehta et al. 2000), suggesting that the effects in these studies may have been mediated via DA D_1 receptors or noradrenergic receptors, possibly in the PFC, in keeping with research in experimental animals (Sawaguchi and Goldman-Rakic 1991; Arnsten and Contant 1992). Indeed, sulpiride is a relatively specific DA D_2/D_3 receptor antagonist and the family of DA D_2 receptors are far more prominent in the striatum than the cortex where they are outnumbered 9:1 by DA D_1 receptors (Camps et al. 1989; Cortes et al. 1989). Moreover, DA D_2 receptor activation can actually oppose the regulation of prefrontal GABAergic activity by DA D_1 receptors in the PFC (Seamans et al. 2001).

An alternative explanation of the apparent improved SWM performance on session 2 could be that sulpiride impaired post-trial learning on session 1, thereby leading to relatively poor performance by those on placebo on session 2 (see Mehta et al. 1999). We must also consider the possibility that differences in task requirements between the delayed-response and self-ordered SWM tasks account for their differential sensitivity to sulpiride. For example, the self-ordered SWM task benefits from a search strategy (Owen et al. 1990) and therefore, the "executive" nature of this task makes it more similar, in some respects, to a planning task than the delayed-response test. It is possible that the strategic component in the self-ordered SWM, mediated by the lateral prefrontal cortex (Owen et al. 1996), opposed deleterious effects of sulpiride in the striatum that may affect SWM (as in the delayed-response task) (Phillips et al. 2004), or putative, task-related dopamine activity antagonised the drug effect (similar to the delayed-response task with "simple distraction").

Overall, the pattern of impairments in this study is compatible with the hypothesis that DA neurotransmission in the striatum plays an important role in orienting, or switching to salient stimuli (Redgrave et al. 1999; Spanagel and Weiss 1999). Thus, not only did sulpiride impair set-switching, but also "protected" against the effects of "switching" to task-irrelevant distractors. Although sulpiride also impaired delayed-response performance without distraction, all the data are not obviously explained by theories that DA mediates working memory per se (Durstewitz et al. 1999, 2000; Goldman-Rakic 1999; Dreher and Burnod 2002), or with the hypothesis that DA neuron firing can act as a prediction error signal in reinforcement learning (Schultz et al. 1997; Suri 2002). Indeed, it is quite difficult to find evidence of sulpiride (or dopaminergic medication withdrawal in patients with Parkinson's disease) modulating associative learning (Lange et al. 1992; Mehta et al. 1999; Mollion et al. 2003). Studies using trial-and-error reinforcement learning tasks in humans will be important to address these issues more directly in future studies.

While the main deficits produced by sulpiride may be best described by its action within the striatum, additional influences within the prefrontal cortex, or via the cortico-striatal circuitry may help explain the overall pattern of findings in this study, including the session-specific effects for the task-set-switching and self-ordered SWM tasks. The present study did not address the influence of sulpiride within distinct brain structures during set-switching and working memory task, but strongly suggest that in order to fully interpret similar studies, combining fMRI or PET neuroimaging techniques with sophisticated neuropsychological methods will be vital for determining the relative contributions of these regions in the effects of dopaminergic agents (Cools et al. 2003; Mehta et al. 2003).

Acknowledgements We thank the volunteers for their participation in this study and Dr. Ulrich Müller for his comments on a draft of this manuscript. This work was supported by a Wellcome Trust Programme Grant awarded to T.W.R., B.J.S., B.J. Everitt and A.C. Roberts and was completed within the MRC Centre for Behavioural and Clinical Neuroscience. M.A.M. was supported by a MRC research studentship.

References

Arnsten AFT (1998) Catecholamine modulation of prefrontal cortical cognitive function. Trends Cognit Sci 2:436–447

Arnsten AF, Contant TA (1992) Alpha-2 adrenergic agonists decrease distractibility in aged monkeys performing the delayed response task. Psychopharmacology 108:159–169

Arnsten AF, Cai JX, Steere JC, Goldman-Rakic PS (1995) DA D_2 receptor mechanisms contribute to age-related cognitive decline: the effects of quinpirole on memory and motor performance in monkeys. J Neurosci 15:3429–3439

Bond AJ, Lader MH (1974) The use of analogue scales in rating subjective feelings. Br J Med Psychol 47:211–218

Bor D, Duncan J, Wiseman RJ, Owen AM (2003) Encoding strategies dissociate prefrontal activity from working memory demand. Neuron 37:361–367

Brown VJ, Robbins TW (1991) Simple and choice reaction time performance following unilateral striatal DA depletion in the rat. Impaired motor readiness but preserved response preparation. Brain 114:513–525

Brozoski TJ, Brown RM, Rosvold HE, Goldman PS (1979) Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. Science 205:929–932

Camps M, Cortes R, Gueye B, Probst A, Palacios JM (1989) Dopamine receptors in human brain: autoradiographic distribution of D_2 sites. Neuroscience 28:275–290

Cochran WG, Cox GM (1957) Experimental designs. Wiley, N.Y.

Collins P, Wilkinson LS, Everitt BJ, Robbins TW, Roberts AC (2000) The effect of DA depletion from the caudate nucleus of the common marmoset (*Callithrix jacchus*) on tests of prefrontal cognitive function. Behav Neurosci 114:3–17

Cools AR (1980) Role of the neostriatal dopaminergic activity in sequencing and selecting behavioural strategies: facilitation of processes involved in selecting the best strategy in a stressful situation. Behav Brain Res 1:361–378

Cools R, Barker RA, Sahakian BJ, Robbins TW (2001a) Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. Cereb Cortex 11:1136–1143

Cools R, Barker RA, Sahakian BJ, Robbins TW (2001b) Mechanisms of cognitive set flexibility in Parkinson's disease. Brain 124:2503–2512

Cools R, Clark L, Bullmore ET, Robbins TW (2003) Dopaminergic modulation of inhibitory control: an event-related fMRI study. Neuroimage 19:S31

Cortes R, Gueye B, Pazos A, Probst A, Palacios JM (1989) Dopamine receptors in human brain: autoradiographic distribution of D_1 sites. Neuroscience 28:263–273

Crofts HS, Dalley JW, Collins P, Van Denderen JC, Everitt BJ, Robbins TW, Roberts AC (2001) Differential effects of 6-OHDA lesions of the frontal cortex and caudate nucleus on the ability to acquire an attentional set. Cereb Cortex 11:1015–1026

Dias R, Robbins TW, Roberts AC (1996) Dissociation in prefrontal cortex of affective and attentional shifts. Nature 380:69–72

di Pellegrino G, Wise SP (1993) Effects of attention on visuomotor activity in the premotor and PFC of a primate. Somatosens Mot Res 10:245–262

Downes JJ, Roberts AC, Sahakian BJ, Evenden JL, Morris RG, Robbins TW (1989) Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. Neuropsychologia 27:1329–1343

Dreher JC, Burnod Y (2002) An integrative theory of the phasic and tonic modes of DA modulation in the PFC. Neural Network 15:583–602

Durstewitz D, Kelc M, Gunturkun O (1999) A neurocomputational theory of the dopaminergic modulation of working memory functions. J Neurosci 19:2807–2822

Durstewitz D, Seamans JK, Sejnowski TJ (2000) DA-mediated stabilization of delay-period activity in a network model of PFC. J Neurophysiol 83:1733–1750

Elliott R, Sahakian BJ, Matthews K, Bannerjea A, Rimmer J, Robbins TW (1997) Effects of methylphenidate on SWM and planning in healthy young adults. Psychopharmacology 131:196–206

Fletcher PC, Anderson JM, Shanks DR, Honey R, Carpenter TA, Donovan T, Papadakis N, Bullmore ET (2001) Responses of human frontal cortex to surprising events are predicted by formal associative learning theory. Nat Neurosci 4:1043–1048

Goldman-Rakic PS (1999) The physiological approach: functional architecture of working memory and disordered cognition in schizophrenia. Biol Psychiatry 46:650–661

Goldman-Rakic PS, Muly EC IIIrd, Williams GV (2000) D(1) receptors in prefrontal cells and circuits. Brain Res Brain Res Rev 31:295–301

Grant DA, Berg EA (1948) A behavioural analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem. J Exp Psychol 38:404–411

Herbert M, Johns MW, Dore C (1976) Factor analysis of analogue scales measuring subjective feelings before and after sleep. Br J Med Psychol 49:373–379

Honey GD, Suckling J, Zelaya F, Long C, Routledge C, Jackson S, Ng V, Fletcher PC, Williams SC, Brown J, Bullmore ET (2003) Dopaminergic drug effects on physiological connectivity in a human cortico-striato-thalamic system. Brain 126:1767–1781

Kimberg DY, D'Esposito M, Farah MJ (1997) Effects of bromocriptine on human subjects depends on working memory capacity. Neuroreport 8:3581–3585

Kimberg DY, Aguirre GK, Lease J, D'Esposito M (2001) Cortical effects of bromocriptine, a D-2 DA receptor agonist, in human subjects, revealed by fMRI. Hum Brain Mapp 12:246–257

Kuroki T, Meltzer HY, Ichikawa J (1999) Effects of antipsychotic drugs on extracellular DA levels in rat medial PFC and nucleus accumbens. J Pharmacol Exp Ther 288:774–781

Lange KW, Robbins TW, Marsden CD, James M, Owen AM, Paul GM (1992) L-Dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. Psychopharmacology 107:394–404

Luciana M, Collins PF (1997) Dopaminergic modulation of working memory for spatial but not object cues in normal volunteers. J Cognit Neurosci 9:330–347

Luciana M, Depue RA, Arbisi P, Leon A (1992) Facilitation of working memory in humans by a D_2 dopamine receptor agonist. J Cognit Neurosci 4:58–67

McCartan D, Bell R, Green JF, Campbell C, Trimble K, Pickering A, King DJ (2001) The differential effects of chlorpromazine and haloperidol on latent inhibition in healthy volunteers. J Psychopharmacol 15:96–104

Mehta MA, Sahakian BJ, McKenna PJ, Robbins TW (1999) Systemic sulpiride in young adult volunteers simulates the profile of cognitive deficits in Parkinson's disease. Psychopharmacology 146:162–174

Mehta MA, Calloway P, Sahakian BJ (2000) Amelioration of specific working memory deficits by methylphenidate in a case of adult attention deficit/hyperactivity disorder. J Psychopharmacol 14:299–302

Mehta MA, Swainson R, Ogilvie AD, Sahakian J, Robbins TW (2001) Improved short-term spatial memory but impaired reversal learning following the DA D_2 agonist bromocriptine in human volunteers. Psychopharmacology 159:10–20

Mehta MA, McGowan S, Lawrence AD, Aitken MRF, Montgomery AJ, Grasby PM (2003) Systemic sulpiride modulates striatal blood flow: relationships to spatial working memory and planning. Neuroimage 20:1982–1994

Milner B (1964) Some effects of frontal lobectomy in man. McGraw-Hill, New York

Mollion H, Ventre-Dominey J, Dominey PF, Broussolle E (2003) Dissociable effects of dopaminergic therapy on spatial versus non-spatial working memory in Parkinson's disease. Neuropsychologia 41:1442–1451

Müller U, von Cramon DY, Pollmann S (1998) D_1- versus D_2-receptor modulation of visuoSWM in humans. J Neurosci 18:2720–2728

Myrtek M, Foerster F (1986) The law of initial value: a rare exception. Biol Psychol 22:227–237

Nelson HE, Willison JR (1991) The revised National Adult Reading Test–Test Manual. NFER-Nelson, London

Owen AM, Downes JJ, Sahakian BJ, Polkey CE, Robbins TW (1990) Planning and spatial working memory following frontal lobe lesions in man. Neuropsychologia 28:1021–1034

Owen AM, Roberts AC, Polkey CE, Sahakian BJ, Robbins TW (1991) Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. Neuropsychologia 29:993–1006

Owen AM, James M, Leigh PN, Summers BA, Marsden CD, Quinn NP, Lange KW, Robbins TW (1992) Fronto-striatal cognitive deficits at different stages of Parkinson's disease. Brain 115:1727–1751

Owen AM, Evans AC, Petrides M (1996) Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. Cereb Cortex 6:31–38

Pantelis C, Barber FZ, Barnes TR, Nelson HE, Owen AM, Robbins TW (1999) Comparison of set-shifting ability in patients with chronic schizophrenia and frontal lobe damage. Schizophr Res 37:251–270

Phillips AG, Ahn S, Floresco SB (2004) Magnitude of dopamine release in medial prefrontal cortex predicts accuracy of memory on a delayed response task. J Neurosci 24:547–553

Postle BR, Jonides J, Smith EE, Corkin S, Growdon JH (1997) Spatial, but not object, delayed response is impaired in early Parkinson's disease. Neuropsychology 11:171–179

Raichle ME, Fiez JA, Videen TO, MacLeod AM, Pardo JV, Fox PT, Petersen SE (1994) Practice-related changes in human brain functional anatomy during nonmotor learning. Cereb Cortex 4:8–26

Redgrave P, Prescott TJ, Gurney K (1999) Is the short-latency DA response too short to signal reward error? Trends Neurosci 22:146–151

Robbins TW (1996) Dissociating executive functions of the prefrontal cortex. Philos Trans R Soc Lond B Biol Sci 351:1463–1470

Roberts AC, De Salvia MA, Wilkinson LS, Collins P, Muir JL, Everitt BJ, Robbins TW (1994) 6-Hydroxydopamine lesions of the prefrontal cortex in monkeys enhance performance on an analog of the Wisconsin Card Sort Test: possible interactions with subcortical dopamine. J Neurosci 14:2531–2544

Rogers RD, Monsell S (1995) Costs of a predictable switch between simple cognitive tasks. J Exp Psychol 124:207–231

Rogers RD, Blackshaw AJ, Middleton HC, Matthews K, Hawtin K, Crowley C, Hopwood A, Wallace C, Deakin JF, Sahakian BJ, Robbins TW (1999) Tryptophan depletion impairs stimulus-reward learning while methylphenidate disrupts attentional control in healthy young adults: implications for the monoaminergic basis of impulsive behaviour. Psychopharmacology 146:482–491

Rogers RD, Andrews TC, Grasby PM, Brooks DJ, Robbins TW (2000) Contrasting cortical and subcortical activations produced by attentional-set shifting and reversal learning in humans. J Cognit Neurosci 12:142–162

Sahakian BJ, Owen AM, Morant NJ, Eagger SA, Boddington S, Crayton L, Crockford HA, Crooks M, Hill K, Levy R (1993) Further analysis of the cognitive effects of tetrahydroaminoacridine (THA) in Alzheimer's disease: assessment of attentional and mnemonic function using CANTAB. Psychopharmacology 110:395–401

Sawaguchi T, Goldman-Rakic PS (1991) D_1 DA receptors in PFC: involvement in working memory. Science 251:947–950

Schultz W, Dayan P, Montague PR (1997) A neural substrate of prediction and reward. Science 275:1593–1599

Seamans JK, Gorelova N, Durstewitz D, Yang CR (2001) Bidirectional dopamine modulation of GABAergic inhibition in prefrontal cortical pyramidal neurons. J Neurosci 21:3628–3638

Spanagel R, Weiss F (1999) The dopamine hypothesis of reward: past and current status. Trends Neurosci 22:521–527

Strange PG (2001) Antipsychotic drugs: importance of DA receptors for mechanisms of therapeutic actions and side effects. Pharmacol Rev 53:119–133

Suri RE (2002) TD models of reward predictive responses in DA neurons. Neural Network 15:523–533

Swainson R, Rogers RD, Sahakian BJ, Summers BA, Polkey CE, Robbins TW (2000) Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. Neuropsychologia 38:596–612

Tucker DM, Hartry-Speiser A, McDougal L, Luu P, deGrandpre D (1999) Mood and spatial memory: emotion and right hemisphere contribution to spatial cognition. Biol Psychol 50:103–125

von Bahr C, Wiesel F-A, Movin G, Eneroth P, Jansson P, Nilsson L, Ogenstad S (1991) Neuroendocrine responses to a single oral dose of remoxipride and sulpiride in healthy female and male volunteers. Psychopharmacology 130:443–448

Wang M, Vijayraghavan S, Goldman-Rakic PS (2004) Selective D_2 receptor actions on the functional circuitry of working memory. Science 303:853–856

Weingartner H, Eckardt M, Molchan S, Sunderland T, Wolkowitz O (1992) Measurement and interpretation of changes in memory in response to drug treatments. Psychopharmacol Bull 28:331–340

Wiesel FA, Alfredsson G, Ehrnebo M, Sedvall G (1982) Prolactin response following intravenous and oral sulpiride in healthy human subjects in relation to sulpiride concentrations. Psychopharmacology 76:44–47

Williams GV, Goldman-Rakic PS (1995) Blockade of DA D_1 receptors enhances memory fields of prefrontal neurons in primate cerebral cortex. Nature 376:572–575

Winer BJ (1971) Statistical principles in experimental design. McGraw-Hill, New York

Zahrt J, Taylor JR, Mathew RG, Arnsten AF (1997) Supranormal stimulation of D_1 dopamine receptors in the rodent prefrontal cortex impairs spatial working memory performance. J Neurosci 17:8528–8535