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Dopaminergic basis for deficits in working memory but not attentional set-shifting in Parkinson's disease

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Abstract

Although Parkinson's disease is a common neurodegenerative disorder characterised by its motoric symptoms, there is an increasing recognition of accompanying impairments in cognition that have a profound impact on the quality of life of these patients. These deficits predominantly affect executive function and impairments of working memory have been frequently reported. However, the underlying neurochemical and pathological basis for these deficits are not well understood. In this study, 20 patients were tested 'on' and 'off' levodopa (L-dopa) medication on a task that allowed different aspects of working memory function such as maintenance, retrieval and manipulation to be tested within the same general paradigm as well as on an unrelated test of attentional set-shifting, which is known to be sensitive to deficits in early Parkinson's disease. Compared to healthy volunteers, PD patients were impaired at manipulation more than maintenance or retrieval of information within working memory. The patients were also impaired at the attentional set-shifting task. However, whereas L-dopa ameliorated the working memory deficit in manipulation (improving both accuracy and cognitive response time), it had no effect on the attentional set-shifting impairment. These results confirm that working memory deficits in PD are both psychologically specific and related to dopamine depletion. It is anticipated that greater understanding of these mechanisms will lead to future therapeutic improvements.

Keywords: Working memory; Parkinson's disease; Dopamine; Caudate nuclei; Frontal lobes; Basal ganglia

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative condition characterised by its clinical triad of motor deficits namely bradykinesia, rigidity and resting tremor. However, 15–20% of patients suffer with frank dementia (Brown & Marsden, 1984) and less severe cognitive impairment is a well recognised feature of the disease that has been shown to be an important predictor for the quality of life (Karlsen, Larsen, Tandberg, & Maland, 1998; Schrag, Jahanshahi, & Quinn, 2000).

The pattern of this cognitive impairment resembles that produced by frontal-lobe damage and includes deficits of 'executive' functions (Downes et al., 1989; Lees & Smith, 1983; Taylor, Saint-Cyr, & Lang, 1986; Downes et al., 1989). Much recent interest has focused on deficits of working memory (Bradley, Welch, & Dick, 1989; Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Cooper, Sagar, & Sullivan, 1993; Gotham, Brown, & Marsden, 1988; Lewis, Cools et al., 2003; Lewis, Dove, Robbins, Barker, & Owen, 2003; Morris et al., 1988; Owen et al., 1992; Owen, Beksinska et al., 1993; Owen, Roberts et al. 1993; Owen, Iddon, Hodges, Summers, &

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Robbins, 1997) given the central role played by this collection of cognitive processes in day-to-day life.

The precise neural and neurochemical bases of working memory disturbances in patients with PD are not well understood. Although PD is characterised by dopaminergic nigrostriatal degeneration, recent functional neuro-imaging studies of dopamine withdrawal in PD patients have suggested a general role for the mesocortical projection in the performance of working memory tasks (Cools, Stefanova, Barker, Robbins, & Owen, 2002; Mattay et al., 2002). Furthermore, non-dopaminergic forms of pathology including noradrenergic, serotoninergic and cholinergic deafferentation of the cortex (Agid, Javoy-Agid, & Ruberg, 1987) along with the presence of cortical Lewy bodies (Byrne, Lennox, Lowe, & Godwin-Austen, 1989; Gibb, Luthert, Janota, & Lantos, 1989) may play a role in some of the cognitive deficits observed. However, previous pathological (Paulus & Jellinger, 1991; Rinne, Rummukainen, Paljarvi, & Rinne, 1989) and ^{18}F-dopa PET studies have confirmed a correlation between caudate dopamine loss and neuropsychological performance in PD patients (Marie et al., 1999) suggesting a preferential role for this system in cognitive impairment (Ito et al., 2002). Furthermore, working memory deficits have been shown previously to be extremely sensitive to the effects of controlled levodopa (L-dopa) withdrawal in groups of patients with PD (Lange et al., 1992) and a central model for understanding these impairments has been the concept of cortico-striatal loops (Alexander, DeLong, & Strick, 1986), which emphasises the functional inter-relationships between the neocortex and the striatum.

It has been demonstrated that working memory is affected by disease progression with more severe impairments in medicated patients at the later stages of the disease than in non-medicated patients with mild clinical symptoms (Morris et al., 1988; Owen et al., 1992). Moreover, it has previously been argued that some aspects of working memory are more severely impaired, and appear to be affected at an earlier stage of the disease, than others. For example, spatial working memory deficits have been widely reported in patients with mild to moderate clinical symptoms (Bradley et al., 1989; Dagher, Owen, Boecker, & Brooks, 1999; Owen et al., 1997; Postle, Jonides, Smith, Corkin, & Growdon, 1997). In contrast, the same patients are unimpaired on analogous tests of verbal and object working memory (Bradley et al., 1989; Owen et al., 1997), suggesting that spatial tasks may be more vulnerable than equivalent non-spatial tasks early in the course of the disease. While some authors have suggested that PD is accompanied by widespread impairments of spatial processing (Le Bras, Pillon, Damier, & Dubois, 1999), an alternative possibility is that the spatial tasks used in these studies differ from the non-spatial tasks in terms of their underlying executive requirements.

In support of this 'processing-specific' theory, Owen, Beksinska et al. (1993) and Owen, Roberts et al. (1993) have demonstrated that *within* spatial working memory, significant impairments are observed in patients with both severe *and* mild clinical symptoms if the task requires the active manipulation of information within memory. In contrast, in spatial working memory tasks that require only maintenance and retrieval of that information deficits are only observed in the patients with more severe clinical symptoms. Further, evidence for this 'processing-specific' hypothesis comes from the results of more recent work (Lewis, Cools et al., 2003; Lewis, Dove et al., 2003) in patients in the earlier clinical stages of the disease. In this study, patients were well matched on a range of clinical and neuropsychological measures, but differed on their performance of a standard clinical executive task. Subjects were tested on a novel working memory task that allowed different aspects of working memory function such as maintenance, retrieval and manipulation to be assessed within the same general paradigm. The findings revealed a specific impairment at manipulating information within verbal working memory, when patients with predefined executive deficits were compared to controls and to a group of patients with no cognitive impairments. However, the groups did not differ in their ability to maintain or retrieve information within verbal working memory. Results from the subsequent functional neuro-imaging study of PD patients with this selective executive impairment (Lewis, Cools et al., 2003; Lewis, Dove et al., 2003) identified a neural correlate for these deficits in working memory operating through a fronto-striatal network. Compared to clinically matched PD patients with no cognitive deficits, patients with selective executive impairment demonstrated significant under activation within the caudate nuclei and prefrontal cortex during the manipulation of information within working memory.

The study presented here sought to identify whether there was a dopaminergic basis for selective processes within working memory including maintenance, retrieval and manipulation of information, in patients with PD. Patients in the earlier stages of the disease were assessed both 'on' and 'off' levodopa, along with a control group of healthy, age-matched volunteers, to determine the effects of dopamine on working memory processes. On the basis of the neuropsychological data presented above, it was predicted that L-dopa would selectively improve performance deficits on those aspects of the task that required manipulation, more than other aspects of working memory such as maintenance and retrieval. To confirm that this effect was not simply global across impaired neuropsychological processes or an effect of task difficulty, patients also underwent testing on an attentional set-shifting paradigm where it was predicted that deficits in patients with mild PD would not be ameliorated by dopamine. The task, modelled on the learned irrelevance procedure devised by Owen, Beksinska et al. (1993) and Owen, Roberts et al. (1993), is sensitive to impairment in PD, but is neither affected by damage to the frontal-lobes nor appears to be sensitive to treatment with L-dopa medication (Owen, Beksinska et al., 1993 and Owen, Roberts et al., 1993).

2. Methods

2.1. Subjects

The 20 non-depressed and non-demented patients included in this study were recruited from the Parkinson's disease Research Clinic at the Cambridge Centre for Brain Repair where they had undergone careful historical review along with physical examination. No significant deficits had been detected in these patients on a neuropsychometric analysis including Mini-mental state examination (Folstein, Folstein, & McHugh, 1975), the National Adult Reading Test (NART) (Nelson, 1982) as an estimate of pre-morbid IQ, testing of verbal and categorical fluency (FAS 60-s (Benton, 1983), animals 90-s (Goodglass, 1972)), along with the motor screening task, pattern and spatial recognition memory (PRM and SRM) and Tower of London planning task (TOL) recorded on the Cambridge Neuropsychological Test Automated Battery: CANTAB (Owen et al., 1992). All patients satisfied UKPDS Brain Bank criteria (Gibb & Lees, 1988) and their only dopaminergic medication was taken as L-dopa preparations, rather than longer acting dopamine agonists. Two patients were taking selegiline, two were on anticholinergics and another two were taking selective serotonin reuptake inhibitors. Permission for the study was obtained from the local research ethical committee and all subjects consented to participation.

For both the working memory and the attentional set-shifting tasks, patients were counterbalanced into two groups of 10 to minimise ordering effects between assessments 'on' and 'off' medication, which were separated by at least a 2-week period. 'Off' medication sessions were performed a minimum of 12 h post last dose of L-dopa medication. At both appointments, patients were assessed on parts I-III of the unified Parkinson's disease rating scale, UPDRS (Fahn & Elton, 1987) and underwent Hoehn and Yahr staging (Hoehn & Yahr, 1967).

For practical reasons (the control data was collected before the PD data) two separate healthy control cohorts performed the working memory and attentional set-shifting paradigms and underwent NART assessment. Nineteen volunteers were tested on the working memory paradigm and a further 20 control subjects performed the attentional set-shifting task. Due to time constraints, the working memory paradigm was conducted by the controls on only one occasion. However as the attentional set-shifting task is likely to have a strong learning component, every subject was tested on two separate occasions, approximately 2 weeks apart, to control for practice related effects in the patients who were also tested twice, but on and off L-dopa.

2.2. Demographics

Summary characteristics for the PD patients and controls are shown in Table 1 and no significant differences were observed between patients and controls for age or NART. Similarly, no significant differences were demonstrated between those PD cohorts tested on and off L-dopa during their initial session for any clinical variable recorded. Patients did, however, show significant motoric deterioration on Hoehn and Yahr staging ($t(19) = 2.1$, $p < 0.001$) and UPDRS ratings ($t(19) = 2.1$, $p < 0.001$) during their 'unmedicated' session.

2.3. Working memory task

This study utilised the same paradigm as had been previously validated in PD patients to explore specific executive deficits (Lewis, Cools et al., 2003; Lewis, Dove et al., 2003). On each trial, subjects were presented with a sequence of four different consonants at 1 s intervals that had to be re-

Table 1
Subject demographics

	Patients ($n = 20$)	Working memory controls ($n = 19$)	Learned irrelevance controls ($n = 21$)
Age (y)	70.2 ± 6	68.3 ± 7	68.2 ± 8
NART	110.2 ± 9.2	114.4 ± 8	112.1 ± 7.6
BDI	7.9 ± 4.2		
Disease duration (y)	6.5 ± 6		
UPDRS (on)	27 ± 18		
UPDRS (off)	55 ± 16		
H&Y (on)	1.9 ± 0.4		
H&Y (off)	2.7 ± 0.4		
MMSE	29 ± 1		
Letter fluency (FAS)	36 ± 12		
Categorical fluency	21 ± 6		
Motor screening latency (ms)	1076 ± 395.3		
PRM (max score 24)	20.5 ± 3		
SRM (max score 20)	15.5 ± 2.3		
TOL (max score 14)	10.3 ± 2.5		
L-dopa (mg)	605.3 ± 339.4		

Values represent mean ± S.D.

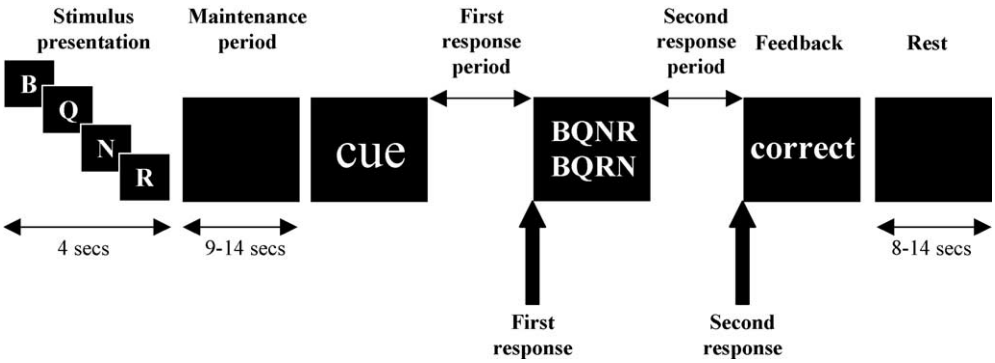

Fig. 1. A single trial from the working memory task. Following presentation of four letters and a retention interval of 9–14 s, a cue signalled one of three pre-learned conditions, maintenance and retrieval only, simple or complex manipulation. The subject responded with a key press ('first response') once the correct solution had been generated in mind, and a second key press ('second response'), to select from two alternative possibilities.

tained sub-vocally in memory in the order in which they were presented (Fig. 1). Stimulus presentation was followed by a variable maintenance period (5–9 s) during which the screen remained blank. The maintenance period ended when a cue word was presented in the centre of the screen that instructed the subject as to whether the letter sequence was to be recalled verbatim, a 'retrieval only' condition requiring no manipulation cued by the word '*same*', or whether the letters had to be reordered in one of two pre-learned ways, which required either 'simple or more complex manipulation'. Specifically, simple manipulation trials, cued by the word '*pairs*', required the subject to recall the digits in the following order: the 3rd, 4th, 1st and 2nd digit of the original memory list, whereas for complex manipulation trials, cued by the word '*middle*', the middle letters were reordered such that the 1st, then the 3rd, then the 2nd and then the 4th letter of the original memory list were recalled. All of these conditions, obviously, relied upon the maintenance and retrieval of remembered information for successful completion but were distinguished by the level of manipulation required. Following the cue, a blank screen was presented until the subject indicated, by pressing a response button under their ring finger that they had the required sequence of letters 'in mind'. Subjects were explicitly instructed to be sure that they had performed any retrieval or manipulative processes fully prior to this initial button press. Therefore, the first response phase extended from the display of the cue word until the first button press. For trials with the cue word '*same*', this period measured the duration of the cognitive processes involved in the retrieval of information maintained within working memory. In addition, for trials with the cue word 'pairs' or 'middle' this phase allowed the duration of the processes involved in the manipulation of information within working memory to be recorded. Finally, for all trial types this first response period included the motor requirements for depressing the response key. This first button response triggered the appearance of two sets of four letters arranged horizontally above and below the centre of the screen. These alternatives were comprised of the same letters and the foil was constructed such that identification of the correct answer required the subject to check through the sequences fully, which reasserted the need for subjects to have completed all cognitive processes required during the first response phase prior to depressing the response key. The subject was required to select the correct answer (from the similar, yet incorrect, foil) by pressing one of the two response keys under their index and middle fingers, which generated feedback on the screen as to whether their chosen answer was correct or wrong. This second response period extending from the display of the alternative answers through until the second button press and served as a motor control for the working memory processes recorded during the first response phase. As both the first and second response periods had similar motoric requirements but differed markedly in their executive demands a more conservative estimate of the cognitive processes involved in working memory was derived by subtracting one period from the other to obtain the cognitive response time (Lewis et al. 2003aLewis, Cools et al., 2003; Lewis, Dove et al., 2003).

All subjects were trained on the task using a purpose written working demonstration program (PowerPoint 2000) and before testing, 25 practice conditions were presented. All subjects demonstrated their understanding of the task and adequate use of the keyboard responses prior to being presented with three blocks of 15 randomised trials of the working memory paradigm, which gave equal weighting to the maintenance and retrieval only, simple and complex manipulation conditions. Behavioural accuracy and cognitive response time data for the patients were analysed with repeated measures analysis of variance, one-way analysis of variance (O-ANOVA) or where appropriate with paired *t*-test analysis using SPSS-PC software. In the analysis of response time data, only 'correct' trials were included.

2.4. Attention set-shifting task

This test was based directly on a version of the intra/extra-dimensional set-shifting task, which has been described in detail elsewhere (Owen, Beksinska et al., 1993; Owen, Roberts et al., 1993). The original task is known to be sensitive to impairments in patients with Parkinson's disease (Owen,

Beksinska et al., 1993; Owen, Roberts et al., 1993), as well as in neurosurgical patients with excisions of the frontal cortex (Owen, Beksinska et al., 1993; Owen, Roberts et al., 1993). As in the original task, in the version used here, the volunteers were required to learn a series of visual discriminations, using feedback provided automatically by the computer. The test began with a simple discrimination and reversal for stimuli varying in only one dimension (i.e., colour). Two additional dimensions (i.e., shape and number) were then introduced and compound discrimination and reversal were tested for the original dimension. At the intra-dimensional shift (IDS) stage new exemplars were introduced from each of the three dimensions, requiring subjects to transfer the previously learnt rule to a novel set of exemplars of the same dimension (e.g., from responding to 'red' to responding to 'blue', irrespective of shape or number). At the extra-dimensional shift (EDS) stage new exemplars were again introduced from each of the three dimensions. However, now the volunteers and patients were required to shift from the previously relevant dimension to one of the previously irrelevant dimensions, chosen pseudo-randomly by the computer. Unlike the original versions of this task (Downes et al., 1989; Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Owen, Beksinska et al., 1993; Owen, Roberts et al., 1993), the version used in this study was adapted to emphasize the learned irrelevance component of attentional set-shifting performance (for details, Slabosz et al., in preparation). Learned irrelevance refers to the inability to learn about previously irrelevant or unimportant information and has been shown to be a central component of set-shifting behaviour that is neither affected by damage to the frontal lobes nor by treatment with dopaminergic medication (Owen, Beksinska et al., 1993; Owen, Roberts et al., 1993). For the purposes of the present study, the main measure of interest was the number of errors committed in making the critical intra- and extra-dimensional shift stages of the task, although a more comprehensive analysis of this data set, including task conditions that are not relevant to the current study is available elsewhere (Slabosz et al., in preparation).

3. Results

3.1. Behavioural data

3.1.1. Working memory task

The mean number of correct responses in each condition is presented in Fig. 2 for the controls and for the patients tested both 'on' and 'off' L-dopa. Because some of the effects of interest (e.g., medication and session) were within-subject factors, yet did not apply to all groups (e.g., controls), while other between-group factors (e.g., pathology) applied to all groups, a mixed analysis was required. Accordingly, to establish whether L-dopa had a significant effect on accuracy in the patients 'on' and 'off' L-dopa and whether there were any practice effects in the patient group, a three-factor (medication, session and condition) repeated measures ANOVA was conducted. This analysis revealed a significant main effect of medication ($F(1, 9) = 27.74$, $p = 0.001$), a significant main effect of condition ($F(1, 9) = 56.53$, $p < 0.0001$) and no significant main effect of session (first versus second) ($F(1, 9) = 1.58$). A significant two-way interaction was also observed between the medication and condition factors ($F(1, 9) = 19.65$, $p = 0.002$), although none of the other interaction terms approached significance. Examination of simple main effects revealed significant improvements in performance accuracy during the medicated session for those trials requiring manipulation ($F(1, 19) = 33.22$, $p < 0.0001$ and $F(1, 19) = 72.27$, $p < 0.0001$, *simple* and *complex* manipulation, respectively) but not in the trials that relied upon only the maintenance and retrieval of information ($F(1, 19) = 0.33$).

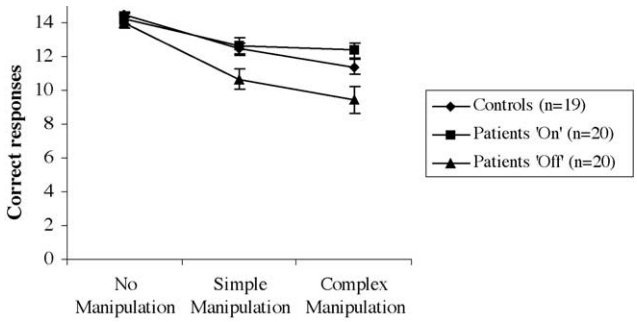

Fig. 2. Working memory: performance accuracy. The mean number of correct responses at each level of task difficulty is shown for controls and the patients 'on' and 'off' medication. The 'no manipulation' condition represents those trials where successful performance required only the maintenance and retrieval of information within working memory. Bars represent standard error of the mean.

To establish whether L-dopa had a significant effect on cognitive response time in the patients (Fig. 3) and whether there were any practice effects in the patient group

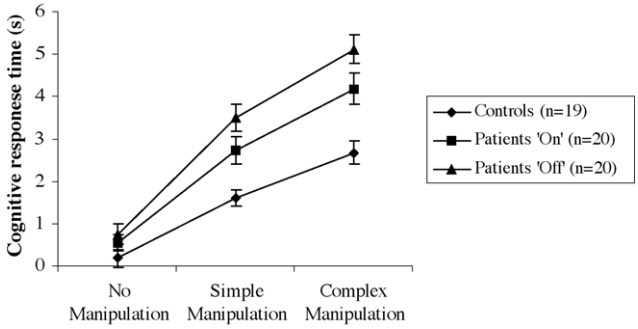

Fig. 3. Working memory: cognitive response time. The mean cognitive response time at each level of task difficulty is shown for controls and the patients 'on' and 'off' medication. The 'no manipulation' condition represents those trials where successful performance required only the maintenance and retrieval of information within working memory. The cognitive response time represents a more conservative estimate of the cognitive processes involved in working memory and was derived by subtracting the second response period from the first response period. Bars represent standard error of the mean.

the same three-factor (medication, session and condition) repeated measures ANOVA was conducted. This analysis revealed a significant main effect of medication ($F(1, 9) = 25.53$, $p = 0.001$), a significant main effect of condition ($F(1, 9) = 241.19$, $p < 0.0001$) and no significant main effect of session (first versus second) ($F(1, 9) = 3.8$, $p = 0.09$). A significant two-way interaction was also observed between the medication and condition factors ($F(1, 9) = 11.11$, $p = 0.01$), while none of the other interaction terms approached significance. Examination of simple main effects revealed significant improvements in cognitive response time during the medicated session for those trials requiring manipulation ($F(1, 19) = 22.59$, $p < 0.0001$ and $F(1, 19) = 35.21$, $p < 0.0001$, simple and complex manipulation, respectively) but not in the trials that relied upon only the maintenance and retrieval of information ($F(1, 19) = 1.26$).

These results confirm that L-dopa significantly improved both accuracy and cognitive response time during the two types of manipulation trials. No significant effect was observed in those trials where only maintenance and retrieval was required. In addition, there were no practice effects between sessions 1 and 2 and this factor did not interact with any of the other variables tested. Therefore, in all subsequent analyses, the patient data were collapsed across the two sessions.

In order to test whether patients tested 'off' L-dopa were significantly impaired relative to controls and, in addition, whether the ameliorative effects of L-dopa restored performance to normal in the patient group, accuracy and cognitive response time in the PD patients were compared directly with those of the healthy volunteers when both 'on' and 'off' L-dopa. A two-way (pathology, condition) ANOVA comparing accuracy in the patients 'off' L-dopa with the healthy volunteers revealed a significant main effect of pathology ($F(1, 37) = 6.66$, $p = 0.01$), a significant main effect of condition ($F(1, 37) = 74.69$, $p < 0.0001$), although the interaction between the two factors did not reach significance ($F(1, 37) = 2.81$, $p = 0.10$). A two-way (pathology, condition) ANOVA comparing cognitive response time in the patients 'off' L-dopa with the healthy volunteers revealed a significant main effect of pathology ($F(1, 37) = 38.35$, $p < 0.0001$), a significant main effect of condition ($F(1, 37) = 361.64$, $p < 0.0001$), and a significant interaction between the two factors ($F(1, 37) = 31.95$, $p < 0.0001$). Examination of simple main effects revealed significant impairments in cognitive response time for those trials requiring manipulation ($F(1, 37) = 53.78$, $p < 0.0001$ and $F(1, 37) = 93.99$, $p < 0.0001$, simple and complex manipulation, respectively) but not in the trials that relied upon only the maintenance and retrieval of information ($F(1, 37) = 2.90$).

These results confirm that there was an overall difference between patients 'off' L-dopa and healthy controls in terms of both accuracy and cognitive response time. Examination of Figs. 2 and 3 suggests that this effect is primarily due to the poor performance of these patients in the two manipulation conditions rather than during the maintenance and retrieval condition. With respect to cognitive response time (Fig. 3), this effect was statistically significant; differences between the groups were observed in the two manipulations conditions but not in the condition requiring only maintenance and retrieval.

To examine whether the ameliorative effects of L-dopa restore working memory functions to normal levels in the PD group, a two-way (pathology, condition) ANOVA comparing accuracy in the patients 'on' L-dopa with the healthy volunteers was conducted. This revealed no significant main effect of pathology ($F(1, 37) = 0.55$), a significant main effect of condition ($F(1, 37) = 55.91$, $p < 0.0001$), and a non-significant trend in the interaction between the two factors ($F(1, 37) = 3.59$, $p = 0.066$). A two-way (pathology, condition) ANOVA comparing cognitive response time in the patients 'on' L-dopa with the healthy volunteers revealed a significant main effect of pathology ($F(1, 37) = 14.21$, $p = 0.001$), a significant main effect of condition ($F(1, 37) = 267.22$, $p < 0.0001$), and a significant interaction between the two factors ($F(1, 37) = 11.15$, $p = 0.002$). Examination of simple main effects revealed significant impairments in cognitive response time for those trials requiring manipulation ($F(1, 37) = 16.95$, $p < 0.0001$ and $F(1, 37) = 32.09$, $p < 0.0001$, simple and complex manipulation respectively), but not in the trials that relied upon only the maintenance and retrieval of information ($F(1, 37) = 0.89$).

These results confirm that there was no overall difference between patients 'on' L-dopa and healthy controls in terms of performance accuracy. There was, however, a residual deficit in cognitive response time and a significant interaction between the condition and pathology factors. Simple main effects confirmed that this was due to residual poor performance of the patients in the two manipulation conditions, rather than during the maintenance and retrieval condition.

3.1.2. Attentional set-shifting task

To establish the within subjects effects of L-dopa on the attentional set-shifting task, the performance of patients at the IDS and the EDS during their medicated and unmedicated sessions were compared using a repeated measures ANOVA. This analysis revealed a significant effect of shift ($F(1, 18) = 34.08$, $p < 0.001$), but no significant effect of medication ($F(1, 18) = 0.453$), and no interaction between the two factors ($F(1, 18) = 0.167$) as shown in Fig. 4.

In order to test the overall effect of pathology, mean error rates at the intra- and extra-dimensional shifting stages were calculated by averaging the PD data for 'on' and 'off' L-dopa sessions since there were no differences between the two medication states. To control for possible practice effects, means were calculated for controls by averaging across the first and second sessions. As expected, there was a significant main effect of pathology ($F(1, 36) = 12.055$, $p < 0.001$) with patients making more errors overall than controls (Fig. 5). There was also a highly significant effect of shift ($F(1, 36) = 80.60$, $p < 0.0001$) with more errors being committed at the extra-dimensional shift stage than at the intra-dimensional

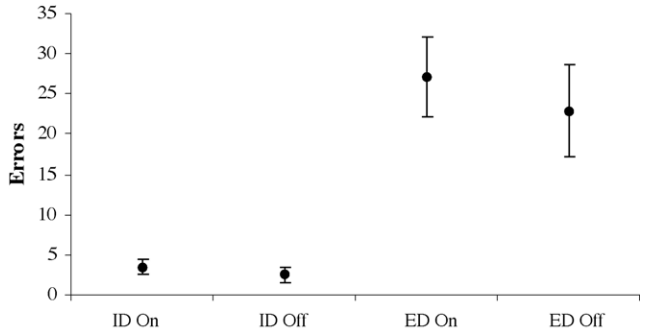

Fig. 4. Attentional set-shifting: Effect of L-dopa on error rate in PD patients. The mean number of errors for both the intra-dimensional (ID) and extra-dimensional (ED) set-shift is shown for the patients 'on' and 'off' medication. Bars represent standard error of the mean.

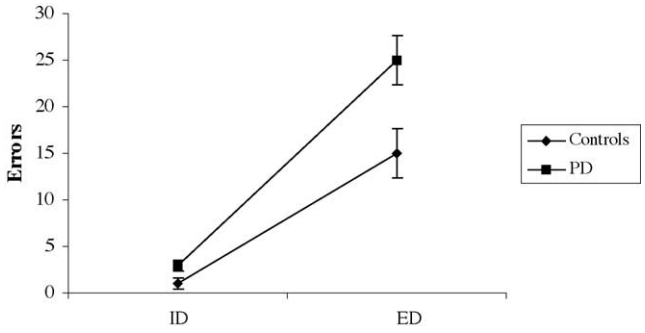

Fig. 5. Attentional set-shifting: effect of pathology on error rate. The mean number of errors for the control subjects over their two testing sessions and the patients recorded 'on' and 'off' medication are shown for both the intra-dimensional (ID) and extra-dimensional (ED) set-shift. Bars represent standard error of the mean.

shift stage. The interaction term was also significant ($F(1, 36) = 4.34, p < 0.05$) demonstrating that the PD group was disproportionately impaired at the extra-dimensional shift stage of the task (Fig. 5).

4. Discussion

The results of this study revealed that dopaminergic medication in patients with mild PD specifically improves the process of manipulation within working memory more than other cognitive processes involved such as maintenance and retrieval. Thus, L-dopa improved both accuracy and cognitive response time when information was manipulated in working memory, but had no effect on retrieval. Moreover, dopaminergic replacement in PD did not ameliorate impairments in attentional set-shifting in the PD group, confirming that this effect is psychologically specific.

Deficits in working memory have been frequently reported in patients with PD (Bradley et al., 1989; Cooper et al., 1991; Cooper et al., 1993; Gotham et al., 1988; Lewis, Cools et al., 2003; Lewis, Dove et al., 2003; Owen, Beksinska et al., 1993; Owen, Roberts et al., 1993; Owen et al., 1997), although few studies have directly related these deficits to dopamine depletion in these patients (Cooper et al., 1992; Costa et al., 2003; Lange et al., 1992). Several studies have shown that non-dopaminergic neurotransmitters contribute to the pattern of cognitive deficits in PD (Aarsland, Laake, Larsen, & Janvin, 2002; Dubois, Pilon, Lhermitte, & Agid, 1990), although the results of electrophysiological studies in animals (Sawaguchi & Goldman-Rakic, 1991; Seamans, Floresco, & Phillips, 1998; Williams & Goldman-Rakic, 1995), human neuro-imaging experiments (Ito et al., 2002; Marie et al., 1999) and clinicopathological data (Paulus & Jellinger, 1991; Rinne et al., 1989) suggest that dopamine may play a particularly important role in modulating cognition.

Dopaminergic neuronal loss represents the primary neuropathology in PD and occurs predominantly in the nigrostriatal tract and to a lesser extent, in the mesocortical pathway (Jellinger, 2001). Previous functional neuro-imaging studies of dopamine withdrawal in PD patients have suggested a general role for the mesocortical projection in the performance of working memory tasks (Cools et al., 2002; Mattay et al., 2002). More specifically, however, a recent functional MRI study of PD patients performing exactly the same working memory task that was used in the current investigation (Lewis, Cools et al., 2003; Lewis, Dove et al., 2003) reported *selective* impairments in manipulation that were associated with reduced activity in the ventro-lateral and dorsolateral prefrontal cortices. It is widely accepted that the prefrontal cortex plays a critical role in aspects of working memory (Fuster, 1997; Goldman-Rakic, 1987; Smith & Jonides, 1999) and a number of neuro-imaging studies in healthy controls have suggested that the manipulation of information within working memory preferentially involves the mid-dorso-lateral prefrontal cortex (Owen, Evans, & Petrides, 1996; Owen et al., 1999; Owen, 2000). The ventro-lateral frontal cortex is also frequently activated in such tasks, but is thought to be specifically involved in more basic mnemonic functions, including encoding and retrieval (Owen et al., 1996; Owen et al., 1999; Owen, 2000). Reduced activity in the caudate nucleus in PD has also been reported during this task (Lewis, Cools et al., 2003; Lewis, Dove et al., 2003), although this effect occurs during both manipulation and retrieval conditions, suggesting that this structure plays a more general role in cognition.

Taken together, these results suggest that dopamine depletion in early PD specifically affects manipulation more than retrieval, within working memory and these deficits may be related to dysfunction of circuitry involving the mid-dorso-lateral and/or the mid-ventro-lateral frontal cortices. In purely cognitive terms, it is not yet clear what it is about the manipulation condition that makes it particularly susceptible to L-dopa therapy, although plausible candidates include attentional switching (Marie et al., 1999; Cools, Barker, Sahakian, & Robbins, 2001), divided attention (Malapani, Pillon, Dubois, & Agid, 1994; Fournet,

Moreaud, Roulin, Naegele, & Pellat, 2000) and depleted attentional resources (Brown, Soliveri, & Jahanshahi, 1998; Pillon et al., 1998).

These results concur closely with several studies that have examined the effects of fronto-striatal dopamine depletion in non-human primates. For example, prefrontal dopamine loss impairs spatial working memory in monkeys, but does not affect extra-dimensional set-shifting (Roberts et al., 1994). It is notable, therefore, that in the current study, the extra-dimensional set-shifting deficit in the patients with PD was not improved by L-dopa medication.

Although control subjects only underwent testing on the working memory paradigm on one occasion (due to time constraints) it seems reasonable to assume that any practice effects in the patient group would, if anything, have improved performance relative to controls. Therefore, such effects cannot account for the deficits observed here. In addition, the dopaminergic effects did not simply reflect improvements in psychomotor retardation, or 'bradyphrenia' (Rogers, Lees, Smith, Trimble, & Stern, 1987), as improvements were observed for both accuracy and cognitive response time measures. Finally, because the deficits of attentional set-shifting were not affected by L-dopa, general effects of task-difficulty can be ruled out. That is to say, dopaminergic medication did not affect performance on all of the tasks that were impaired in the patient group. Thus, manipulation of information within working memory would appear to be more sensitive to dopamine loss than maintenance and retrieval and, indeed, the processes that are required to shift attentional-set.

However, PD is a progressive neurodegenerative disorder and the patients included in this study were in the early clinical stages of disease and presumably had less severe dopamine depletion than patients with more severe clinical symptoms. It is possible that in the later stages of the disease more profound dopamine depletion would produce deficits in maintenance and retrieval, which might prove sensitive to amelioration with L-dopa. Indeed, such a proposal would be in keeping with a previous study that has demonstrated more global 'frontal-lobe' improvements following L-dopa medication in patients with more severe PD (Lange et al., 1992) and also with data suggesting that early executive dysfunction in PD is predictive of frank dementia later in the disease (Woods & Troster, 2003).

It is also worth noting that although deficits in performance accuracy in the PD patients appeared to be restored to normal levels by dopaminergic medication, the deficits in cognitive reaction time were not (although significant improvements were observed). Parkinson's disease is characterised by a range of non-dopaminergic forms of pathology, including noradrenergic, cholinergic and serotonergic deafferentation of the cortex (Agid et al., 1987), and cortical Lewy bodies (Byrne et al., 1989; Gibb et al., 1989), although all these tend to be more evident late in the course of the disease. Whether the residual deficit in cognitive reaction time reflects one or more of these alternative forms of pathology or the sub-optimal restorative effects of dopaminergic medication remains to be seen.

The fact that attentional set-shifting was unaffected by L-dopa medication at all in this study suggests that deficits in this task may also be mediated by non-dopaminergic forms of pathology in PD. At first glance, this result appears to contradict a previous study in which L-dopa was shown to improve attentional set-shifting performance in a group of patients with severe PD (Lange et al., 1992). However, in that study dopamine improved performance at all stages of task and could not be shown to be related to extra-dimensional set-shifting specifically. Interestingly, in non-human primates, neither prefrontal (Roberts et al., 1994) nor caudate (Collins, Wilkinson, Everitt, Robbins, & Roberts, 2000) dopamine depletion affects extra-dimensional set-shifting specifically. Comparisons between different groups of patients with mild PD have also suggested previously that L-dopa may improve attentional set-shifting in such patients (e.g., Downes et al., 1989; Owen et al., 1992). However, it is important to note that the attentional set-shifting task used in the current study differed in several important ways to that used in these previous investigations (for a detailed account, see Slabosz et al., in preparation). In particular, the task used in this study employed three dimensions in the manner used by Owen, Beksinska et al. (1993) and Owen, Roberts et al. (1993) and specifically emphasises the learned irrelevance component of attentional set-shifting. Learned irrelevance refers to the inability to learn about previously irrelevant or unimportant information and has been shown to be a central component of set-shifting behaviour that is neither affected by damage to the frontal lobes, nor by treatment with dopaminergic medication (Owen, Beksinska et al., 1993; Owen, Roberts et al., 1993).

This study identifies for the first time the differential role of dopaminergic therapy in PD for specific processes within working memory and is broadly consistent with the general notion that executive tasks have different optimal levels of dopamine for their most effective performance (Robbins, 2000). Moreover, the results are also consistent with previous findings in PD, which have demonstrated that L-dopa may have different, and sometimes opposing, effects on specific aspects of executive function (Cools et al., 2001) and it would be interesting to explore this finding with future functional neuro-imaging studies. Given the impact of cognitive impairments and frank dementia in the management of this disease (Brown & Marsden, 1984; Karlsen et al., 1998; Schrag et al., 2000), it is hoped that a greater understanding of the processes underlying these deficits will lead to improvements in future therapeutic strategies.

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References

Aarsland, D., Laake, K., Larsen, J. P., & Janvin, C. (2002). Donepezil for cognitive impairment in Parkinson's disease: A randomised controlled study. *Journal of Neurology, Neurosurgery, and Psychiatry*, *72*, 708–712.

Agid, Y., Javoy-Agid, E., & Ruberg, M. (1987). Biochemistry of neurotransmitters in Parkinson's disease. In C. D. Marsden, et al. (Eds.), *Movement disorders* (pp. 166–230). London: Butterworth.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience*, *9*, 357–381.

Benton, A. L. (1983). Differential behavioural effects of frontal lobe disease. *Neuropsychologia*, *6*, 53–60.

Bradley, V. A., Welch, J. L., & Dick, D. J. (1989). Visuospatial working memory in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *52*, 1228–1235.

Brown, R. G., & Marsden, C. D. (1984). How common is dementia in Parkinson's disease? *Lancet*, *2*, 1262–1265.

Brown, R. G., Soliveri, P., & Jahanshahi, M. (1998). Executive processes in Parkinson's disease—random number generation and response suppression. *Neuropsychologia*, *36*, 1355–1362.

Byrne, E. J., Lennox, G., Lowe, J., & Godwin-Austen, R. B. (1989). Diffuse Lewy body disease: Clinical features in 15 cases. *Journal of Neurology, Neurosurgery, and Psychiatry*, *52*, 709–717.

Collins, P., Wilkinson, L. S., Everitt, B. J., Robbins, T. W., & Roberts, A. C. (2000). The effect of dopamine depletion from the caudate nucleus of the common marmoset (*Callithrix jacchus*) on tests of prefrontal cognitive function. *Behavioral Neuroscience*, *114*, 3–17.

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001). Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cerebral Cortex*, *11*, 1136–1143.

Cools, R., Stefanova, E., Barker, R. A., Robbins, T. W., & Owen, A. M. (2002). Dopaminergic modulation of high-level cognition in Parkinson's disease: The role of the prefrontal cortex revealed by PET. *Brain*, *125*, 584–594.

Cooper, J. A., Sagar, H. J., Doherty, S. M., Jordan, N., Tidswell, P., & Sullivan, E. V. (1992). Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease. A follow-up study of untreated patients. *Brain*, *115*, 1701–1725.

Cooper, J. A., Sagar, H. J., Jordan, N., Harvey, N. S., & Sullivan, E. V. (1991). Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. *Brain*, *114*, 2095–2122.

Cooper, J. A., Sagar, H. J., & Sullivan, E. V. (1993). Short-term memory and temporal ordering in early Parkinson's disease: Effects of disease chronicity and medication. *Neuropsychologia*, *31*, 933–949.

Costa, A., Peppe, A., Dell'Agnello, G., Carlesimo, G. A., Murri, L., Bonuccelli, U., et al. (2003). Dopaminergic modulation of visual-spatial working memory in Parkinson's disease. *Dementia and Geriatric Cognitive Disorder*, *15*, 55–66.

Dagher, A., Owen, A. M., Boecker, H., & Brooks, D. J. (1999). Mapping the network for planning: A correlational PET activation study with the Tower of London task. *Brain*, *122*, 1973–1987.

Downes, J. J., Roberts, A. C., Sahakian, B. J., Evenden, J. L., Morris, R. G., & Robbins, T. W. (1989). Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: Evidence for a specific attentional dysfunction. *Neuropsychologia*, *27*, 1329–1343.

Dubois, B., Pilon, B., Lhermitte, F., & Agid, Y. (1990). Cholinergic deficiency and frontal dysfunction in Parkinson's disease. *Annals of Neurology*, *28*, 117–121.

Fahn, S., & Elton, R. (1987). Unified Parkinson's disease rating scale. In S. Fahn, et al. (Eds.), *Recent developments in Parkinson's disease* (pp. 153–163). New Jersey: Macmillan Health Care Information.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*, 189–198.

Fournet, N., Moreaud, O., Roulin, J. L., Naegele, B., & Pellat, J. (2000). Working memory functioning in medicated Parkinson's disease patients and the effect of withdrawal of dopaminergic medication. *Neuropsychology*, *14*, 247–253.

Fuster, J. M. (1997). *The prefrontal cortex*. New York: Raven Press.

Gibb, W. R., & Lees, A. J. (1988). A comparison of clinical and pathological features of young- and old-onset Parkinson's disease. *Neurology*, *38*, 1402–1406.

Gibb, W. R., Luthert, P. J., Janota, I., & Lantos, P. L. (1989). Cortical Lewy body dementia: Clinical features and classification. *Journal of Neurology, Neurosurgery, and Psychiatry*, *52*, 185–192.

Goldman-Rakic, P. S. (1987). Circuitry of the primate prefrontal cortex and regulation of behaviour by representational memory. In F. Plum (Ed.), *Handbook of physiology* (pp. 373–517). Washington DC: The American Physiological Society.

Goodglass, H. (1972). *Assessment of aphasia and related disorders*. Philadelphia: Lea and Febiger.

Gotham, A. M., Brown, R. G., & Marsden, C. D. (1988). Frontal cognitive function in patients with Parkinson's disease on and off levodopa. *Brain*, *111*, 299–321.

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: Onset, progression and mortality. *Neurology*, *17*, 427–442.

Ito, K., Nagano-Saito, A., Kato, T., Arahata, Y., Nakamura, A., Kawasumi, Y., et al. (2002). Striatal and extrastriatal dysfunction in Parkinson's disease with dementia: A 6-[18F]fluoro-L-dopa PET study. *Brain*, *125*, 1358–1365.

Jellinger, K. A. (2001). The pathology of Parkinson's disease. *Advances in Neurology*, *86*, 55–72.

Karlsen, K. H., Larsen, J. P., Tandberg, E., & Maland, J. G. (1998). Quality of life measurements in patients with Parkinson's disease. A community-based study. *European Journal of Neurology*, *5*, 443–450.

Lange, K. W., Robbins, T. W., Marsden, C. D., James, M., Owen, A. M., & Paul, G. M. (1992). L-dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. *Psychopharmacology (Berlin)*, *107*, 394–404.

Le Bras, C., Pillon, B., Damier, P., & Dubois, B. (1999). At which steps of spatial working memory processing do striatofrontal circuits intervene in humans? *Neuropsychologia*, *37*, 83–90.

Lees, A. J., & Smith, E. (1983). Cognitive deficits in the early stages of Parkinson's disease. *Brain*, *106*, 257–270.

Lewis, S. J., Cools, R., Robbins, T. W., Dove, A., Barker, R. A., & Owen, A. M. (2003). Using executive heterogeneity to explore the nature of working memory deficits in Parkinson's disease. *Neuropsychologia*, *41*, 645–654.

Lewis, S. J. G., Dove, A., Robbins, T. W., Barker, R. A., & Owen, A. M. (2003). Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. *Journal of Neuroscience*, *23*, 6351–6356.

Malapani, C., Pillon, B., Dubois, B., & Agid, Y. (1994). Impaired simultaneous cognitive task performance in Parkinson's disease: A dopamine-related dysfunction. *Neurology*, *44*, 319–326.

Marie, R. M., Barre, L., Dupuy, B., Viader, F., Defer, G., & Baron, J. C. (1999). Relationships between striatal dopamine denervation and frontal executive tests in Parkinson's disease. *Neuroscience Letters*, *260*, 77–80.

Mattay, V. S., Tessitore, A., Callicott, J. H., Bertolino, A., Goldberg, T. E., Chase, T. N., et al. (2002). Dopaminergic modulation of cortical function in patients with Parkinson's disease. *Annals of Neurology*, *51*, 156–164.

Morris, R. G., Downes, J. J., Sahakian, B. J., Evenden, J. L., Heald, A., & Robbins, T. W. (1988). Planning and spatial working memory in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *51*, 757–766.

Nelson, H. E. (1982). *National adult reading test manual*. Windsor: NFER-Nelson.

Owen, A. M. (2000). The role of the lateral frontal cortex in mnemonic processing: The contribution of functional neuroimaging. *Experimental Brain Research, 133*, 33–43.

Owen, A. M., Beksinska, M., James, M., Leigh, P. M., Summers, B. A., Marsden, C. D., et al. (1993). Visuospatial memory deficits at different stages of Parkinson's disease. *Neuropsychologia, 31*, 627–644.

Owen, A. M., Downes, J. J., Sahakian, B. J., Polkey, C. E., & Robbins, T. W. (1990). Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia, 28*, 1021–1034.

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

Owen, A. M., Herrod, N. J., Menon, D. K., Clark, J. C., Downey, S. P., Carpenter, T. A., et al. (1999). Redefining the functional organization of working memory processes within human lateral prefrontal cortex. *European Journal of Neuroscience, 11*, 567–574.

Owen, A. M., Iddon, J. L., Hodges, J. R., Summers, B. A., & Robbins, T. W. (1997). Spatial and non-spatial working memory at different stages of Parkinson's disease. *Neuropsychologia, 35*, 519–532.

Owen, A. M., James, M., Leigh, P. N., Summers, B. A., Marsden, C. D., Quinn, N. P., et al. (1992). Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain, 115*, 1727–1751.

Owen, A. M., Roberts, A. C., Hodges, J. R., Summers, B. A., Polkey, C. E., & Robbins, T. W. (1993). Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. *Brain, 116*, 1159–1175.

Paulus, W., & Jellinger, K. (1991). The neuropathologic basis of different clinical subgroups of Parkinson's disease. *Journal of Neuropathology and Experimental Neurology, 50*, 743–755.

Pillon, B., Deweer, B., Vidailhet, M., Bonnet, A. M., Hahn-Barma, V., & Dubois, B. (1998). Is impaired memory for spatial location in Parkinson's disease domain specific or dependent on strategic processes? *Neuropsychologia, 36*, 1–9.

Postle, B. R., Jonides, J., Smith, E. E., Corkin, S., & Growdon, J. H. (1997). Spatial, but not object, delayed response is impaired in early Parkinson's disease. *Neuropsychology, 11*, 171–179.

Rinne, J. O., Rummukainen, J., Paljarvi, L., & Rinne, U. K. (1989). Dementia in Parkinson's disease is related to neuronal loss in the medial substantia nigra. *Annals of Neurology, 26*, 47–50.

Robbins, T. W. (2000). Chemical neuromodulation of frontal-executive functions in humans and other animals. *Experimental Brain Research, 133*, 130–138.

Roberts, A. C., De Salvia, M. A., Wilkinson, L. S., Collins, P., Muir, J. L., Everitt, B. J., et al. (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. *Journal of Neuroscience, 14*, 2531–2544.

Rogers, D., Lees, A. J., Smith, E., Trimble, M., & Stern, G. M. (1987). Bradyphrenia in Parkinson's disease and psychomotor retardation in depressive illness. An experimental study. *Brain, 110*, 761–776.

Sawaguchi, T., & Goldman-Rakic, P. S. (1991). D1 dopamine receptors in prefrontal cortex: Involvement in working memory. *Science, 251*, 947–950.

Schrag, A., Jahanshahi, M., & Quinn, N. (2000). What contributes to quality of life in patients with Parkinson's disease? *Journal of Neurology, Neurosurgery, and Psychiatry, 69*, 308–312.

Seamans, J. K., Floresco, S. B., & Phillips, A. G. (1998). D1 receptor modulation of hippocampal-prefrontal cortical circuits integrating spatial memory with executive functions in the rat. *Journal of Neuroscience, 18*, 1613–1621.

Slabosz, A., Lewis, S. J. G., Smigasiewicz, K., Szymura, B., Barker, R. A., & Owen, A. M. (in preparation). *Brain*.

Smith, E. E., & Jonides, J. (1999). Storage and executive processes in the frontal lobes. *Science, 283*, 1657–1661.

Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. (1986). Frontal lobe dysfunction in Parkinson's disease. The cortical focus of neostriatal outflow. *Brain, 109*, 845–883.

Williams, G. V., & Goldman-Rakic, P. S. (1995). Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature, 376*, 572–575.

Woods, S. P., & Troster, A. I. (2003). Prodromal frontal/executive dysfunction predicts incident dementia in Parkinson's disease. *Journal of International Neuropsychological Society, 9*, 17–24.