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# Dopaminergic modulation of high-level cognition in Parkinson's disease: the role of the prefrontal cortex revealed by PET

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## Summary

**This study examined the effects of L-dopa medication in patients with Parkinson's disease on cortical and subcortical blood flow changes during two tasks known to involve frontostriatal circuitry. Eleven patients with Parkinson's disease were scanned on two occasions, one ON L-dopa medication and one OFF L-dopa medication, during performance of the Tower of London planning task and a related test that emphasized aspects of spatial working memory. L-dopa-induced decreases were observed in the right dorsolateral prefrontal cortex during performance of both the planning and the spatial working memory tasks compared with the visuomotor control task. Conversely, L-dopa-induced blood flow increases were observed in the right occipital lobe during the memory task relative to the control task. Data from age-matched healthy volunteers demonstrated that L-dopa effectively normalized blood flow in these regions in the patient group. Moreover, a significant correlation was found between L-dopa-induced, planning related blood flow decreases in the right dorsolateral prefrontal cortex and L-dopa-induced changes in performance on the planning task. These data suggest that L-dopa ameliorates high-level cognitive deficits in Parkinson's disease by inducing relative blood flow changes in the right dorsolateral prefrontal cortex.**

**Keywords**: Parkinson's disease; dopamine; high-level cognition; dorsolateral prefrontal cortex

## Introduction

Motor disturbances in Parkinson's disease are accompanied by intellectual impairment, even in the earliest stages of the disease, and it has been suggested that frontal lobe dysfunction may underlie these deficits (Gotham *et al*., 1988; Owen *et al*., 1992, 1993*a*, *b*, 1995*a*, *b*). For example, accumulating evidence indicates that cognitive planning and spatial working memory deficits, often associated with damage to the prefrontal cortex, are core features of Parkinson's disease (Mishkin, 1957; Gross and Weiskrantz, 1962; Shallice, 1982; Morris *et al*., 1988; Owen *et al*., 1990, 1992, 1993*a*, 1995*a*, *b*, 1996*a*, *b*, 1997; Jonides *et al*., 1993; McCarthy *et al*., 1994; Baker *et al*., 1996; Gabrieli *et al*., 1996; Postle *et al*., 1997; Collins *et al*., 1998; Pillon *et al*., 1998; West *et al*., 1998; Dagher *et al*., 1999; Le Bras *et al*., 1999).

In general, however, dopamine depletion, the cardinal neurochemical feature of Parkinson's disease, is relatively low in the frontal lobe compared with the striatum (Agid *et al*., 1987; Kish *et al*., 1988). It seems unlikely, therefore, that frontal lobe dysfunction alone can account for the 'frontal-like' symptoms observed. In keeping with this notion, Owen *et al*. (1998) observed abnormal blood flow in the basal ganglia in patients with Parkinson's disease during performance of the Tower of London planning task and a related test of spatial working memory. This blood flow change in patients was accompanied by a performance deficit, similar to that seen in patients with frontal lobe damage, although no abnormalities in regional cerebral blood flow were observed in the prefrontal cortex (see also Owen *et al*., 1996*a*). A more recent study (Dagher *et al*., 2001) has replicated this pattern of abnormal blood flow in the basal ganglia but normal blood flow in the cortex, again using the Tower of London task in patients with Parkinson's disease. Together, these data suggest that in Parkinson's disease, dopamine depletion

disrupts basal ganglia outflow and consequently affects the expression of prefrontal functioning by interrupting fronto-striatal circuitry (Alexander *et al*., 1986). Perhaps unsurprisingly, therefore, subtle performance differences have been observed between patients with Parkinson's disease and patients with frontal lobe lesions (for example, see Owen *et al*., 1993*b*)

Administration of L-dopa to patients with Parkinson's disease has repeatedly been shown to improve performance on both the Tower of London planning task (Lange *et al*., 1992; Owen *et al*., 1995*a*) and on tests of spatial working memory (Lange *et al*., 1992; Kulisevsky *et al*., 1996; Fournet *et al*., 2000), although the precise neural locus of this effect is unknown. Abundant evidence from both lesion and electrophysiological studies in non-human primates (Brozoski *et al*., 1979; Glowinski *et al*., 1984; Sawaguchi *et al*., 1990; Yang and Mogenson, 1990; Sawaguchi and Goldman-Rakic, 1991; Goldman-Rakic, 1992; Roberts *et al*., 1994; Williams and Goldman-Rakic, 1995; Arnsten, 1998) and neuroimaging studies in humans (Daniel *et al*., 1991; Friston *et al*., 1992; Grasby *et al*., 1992; Mattay *et al*., 1996, 2000, 2002; Mehta *et al*., 2000) suggests that the dorsolateral prefrontal cortex is the critical locus for dopaminergic effects on high level cognitive functions such as planning and working memory. For example, dopamine (6-OHDA) lesions in the dorsolateral prefrontal cortex of the monkey impair performance on a spatial delayed alternation task, whilst administration of dopamine agonists reverses this impairment (Brozoski *et al*., 1979). In healthy human volunteers, improvement of performance on a self-ordered spatial working memory task, following methylphenidate (a monoamine enhancer) administration has been shown to be accompanied by a task-related blood flow reduction in the dorsolateral prefrontal cortex (Mehta *et al*., 2000)

In the present study, we used positron emission tomography (PET) to examine the critical locus of the effect of dopaminergic medication on high level cognitive functioning in patients with Parkinson's disease. Eleven patients were scanned on two occasions during performance of a cognitive planning task (the 'Tower of London') and a related test that emphasized aspects of spatial working memory, but required minimal planning. The tasks were identical to those used previously to investigate planning and spatial working memory in patients with Parkinson's disease tested only OFF L-dopa (Owen *et al*., 1998). On one occasion, patients were scanned while taking their dopaminergic medication as usual. On the other occasion, they were asked to abstain from their medication for at least 18 h prior to their visit to the imaging centre.

In line with the results from previous studies (Owen *et al*., 1998; Mehta *et al*., 2000), we predicted that administration of L-dopa medication in patients with Parkinson's disease would result in task-related blood flow changes in the dorsolateral prefrontal cortex, in the basal ganglia, or in both.

# Methods

## *Subjects*

Eleven right-handed patients with mild to moderate Parkinson's disease (four females) were seen on two occasions separated by ~1 week [mean age 57.8 years, SEM (standard error of the mean) 2.5]. Six right-handed age-matched controls, (two females, mean age 58 years, SEM 2.3) were also scanned on two occasions while performing the same tasks. All patients presented at a general neurology clinic and were diagnosed by a consultant neurologist (R.A.B.) as having idiopathic Parkinson's disease according to UK Brain Bank criteria. All had Hoehn and Yahr disease severity ratings of I to III (Hoehn and Yahr, 1967) in the ON state (mean rating 1.95, SEM 0.17). The mean duration of the disease was 5.1 years (SEM 1.5). Patients with a significant medical history not related directly to their Parkinson's disease (e.g. stroke, head injury, clinical dementia or depression) were not referred for the study. All eleven patients included in the study were receiving daily L-dopa preparations and all were responding well. Two patients were also taking a dopamine receptor agonist, two a dopamine activity enhancer (amantadine and entacapone), two a MAO-B (monoamine oxidase B) inhibitor and one a betablocker and an antidepressant. None were suffering from a confusional state at the time of testing. For the purposes of the study, the patients were asked to undergo a PET scan on two occasions. On one of the two occasions, they were asked to abstain from taking their L-dopa medication the night before the PET scan was scheduled to take place, at least 18 h prior to the experiment. On the other occasion, which was separated from the first by ~1 week, the patients were asked to continue taking their medication as usual. The order in which the patients were scanned ON and OFF their medication was counterbalanced, so that six of the patients were ON their medication and five of the patients were OFF their medication on the first occasion.

Ethical considerations precluded scanning in healthy control volunteers ON and OFF L-dopa in order that direct comparisons could be made between the patients and a group of subjects without dopamine loss. However, six healthy control subjects were scanned while performing the three behavioural tasks and *post hoc* comparisons were made with patients in those areas where significant drug effects were observed.

All subjects gave informed consent for participation in the study after its nature and possible consequences were explained to them. The study was approved by the Cambridge Local Research Ethics Committee.

## *Image acquisition and data analysis*

Six PET scans were obtained on each of two occasions for each subject using the General Electrics Advance system (General Electrics, Milwaukee, Wis., USA). This produces 35 simultaneous image slices per scan at an intrinsic resolution

of ~4.0 × 5.0 × 4.5 mm. For each scan, regional cerebral blood flow was measured using the bolus $H_2{}^{15}O$ methodology. The subjects received a 20 s intravenous bolus of $H_2{}^{15}O$ through a forearm cannula at a concentration of 300 MBq/ml and a flow rate of 10 ml/min just prior to PET data acquisition. With this method, each scan provides an image of regional cerebral blood flow integrated over a period of 90 s from when the tracer first enters the cerebral circulation. The scans were pre-processed individually and then combined with the other subjects' scans for collective statistical analysis. Both processes were carried out using the Statistical Parametric Mapping 99 (SPM99) package provided by the Wellcome Department of Cognitive Neurology, London, UK. For pre-processing, the scans were: (i) realigned to the first scan and then *post hoc* to a created mean; (ii) normalized for global cerebral blood flow value and also spatially normalized to conform to the standard brain described by Talairach and Tournoux (1988); and (iii) spatially smoothed using an isotropic Gaussian kernel at 16 mm. The data were adjusted for the effects of global image signal, which was justified by a *post hoc* comparison of global counts revealing no differences between the ON and OFF L-dopa state [$T(10) = -1.5$, $P = 0.2$]. Blood flow changes between the ON and OFF L-dopa condition were then estimated for each voxel according to the general linear model, as implemented by the SPM99 method. To reduce scan order and movement artefacts, six movement parameters and a scan time order covariate were calculated relative to the anterior commissure (Matthew Brett, personal communication). These parameters were then entered as covariates of no interest into SPM99. An intensity threshold set at $P \leqslant 0.001$ (uncorrected for multiple comparisons) was applied for activations occurring within the dorsolateral prefrontal cortex and the basal ganglia for specific comparisons (Worsley *et al*., 1992, 1996). The uncorrected threshold was used on account of the predictions made, *a priori*, about activation occurring within the dorsolateral prefrontal cortex and the basal ganglia. Significant peaks only are reported. This threshold, based on 3D Gaussian random field theory, predicts the likelihood of obtaining a false positive in an extended 3D field.

Supplementary analyses were conducted to further analyse the significant drug by task interaction effects. First, voxel values were extracted from each scan for regions in which a significant task by drug interaction effect was observed. Non-parametric Spearman correlation coefficients were then calculated between these voxel values and performance measures. Previous studies have demonstrated that L-dopa significantly improves performance in Parkinson's disease with tasks similar to those used in the current study (Lange *et al*., 1992). Therefore, one-tailed analyses were used to test the hypothesis that the observed task-related, L-dopa-induced decreases in the prefrontal cortex were related to improvements in performance. These correlational analyses were restricted to those between L-dopa-induced differences in latency performance measures and L-dopa-induced blood flow differences in the dorsolateral prefrontal cortex.

A second *post hoc* analysis, in which both patients and control subjects were included, was performed to identify baseline levels of blood flow in those areas found to be significantly modified by L-dopa in patients. Thus, blood flow values were extracted from control subjects (*post hoc*) for only those voxels for which a significant task by drug interaction was found in the 'patients analysis' (described above). Repeated measures ANOVAs (analyses of variance) and simple effects analyses were performed to compare control subjects with patients ON and patients OFF L-dopa separately.

## *Stimuli and testing conditions*

There were two experimental conditions and one control condition in this study. All stimuli were presented on a high-resolution, touch-sensitive computer screen. One of the experimental tasks was based directly on the Tower of London planning task; we refer to this condition as 'planning'. The other experimental condition required that subjects monitor, and then reproduce, short (three moves) or long (four or five moves) sequences of moves. This was designed to emphasize spatial working memory rather than planning ability and we refer to this condition as 'spatial working memory'. A further 'control' condition was included which involved similar visual stimuli and motor responses to the planning and spatial working memory tasks, but which required little planning and minimal working memory. We refer to this condition as 'visuomotor control'. These conditions have been described previously by Owen *et al*. (1996*a,* 1998) and the reader is referred to these papers for a more detailed description of the tasks.

During each scanning session, patients performed the planning task, the visuomotor control task and spatial working memory task in that order. This procedure was repeated, so that in each session, patients performed each task twice; this corresponded to the six scans. It was not possible to randomize the order of the tasks because both the visuomotor control task and the spatial working memory task were 'yoked' to the planning task (see below for description of tasks). However, this does not systematically confound the results of this study since the same fixed order was used for both visits.

In each of the three testing conditions, the subjects were presented with two sets of three coloured 'balls' (i.e. circles), one in the top half of the screen and the other in the bottom half. The three balls were distributed in three 'pockets' (or 'socks'), which could hold one, two or three balls. On each trial, a red ball, a blue ball and a green ball were placed in predetermined positions in both the upper and the lower pockets of each of the two displays. The subjects were told that the balls in the top half of the screen could not be rearranged, but any ball in the bottom half of the screen could be moved between pockets.

Although each of the six scans lasted only 90 s, the tasks were always begun 10 s before scanning and continued after

scanning until a total of 120 s had elapsed. The scans were separated by ~8 min during which time the requirements for the next condition were explained to the subject. In addition, a fixed number of practice problems were administered before each scan to ensure that the requirements of the task had been fully understood.

### *Planning*

Subjects were asked to copy the top arrangement of 'balls' by moving 'balls' around in the bottom arrangement. Two types of moves were not allowed: (i) placing a ball high in a pocket when there was no other ball beneath to support it; and (ii) trying to remove a ball while there was another sitting above it in the same pocket. When such moves were attempted, there was no response from the computer. Patients were told not to make a first move until they were confident that they could execute the entire sequence needed to solve the problem. An easy three-move version was given to three patients, who were unable to perform the more difficult four- and five-move versions of the same task. The computer recorded the number of moves made by the subject to rearrange the balls, as well as the selection and movement latencies for each move.

### *Spatial working memory*

During this condition, a mnemonic variant of the planning task was employed which involved similar visual stimulation and motor responses, but minimal planning. The subjects were instructed to watch while the computer made a series of single moves in the bottom half of the screen, and then asked to attempt to repeat this sequence once all the balls returned to their original positions. These computer-generated moves were 'yoked' to the planning condition in that they were paced according to the speed of that particular subject in the planning scan. The subject was required to observe and remember each sequence of four or five moves (or three moves in the easy version), and then to repeat that same sequence. Since 'wrong moves' were disallowed, only latencies for each correct move made by the subject were recorded.

### *Visuomotor control*

During this condition, a control task was employed which involved identical visual stimuli and motor responses to the planning and spatial working memory tasks. Subjects were instructed simply to touch a series of locations in the bottom half of the screen that were 'highlighted' with yellow rings. For each patient, the sequence of moves required in this control task corresponded exactly to the moves produced by that individual when performing the problems in the planning condition. In addition, the computer used the stored selection and movement latencies from that subject in the previous condition, to pace the patient's responses in the control condition. The computer recorded the selection latencies for each move.

## *Performance indices*

The main indices of performance in the planning task were the proportion of total problems solved in the minimum number of moves (i.e. 'perfect' solutions) [2*arcsin($\sqrt{x}$) transformed; Howell, 1997], and the proportion of problems solved within the maximum allowed (also arcsin transformed). Log-transformed initial thinking times [lg(10) transformed] were calculated by subtracting the first latency in the visuomotor control task from the first latency in the planning task for each problem. Subsequent thinking times [also lg(10) transformed] were calculated by averaging the differences between the subsequent planning and visuomotor latencies for each problem. Log-transformed memory times were calculated by averaging the memory latencies for each problem. These measures were calculated by averaging over four- and five-move problems for each of the two separate sessions. In addition, the actual number of movements made by the patients during the planning condition at each difficulty level was recorded. For control purposes, the spatial working memory task required subjects to reproduce previously presented 'perfect' solutions. Any incorrect selection by the subject elicited no response from the computer (i.e. they were required to try again until the correct move was found). Therefore, it was not possible to acquire any absolute measure of performance accuracy on these two tasks during the scans. However, deficits in performance accuracy have been widely reported in Parkinson's disease patients (e.g. Morris *et al*., 1988; Owen *et al*., 1992, 1993*a*, 1995*a*). Like the visuomotor control condition, the timing of moves during the spatial working memory task was yoked directly to the planning condition such that overall, the number of responses required within the 90 s performance period was approximately equivalent. The data for the ON session for one patient were lost following a technical error. One patient performed only three-move problems in the OFF condition. Performance at the three-move level was not included in the analysis since only two patients performed such problems.

# Results

## *Regional cerebral blood flow*

### *Spatial working memory*

Comparison of spatial working memory task-related blood flow differences in the ON L-dopa and OFF L-dopa conditions revealed a significant interaction in the right dorsolateral prefrontal cortex (at coordinates $x, y, z = 38, 28, 22$; $T = 3.3$; $P = 0.001$) (Fig. 1A) and in the right occipital lobe (at coordinates $x, y, z = 14, -84, 26$; $T = 4.8$; $P < 0.001$). The OFF condition was associated with an increase in blood flow in the right dorsolateral prefrontal cortex during the memory task relative to the control task, while, in the ON condition, no

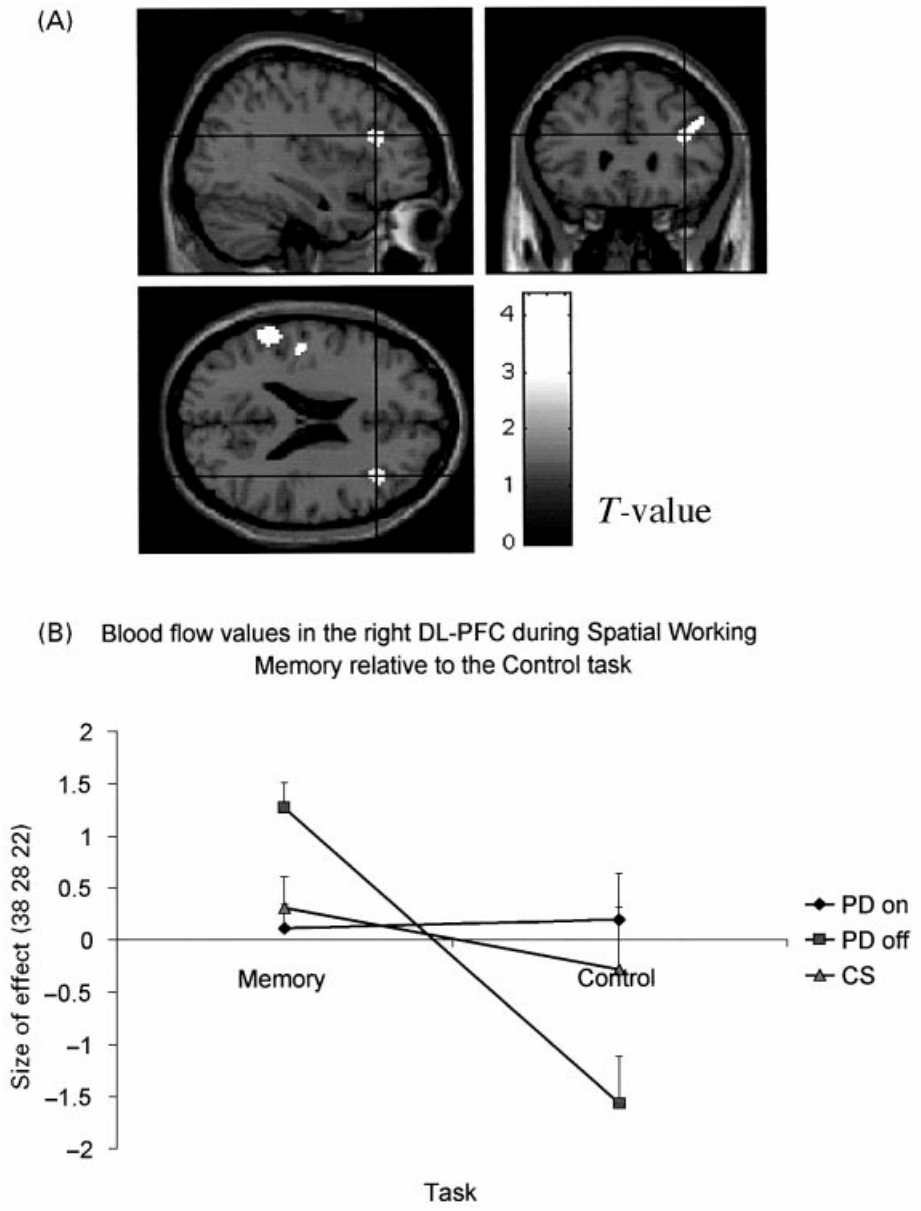


**Fig. 1** The average PET image (statistical parametric map) is shown as sagittal, coronal and transverse sections superimposed upon the MNI (Montreal Neurological Institute) template brain (individual brain considered most typical of the 305 brains used to define the MNI standard) for the drug-by-memory task interaction contrast (spatial working memory task-related blood flow changes modulated by L-dopa). (**A**) A significant peak was observed in the right dorsolateral prefrontal cortex (at coordinates $x$, $y$, $z$ = 38, 28, 22; this image was rendered using an uncorrected threshold of $P < 0.005$). (**B**) Blood flow was increased during the spatial working memory task relative to the visuomotor control task in the OFF condition, but blood flow did not differ between the tasks in the ON condition. *Post hoc* comparisons with baseline voxel values, extracted from healthy volunteers, revealed that the blood flow pattern in the ON state was similar to that in control subjects, whereas the pattern in the OFF state was not. PD = Parkinson's disease subjects; CS = control subjects.

significant change was observed (Fig. 1B). Conversely, L-dopa induced blood flow increases in the right occipital lobe during the memory task relative to the control task.

*Post hoc* simple effect analyses of these drug-by-task interaction effects revealed that L-dopa affected blood flow during both the memory task and the control task. In other words, there were significant differences between patients' blood flow ON and OFF L-dopa during both the memory task (prefrontal cortex $P = 0.01$; occipital lobe $P = 0.04$) and the control task (prefrontal cortex $P = 0.04$; occipital lobe $P = 0.001$).

In order to investigate these changes further, *post hoc* comparisons were made with baseline blood flow data, extracted from age-matched healthy controls. These analyses revealed that, in patients, L-dopa normalized blood flow levels in the dorsolateral prefrontal cortex and the occipital

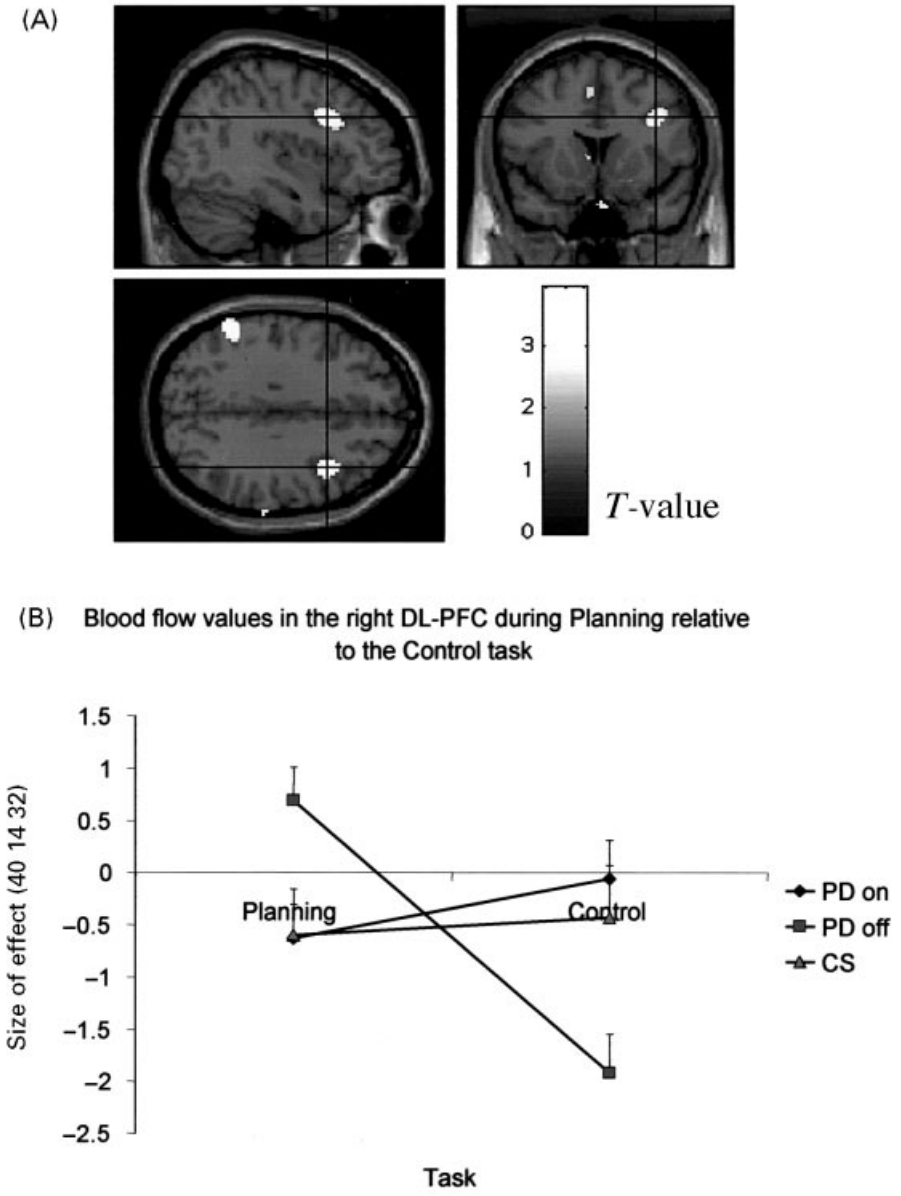


**Fig. 2** The average PET image superimposed upon the MNI template brain and graph of planning task-related blood flow differences between the ON and OFF conditions. (**A**) A significant peak was observed in the right dorsolateral prefrontal cortex (at coordinates *x*, *y*, *z* = 40, 14, 32; this image was rendered using an uncorrected threshold of $P < 0.01$). (**B**) Blood flow was increased during the planning task relative to the visuomotor control task in the OFF condition, but in the ON condition blood flow did not differ between the planning task and the visuomotor control task. *Post hoc* comparison with data from normal volunteers showed that L-dopa normalized blood flow in this area. PD = Parkinson's disease subjects; CS = control subjects.

lobe. Repeated measures analyses confirmed these observations. Thus, in the prefrontal cortex, there was a significant group by task interaction when patients OFF L-dopa were compared with controls [$F(1,15) = 5.6$, $P = 0.03$], but not when patients ON L-dopa were compared with controls [$F(1,15) = 0.9$, $P = 0.4$]. In the right occipital lobe, there was a significant group by task interaction when patients OFF L-dopa were compared with controls [$F(1,15) = 8.2$, $P = 0.01$], but not when patients ON L-dopa were compared with controls [$F(1,15) = 2.4$, $P = 0.14$].

## *Planning*

Comparison of planning task-related blood flow differences in the ON L-dopa and OFF L-dopa conditions revealed a similar pattern to the memory task comparison. A significant planning task by drug interaction was again found in the right dorsolateral prefrontal cortex (at coordinates *x*, *y*, *z* = 40, 14, 32; $T = 3.4$; $P = 0.001$) (Fig. 2A). The OFF condition was associated with a relative increase in blood flow in the right dorsolateral prefrontal cortex during the planning task relative to the control task while, in the ON condition, no

significant difference was observed between the planning and control tasks (Fig. 2B).

The effect in the occipital lobe was also present but did not reach significance according to our criteria. *Post hoc* simple effect analyses of the drug-by-task interaction effect in the prefrontal cortex revealed that L-dopa affected both planning task-related ($P = 0.006$) and control task-related processes ($P = 0.012$).

To investigate these changes further, *post hoc* comparisons were made with baseline blood flow data extracted from age-matched healthy controls. These analyses revealed that L-dopa normalized blood flow levels in the dorsolateral prefrontal cortex. There was a significant group by task interaction effect when patients OFF L-dopa were compared with controls [$F(1,15) = 5.8$, $P = 0.03$], but not when patients ON L-dopa were compared with controls [$F(1,15) = 0.25$, $P = 0.6$].

Finally, although the data were variable, significant correlations were found between the blood flow change in the right dorsolateral prefrontal cortex during the planning task following L-dopa (i.e. blood flow during planning OFF minus blood flow during planning ON) and performance change following L-dopa in terms of initial thinking time [Spearman $r(18) = 0.44$, $P = 0.035$] and subsequent thinking time (Spearman $r(18) = 0.49$, $P = 0.02$]. Thus, the greater the blood flow change during the planning task relative to the control task in the right prefrontal cortex, the greater the performance change on the most difficult planning problems.

### *Main drug effects*

Over all task conditions, administration of L-dopa was found to be associated with increased blood flow centred on the left globus pallidus/subthalamic nucleus (at coordinates $x, y, z = -8, 0, -2$; $T = 4.75$) and decreased blood flow in the superior temporal gyrus ($x, y, z = 62, 18, -12$; $T = 5.93$), the precuneus ($x, y, z = 12, -60, 26$; $T = 5.29$) and the insula ($x, y, z = 50, -28, 22$; $T = 4.92$).

### *Behavioural data*

Repeated measures analyses revealed no significant differences between patients' performance in the ON L-dopa state and performance in the OFF L-dopa state. Patients ON solved 44% (SEM = 9%) of all problems perfectly and patients OFF solved 45% (SEM = 5%) of all problems perfectly [$F(1,9) = 0.008$, $P = 0.9$]. Similarly, the proportion of problems solved within the maximum number of problems allowed did not significantly differ between the patients ON and OFF L-dopa [$F(1,9) = 0.03$, $P = 0.9$]. Patients ON solved 66.7% (SEM = 9%) of problems within the maximum allowed, while patients OFF solved 70.8% (SEM = 5%) within the maximum allowed. There was also no difference in terms of initial thinking time [$F(1,9) = 1.02$, $P = 0.34$], subsequent thinking time [$F(1,9) = 0.04$, $P = 0.8$] or 'memory' time [$F(1,9) = 0.3$, $P = 0.6$] (see Table 1).

**Table 1** *Mean (SEM) thinking times for the Tower of London planning task*

| | Initial thinking time (s) | Subsequent thinking time (s) |
|---|---|---|
| Controls | 3.8 (0.47) | 0.54 (0.1) |
| Patients ON | 4.9 (0.9) | 1.76 (0.5) |
| Patients OFF | 3.9 (0.4) | 1.6 (0.36) |

Like patients, control subjects were scanned on two occasions in order to evaluate practice effects. However, there were no significant differences between performance on the first and second occasion. Control subjects solved 57% (SEM = 8%) of all problems perfectly and 78% (SEM = 5%) within the maximum number of problems allowed. There were no consistent significant differences between performance of control subjects and patients with Parkinson's disease in terms of any of the measures. A repeated measures analyses on the number of movements made revealed a significant effect of difficulty level [$F(1,8) = 7.69$, $P = 0.024$]. As expected, subjects made more moves on five-move problems than on four-move problems. The main effect of medication also tended towards significance [$F(1,8) = 4.77$, $P = 0.06$]: patients OFF medication tended to make fewer movements over both levels than patients ON medication. The interaction of medication by difficulty for the number of movements was not significant [$F(1,8) = 1.95$, $P = 0.2$]).

## Discussion

To our knowledge, this is the first study to have examined L-dopa-induced, task-related regional cerebral blood flow changes in patients with Parkinson's disease using high-level cognitive tasks.

L-Dopa normalized relative blood flow levels in the right dorsolateral prefrontal cortex in patients with Parkinson's disease by decreasing cerebral blood flow during both the spatial working memory and planning tasks relative to the control task. This task-specific, L-dopa-induced neuromodulation of the dorsolateral prefrontal cortex is broadly consistent with both animal studies (Brozoski *et al*., 1979; Glowinski *et al*., 1984; Yang and Mogenson, 1990; Sawaguchi and Goldman-Rakic, 1991; Goldman-Rakic, 1992; Roberts *et al*., 1994; Williams and Goldman-Rakic, 1995; Zahrt *et al*., 1997; Arnsten, 1998) and imaging studies in humans (Daniel *et al*., 1991; Friston *et al*., 1992; Grasby *et al*., 1992; Mattay *et al*., 1996, 2000, 2002; Mehta *et al*., 2000).

The current study was designed specifically to examine the modulatory effects of L-dopa in patients. Whole-brain comparisons with a group of control subjects ON and OFF L-dopa were not feasible. *Post hoc* comparisons to baseline blood flow values (extracted from age-matched healthy volunteers) were performed, however, in those regions in

which a significant drug by task interaction effect was found in the patients. The results confirmed that L-dopa normalized task-related blood flow levels in the dorsolateral prefrontal cortex and the occipital lobe.

Previous data have suggested that the 'frontal-like' cognitive deficits in patients with Parkinson's disease reflect basal ganglia pathology, disrupting the flow of information through frontostriatal circuitry (Owen *et al*., 1998; Dagher *et al*., 2001). On this basis, the current study examined L-dopa-induced changes in the basal ganglia. Contrary to expectations, no significant changes were observed, raising the possibility that L-dopa may modulate cognitive deficits in patients with Parkinson's disease by acting directly on the dorsolateral prefrontal cortex.

The similarity between the pattern of results for the spatial working memory and planning tasks suggests that the effects observed reflect a dopamine-sensitive substrate common to both tasks. The physiological mechanism underlying the observed L-dopa-induced blood flow changes, however, is not clear. One possibility is that these changes reflect a direct vasodilatory effect on cerebral blood vessels (Leenders *et al*., 1985; Sabatini *et al*., 1991; Krimer *et al*., 1998). However, a direct vascular effect would be expected to produce global and not regionally specific changes. Regionally localized L-dopa-induced effects were observed in the current study and, moreover, *post hoc* comparison of global counts revealed no significant differences between the ON and OFF L-dopa state. In addition, task by drug interaction effects were observed in regions other than the regions in which main drug effects were seen. Finally, L-dopa induced both task-specific decreases (in the prefrontal cortex) and task-specific increases (in the occipital cortex) within the same patient group, again arguing against a generalized vascular mechanism. We hypothesize, therefore, that the blood flow changes observed reflect the neuromodulatory effects of dopamine on the prefrontal cortex, resulting from local changes in neuronal firing.

Previous studies (Foote *et al*., 1975; Johnson *et al*., 1983; Robbins and Everitt, 1987; Sawaguchi *et al*., 1990) have demonstrated that catecholamines may act by enhancing the signal-to-noise ratio of local neuronal firing patterns, i.e. suppressing spontaneous background neural firing while enhancing cortical neural responses to the stimulus. Both Daniel *et al*. (1991) and Mattay *et al*. (1996, 2000) have demonstrated that, in humans, dextroamphetamine increases the signal-to-noise ratio in task-relevant neural regions, increasing blood flow in areas most relevant to a task and decreasing blood flow in areas less relevant for that task. However, in the current study, relative drug-induced decreases were observed in the right dorsolateral prefrontal cortex. Although these results might seem at odds with existing data (eg. Daniel *et al*., 1991; Mattay *et al*., 1996, 2000*a*), they are consistent with other imaging studies using dopaminergic agents in healthy volunteers (Friston *et al*., 1992; Grasby *et al*., 1992; Mehta *et al*., 2000) and patients with Parkinson's disease (Mattay *et al*., 2002). For example, Mehta *et al*. (2000) also showed drug (methylphenidate)-induced task-related decreases in the dorsolateral prefrontal cortex using a self-ordered spatial working memory task. Similarly, Friston *et al*. (1992) showed apomorphine-induced attenuation of memory-related activation in the dorsolateral prefrontal cortex. Together, these findings cast some doubt on the suggestion that dopaminergic agents consistently increase blood flow in task-relevant areas and decrease blood flow in task-irrelevant areas (Daniel *et al*., 1991; Mattay *et al*., 2000). An alternative suggestion supported by the results of Mehta *et al*. (2000) and those of the current study is that the blood flow reduction in the dorsolateral prefrontal cortex is related to increased efficiency, i.e. increased signal-to-noise ratio within the prefrontal cortex. In keeping with this suggestion, a significant correlation was observed in the current study between the L-dopa-induced blood flow change in the right dorsolateral prefrontal cortex and the L-dopa-induced change in performance on the planning task. Thus, correlations were observed with both initial and subsequent thinking time, measures previously shown to be sensitive to withdrawal of L-dopa medication in patients with Parkinson's disease (Lange *et al*., 1992). The fact that no overall behavioural effect of L-dopa was observed probably reflects differences between the patients selected for this study and those investigated previously (e.g. Lange *et al*., 1992). For example, unlike those in the previous behavioural study (Lange *et al*., 1992), those patients in the current study had extensive practice on the tasks beforehand. This practice may have masked a behavioural effect of the drug manipulation. Secondly, for the purposes of the current study, it was necessary to select relatively mildly affected patients who were able to perform the tasks satisfactorily in the scanner, while the patients in the previous behavioural study were demonstrably more clinically disabled (Lange *et al*., 1992).

In the present study, the task-related, L-dopa-induced decrease in the right dorsolateral prefrontal cortex was accompanied by a significant relative increase in the right occipital lobe. This pattern of results is strikingly similar to that obtained by Furey *et al*. (2000) who administered a cholinergic agent (physostigmine) to healthy volunteers and, like the present study, observed working memory-related decreases in the prefrontal cortex that were accompanied by increases in the extrastriate cortex. On this basis, it was suggested that prefrontal regions modulate visual selection processes resulting in the observed opposing effects in the two regions. It has been suggested that 'prefrontal neurones have properties ideal for attentional templates that bias competition in extrastriate visual cortex in favour of behaviourally relevant visual field items' (Miller, 2000). The proposed signal-to-noise ratio enhancing function of dopamine may correspond functionally to this process of selective attention, by which increased responses (or

activations) are produced in visual areas (Corbetta *et al*., 1991; Furey *et al*., 2000) by attentional controlling mechanisms in the frontal lobe. In this study, both the memory and planning tasks require the selective representation of only that information needed to guide the selection of responses. Whether such a function is indeed mediated by prefrontal dopamine (and modulated by dopaminergic medication in patients with Parkinson's disease) in a similar manner to that described by Furey *et al*. (2000) for acetylcholine requires further investigation.

Significant drug by task effects in the dorsolateral prefrontal cortex were observed only in the right hemisphere in the present study. These effects are clearly not the result of disproportionate involvement of one or the other hemisphere in the patients tested as symptoms started on the right side in five patients and on the left side in five patients. Although human imaging studies using monoaminergic agents in healthy volunteers have shown predominantly left-lateralized interaction effects using cognitive tasks (Daniel *et al*., 1991; Friston *et al*., 1992; Grasby *et al*., 1992; Mattay *et al*., 1996; Mehta *et al*., 2000), most studies have not reported statistically significant differences between the left and the right hemispheres. It seems likely that the task-related drug-induced effects would be most significant in the hemisphere that is most strongly associated with the task. Thus, both the Wisconsin Card Sorting Test and various tests of verbal memory that are predominantly associated with left hemisphere activation (Berman and Weinberger, 1990; Paulesu *et al*., 1993) yield drug-induced effects in the same hemisphere (Daniel *et al*., 1991; Friston *et al*., 1992; Grasby *et al*., 1992; Mattay *et al*., 1996). On the other hand, the visuospatial tasks used in the current study probably depend more heavily on right hemisphere mechanisms (Milner, 1971) and, accordingly, the significant drug-induced blood flow changes were observed in the right dorsolateral prefrontal cortex.

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