

Abnormal basal ganglia outflow in Parkinson's disease identified with PET

Implications for higher cortical functions

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Summary

In this study we examined the effects of striatal dopamine depletion on cortical and subcortical blood flow changes during two tasks known to involve frontostriatal circuitry. Regional cerebral blood flow was measured in six patients with moderate Parkinson's disease and in six age-matched control subjects while they performed easy and difficult versions of a modified Tower of London planning task and a mnemonic variant of this task that required short-term retention and reproduction of problem solutions, as well as a control condition that involved identical visual stimuli and motor responses. Relative to control conditions, the planning task was associated with an increase in cerebral blood flow centred on the internal segment of the right globus pallidus in the age-matched control subjects, and a decrease in the same region in

the patients with Parkinson's disease. A similar inverse relationship between the task-specific blood flow change observed in the control group and that observed in the Parkinson's disease patients was not found in any other subcortical or cortical area examined, including regions of the dorsolateral frontal cortex known to be involved in this task. When blood flow in the spatial working memory task was examined, a similarly specific dissociation between the two groups of subjects was observed at similar coordinates in the right pallidum. We conclude that striatal dopamine depletion disrupts the normal pattern of basal ganglia outflow in Parkinson's disease and consequently, affects the expression of frontal-lobe functions by interrupting normal transmission of information through frontostriatal circuitry.

Keywords: dopamine; frontal cortex; planning; striatum; working memory

Abbreviations: AC-PC = anterior-posterior commissure (line); GPi = internal segment of the globus pallidus; rCBF = regional cerebral blood flow

Introduction

Traditionally, the basal ganglia have been associated with motor processes, although recent evidence suggests that they may also subserve parallel cognitive functions. For example, in Parkinson's disease, the characteristic triad of motor deficits, bradykinesia, rigidity and tremor, is accompanied by a progressive pattern of neuropsychological impairment, which, in its earliest stages, resembles that seen after frontal-lobe excisions in patients (Gotham *et al.*, 1988; Downes *et al.*, 1989; Owen *et al.*, 1992, 1993a, b, 1995a, b). These deficits may reflect damage to one or more corticostriatal circuits that parallel the 'motor loop' described by Alexander *et al.* (1986), but which subserve cognitive, rather than motor, functions. According to this model, the widespread topographically organized cortical projections which

converge upon the striatum, project back, via pallidal, nigral and thalamic structures, to discrete frontal regions. The fact that Parkinson's disease is associated with profound dopamine depletion both in the striatum and, less so, in the prefrontal cortex (Scatton *et al.*, 1983; Agid *et al.*, 1987; Kish *et al.*, 1988), suggests that the 'frontal-like' deficits observed result from either, or both, of these forms of pathology (Lange *et al.*, 1992).

In the current study, we have used PET to examine how blood flow in the frontal cortex and in the basal ganglia may be affected in Parkinson's disease, during two cognitive tasks known to involve frontostriatal circuitry. Six patients with Parkinson's disease and six age-matched control subjects were scanned during a test of high-level planning (the 'Tower

of London') and a related test that emphasized aspects of spatial working memory, but required minimal planning. Previous evidence from patients (Shallice, 1982; Owen *et al.*, 1990, 1995a, b, 1996c), and from functional imaging studies in healthy control subjects suggests that, in humans, both cognitive planning (Owen *et al.*, 1996a; Baker *et al.*, 1996), and spatial working memory (Jonides *et al.*, 1993; McCarthy *et al.*, 1994; Owen *et al.*, 1996b), involve the mid-dorsolateral frontal cortex. Planning and spatial working memory deficits have also been reported in Parkinson's disease (Morris *et al.*, 1988; Owen *et al.*, 1992, 1993a; Robbins *et al.*, 1994), even early in the disease process (Owen *et al.*, 1995a). However, it is not clear how these functional deficits in Parkinson's disease relate to the cortical (e.g. frontal) and subcortical (e.g. striatal) neuropathological changes that accompany this disorder. Previous functional imaging studies using PET or SPECT (single photon emission computed tomography) have demonstrated that motor slowing in Parkinson's disease (bradykinesia), is accompanied by reduced regional cerebral blood flow (rCBF) in the supplementary motor area, an effect that is at least partially reversed by dopaminergic medication (Jenkins *et al.*, 1991; Playford *et al.*, 1992; Rascol *et al.*, 1992, 1994; Jahanshahi *et al.*, 1995). By analogy, we predicted that cognitive planning and spatial working memory would be associated with reduced rCBF changes in the mid-dorsolateral frontal cortex in patients with Parkinson's disease, as a result of subcortical pathological changes affecting the functional integrity of the underlying cortico-striato-thalamo-cortical loop which projects to this region of the frontal lobe.

Material and methods

PET and MRI

PET scans were obtained using the Scanditronix PC-2048 system which produces 15 image slices at an intrinsic resolution of $5.0 \times 5.0 \times 6.0$ mm (Evans *et al.*, 1991a). In this study, the resultant 'field of view', within which PET data from all 12 subjects was obtained, extended from 25 mm below the anterior-posterior commissure (AC-PC) line to 64 mm above it. Using the bolus $H_2^{15}O$ methodology (Raichle *et al.*, 1983), without arterial sampling (Fox and Raichle, 1984), the relative distribution of rCBF was measured in baseline and activated conditions. For each subject, an individual, high-resolution MRI study (63 2 mm slices) was also obtained from a 1.5-T Philips Gyroscan, and re-sliced so as to be co-registered with the PET data (Evans *et al.*, 1991b). An orthogonal coordinate frame was then established based on the AC-PC line, as defined in the MRI volume (Evans *et al.*, 1992). These coordinates were used to apply a trilinear resampling of each pair of MRI and PET data sets into a standardized stereotaxic coordinate system (Talairach and Tournoux, 1988). To overcome residual anatomical variability persisting after stereotaxic standardization, the PET images were reconstructed with a

20-mm filter and then normalized for global rCBF and averaged across subjects within each scanning condition. The mean state-dependent change (cerebral blood flow) image volume was obtained (Fox *et al.*, 1985), and converted to a *t*-statistic volume by dividing each voxel by the mean standard deviation in normalized rCBF for all intra-cerebral voxels (Worsley *et al.*, 1992).

Individual MRI images were subjected to the same averaging procedure, such that composite stereotaxic image volumes sampled at ~ 1.5 mm in each dimension were obtained for both *t*-statistic and MRI volumes. Anatomical and functional images were merged to allow direct localization on the MRI images of *t*-statistic peaks which were identified by an automatic peak-detection algorithm. In an initial analysis, the patterns of rCBF change in the patients and in the control subjects were compared directly.

The significance of a given rCBF difference was assessed by application of an intensity threshold to the *t*-statistic images (Worsley *et al.*, 1992, 1996). This threshold, based on 3D Gaussian random field theory, predicts the likelihood of obtaining a false positive in an extended 3D field. An initial exploratory search was conducted, involving all peaks within the grey matter (volume 600 cm^3), and the threshold for reporting a peak as significant was set at $t = 3.5$. Correcting for multiple comparisons, a *t*-value of 3.5 yields a false positive rate of only 0.58 in 200 resolution elements (resels) (each of which has dimensions $20 \times 20 \times 7.6$ mm), which approximates the volume of cortex scanned. Corrected *P*-values were calculated for these peaks using the following scaling factor (Worsley *et al.*, 1992, 1996).

$$R/4\pi^2 \times (4 \times \log 2)^{1.5} \times (t^2 - 1) \times e^{-t^2/2}$$

where R = search volume in resels and t = *t*-statistic.

We also undertook two directed searches, in the frontal cortex and in the basal ganglia, which were based on the results of our previous PET study (Owen *et al.*, 1996a) and on the results of behavioural comparisons between patients with frontal lobe damage and patients with Parkinson's disease, using similar tasks to those used in the present study (e.g. Owen *et al.*, 1990, 1992, 1993a, b, 1995a; Owen and Robbins, 1994). For these directed searches, *P*-values were corrected according to the equation above, with the search volumes set at 150 cm^3 (50 resels) for frontal cortex and 22 cm^3 (7.23 resels), for basal ganglia (Worsley *et al.*, 1996). For the directed search, all peaks above a threshold of $t = 3.0$ are reported, along with corrected *P*-values in order that clear comparisons can be made between patients and control subjects, even where significant differences were not found. This threshold corresponds to a false positive error rate on 0.5 per 50 resels scanned.

Using the same approach, supplementary analyses were also conducted to examine rCBF changes in the patients and in the control subjects separately. Where significant differences were found, the nature of the effect was explored qualitatively by extracting mean normalized blood flow values (ml/100 g/min), for each scanning condition, from either the

six patients or from the six control subjects. The normalized data were sampled using a 5-mm diameter region-of-interest centred around the coordinates of the peak difference between the two groups.

Subjects

Control subjects

Six normal right-handed volunteers, four male and two female, participated in the study. Each underwent seven, 60-s PET scans within a single session, five of which pertain to the study reported here. All of the subjects were selected to be within the age range 50–61 years (mean 57.66 years, SEM 2.17 years). The PET data from these six subjects, in combination with those of six younger control volunteers, have already been reported in a larger PET study of cognitive planning (Owen *et al.*, 1996a).

Parkinson's disease patients

Six right-handed patients with idiopathic Parkinson's disease, four male and two female also participated in the study (mean age 60.1 years, SEM 2.56 years). All were out-patients at the Montreal Neurological Institute and were referred consecutively by the consultant neurologist (A.D.) if a diagnosis of idiopathic Parkinson's disease was reached, in the absence of clinical dementia or depression (see below). Patients with a significant medical history not related directly to their Parkinson's disease (e.g. stroke, head injury) were not referred for the study. The severity of clinical symptoms was also assessed by the neurologist according to the Hoehn and Yahr, five-point rating scale (Hoehn and Yahr, 1967). In cases where medicated patients were experiencing response fluctuations, the Hoehn and Yahr rating referred to the 'on' rather than the 'off' (medication) condition. All six patients included in this study were receiving daily L-dopa preparations and all were responding well. None were suffering from a confusional state at the time of testing. For the purposes of the study, the patients were asked to discontinue their L-dopa medication the night before the PET scan was scheduled to take place. Thus, at the time of scanning, all subjects had been off their dopaminergic medication for at least 12 h. All six patients had moderate/severe clinical symptoms and were rated as Hoehn and Yahr stage III, with an average disease duration of 7.2 years (SEM 1.2 years). Exclusion criteria for the medicated Parkinson's disease patients included clinical dementia assessed using the Mini-Mental State Examination (Folstein *et al.*, 1975). Specifically, all six patients scored 30/30 on the Mini-Mental State Examination. Patients with significant affective disturbance as identified during their standard neurological examination were also not referred for the study.

All subjects gave informed, written consent for participation in the study after its nature and possible consequences were explained to them. The study was

approved by the Ethics Committee of the Montreal Neurological Institute.

Stimuli and testing conditions

There were four experimental conditions and one control condition in this study. These conditions have been described previously by Owen *et al.* (1996a). All stimuli were presented on a high-resolution, touch-sensitive computer screen. Two of the experimental conditions were based directly on the Tower of London planning task, which has previously been shown to be sensitive to deficit in patients with Parkinson's disease (Owen *et al.*, 1992, 1995a), and in neurosurgical patients with frontal lobe excisions (Owen *et al.*, 1990, 1995a). We refer to these conditions as 'Simple Planning' and 'Difficult Planning'. The other two experimental conditions required that subjects monitor, and then reproduce, short (three moves) or long (four or five moves) sequences of moves, and were designed to emphasize spatial working memory rather than planning ability. We refer to these two conditions as 'Simple Spatial Working Memory' and 'Difficult Spatial Working Memory', respectively. Deficits in spatial working memory have also been demonstrated in patients with Parkinson's disease (Owen *et al.*, 1992, 1993a), and in patients with frontal lobe damage (Owen *et al.*, 1990, 1995b, 1996c; Ptito *et al.*, 1995). In addition, a plethora of recent experimental studies in monkeys (for review, see Goldman-Rakic, 1990), and functional neuroimaging studies in human subjects (Jonides *et al.*, 1993; McCarthy *et al.*, 1994; Owen *et al.*, 1996b), have demonstrated that the frontal cortex plays a critical role in certain aspects of spatial working memory.

The Simple Planning and Simple Spatial Working Memory tasks were designed to provide a baseline against which to examine the extent of activation in the other two, more difficult, experimental conditions. In addition, however, a further 'control' condition was included, which involved similar visual stimuli and motor responses to the Difficult Planning and Difficult Spatial Working Memory tasks, but which required little planning and minimal working memory. We refer to this condition as 'Visuomotor Control'.

In each of the five 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 (Fig. 1). 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 by touching it with the index finger of the right hand, and then by touching one of the empty positions in one of the other pockets. Once touched, a ball would be circled by a yellow ring, indicating that it was ready to be moved. When an empty pocket was

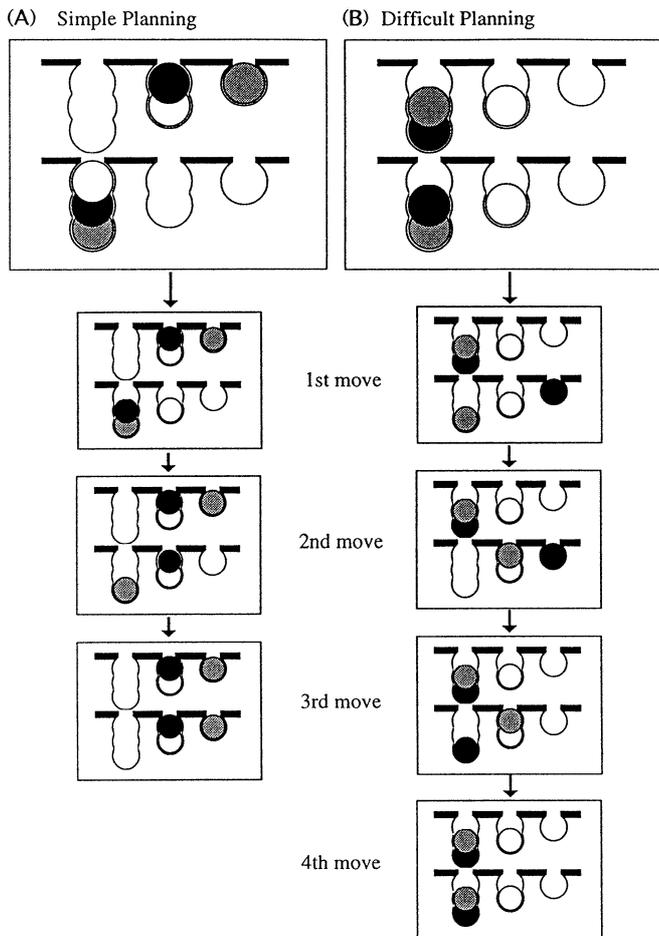


Fig. 1 Two trials from the computer version of Tower of London task. Subjects are required to move the balls in the bottom half of the screen to match the goal arrangement presented in the top half of the screen. The problem shown on the left (A) is from the Simple Planning condition and requires three moves. These moves are shown schematically below the problem. A four-move problem is also shown on the right side of the figure (B) and is taken from the Difficult Planning condition. Again the correct sequence of moves is shown below the problem.

touched, that location was also circled in yellow momentarily, before the selected ball moved, automatically, from its original position to the new one. At any time, the subject could cancel his/her selection of a ball by touching it a second time. 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.

Although each of the five scans lasted only 60 s, the tasks were always begun 10 s before scanning and continued, after scanning, until 90 s, in total, had elapsed. The scans were separated by ~10 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.

Simple Planning

The subjects were told that they would be presented with a set of problems to solve during scanning. For each problem, the starting position of the balls in the bottom half of the screen was varied such that a solution could be reached in exactly three moves (Fig. 1A). The subjects were told to examine the position of the balls in each problem and to attempt to find the three-move solution. They were told not to make a first move until they were confident that they could execute the entire sequence needed to solve the problem. However, it is important to point out that the three-move Tower of London problems require very little cognitive planning, and can thus be solved using a simple, visual matching-to-sample strategy. This strategy, whereby each ball in the bottom half of the screen is moved directly to the position corresponding to the same coloured ball in the top half of the screen, is illustrated in Fig. 1A. After the subject had successfully completed a problem, or after a total of seven moves had been made, the screen cleared for 0.5 s, and the next problem was presented. 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.

Difficult Planning

The same procedure was used as in the Simple Planning condition, except that now all problems required four- or five-move solutions (Fig. 1B). The subjects were instructed accordingly, and four- or five-move problems were presented in a fixed pseudo-random order during the 90-s performance period. Again, they were encouraged not to make a first move until they were confident that they could execute the entire sequence needed to solve the particular problem. The computer presented the next problem automatically when a solution was completed, or when a maximum of nine moves were made for four-move problems and 12 moves for five-move problems. Unlike the three-move Tower of London problems presented in the Simple Planning condition, these more difficult problems could not be solved using a visual matching-to-sample strategy. In fact, in many cases, these problems require the subject to make visually counter-intuitive moves (i.e. to move a ball away from its final destination) in order to execute the appropriate solution, which involves a considerable amount of 'thinking ahead' or 'planning'. This more complex task requirement is illustrated in Fig. 1B.

Simple 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. To prevent inadvertent planning, the stationary configuration of the balls in the top half of the screen matched the initial configuration of the balls in the bottom half of the screen. The subjects were instructed to watch while the computer made a series

of single moves in the bottom half of the screen, and then to attempt to repeat this sequence, once all the balls returned to their original positions. During each trial, the balls in the bottom half of the screen moved, one at a time, from pocket to pocket. These moves were 'yoked' to the Simple Planning condition in that they were paced according to the speed of that particular subject in the Simple Planning scan. The moves themselves did not necessarily correspond to the individual's actual moves, but were the sequence of moves that would have produced a perfect solution in the planning condition. The subject was required to observe and remember each sequence of three moves, and then to repeat that same sequence. To restrict the overall number of moves and to ensure that subjects remained 'within' the remembered sequence, incorrect responses (or 'wrong' moves), elicited no response from the computer. The cue for the subjects to begin reproducing the sequence (i.e. the end of each demonstration series) was when a ball was circled by a yellow ring (i.e. 'highlighted'), which also directed the subject's attention towards the first ball to be moved.

Difficult Spatial Working Memory

This condition was identical in terms of procedure to the Simple Spatial Working Memory condition, except that sequences of four or five moves were now presented. Thus, for each problem, the subject was required to observe and remember a sequence of four or five moves, and then to repeat that same sequence to complete the trial.

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. Again, to prevent inadvertent planning, the initial configuration of the balls in the top half of the screen matched the initial configuration of the balls in the bottom half of the screen. The subjects were instructed simply to touch a series of locations in the bottom half of the screen which were highlighted with yellow rings. For each subject, the sequence of moves required in this control task corresponded exactly to the moves produced by that individual when performing the problems in the Difficult Planning condition. In addition, the computer used the stored selection and movement latencies from that subject in the previous condition, to pace the subject's responses in the control condition. As the subjects made each selection, the balls moved from pocket to pocket as before and, in this way, the subjects experienced the same visual stimuli and made the same series of arm movements (at exactly the same pace) as in the Difficult Planning condition. The subjects, of course, were unaware of this procedure and were simply required to touch a series of externally defined positions on the computer screen. The computer recorded the selection latencies for each move.

One potentially confounding difference between this

Visuomotor Control condition and the four planning and memory tasks is that the former required a series of externally guided responses, whilst the latter conditions involved internally guided movements. For this reason, rCBF comparisons were drawn between the two planning conditions and between the two memory conditions (each comparison being matched with respect to the type of movements made), as well as between each of these conditions and the Visuomotor Control.

The planning, control and spatial working memory conditions described above were always presented in that sequence. However, the order in which the simple and difficult conditions were presented was fully counterbalanced across subjects.

Performance indices

The main index of performance in the planning task was the proportion of problems solved in the minimum number of moves (i.e. the proportion of perfect solutions), calculated for the three-move problems (in the Simple Planning condition), and for the four- and five-move problems (in the Difficult Planning condition). In addition, the actual number of movements made by the Parkinson's disease patients and the age-matched control subjects during the two planning conditions were recorded and compared. For control purposes, the memory tasks 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 previously using similar spatial working memory tasks (e.g. Morris *et al.*, 1988; Owen *et al.*, 1992, 1993a, 1995a). Like the Visuomotor Control condition, the two working memory tasks were yoked directly to the Simple Planning and Difficult Planning conditions such that overall, the number of responses made within the 90-s performance period were equivalent in the planning, spatial working memory and Visuomotor Control conditions.

Results

Performance indices

The percentage of planning problems solved within the minimum number of moves is shown in Fig. 2 for the Simple (three-move) and the Difficult (four- or five-move) Planning conditions. In general, the age-matched control subjects performed well, solving 90% (three moves) and 74% (four and five moves) of all the problems perfectly. The Parkinson's disease patients also performed the Simple Planning task well (85% solved perfectly), but, as expected, they solved fewer (40%) of the Difficult Planning problems successfully. Analysis of variance with repeated measures confirmed that

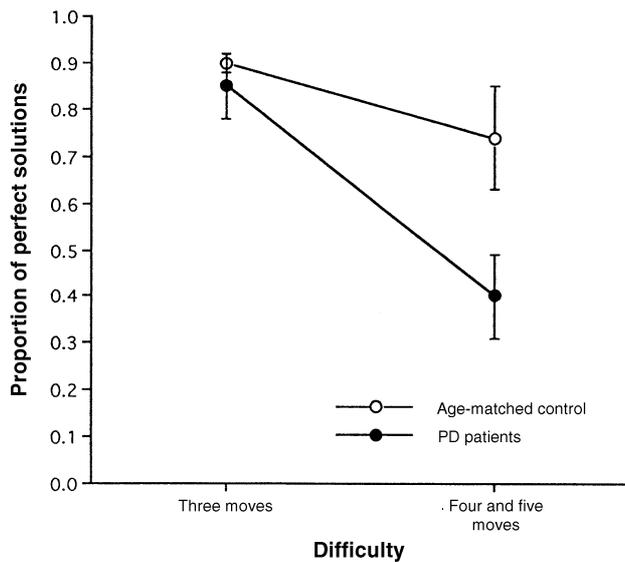


Fig. 2 Performance data from the Tower of London planning task. The proportion of problems solved in the minimum number of moves as a function of task difficulty. Performance data shown are based on scores collected in the Simple Planning condition (three moves) and in the Difficult Planning condition (four or five moves). Bars represent standard error of the mean. PD = Parkinson’s disease.

there was a significant main effect of group, with the Parkinson’s disease patients producing fewer perfect solutions overall than the control subjects [$F(1,10) = 8.15, P < 0.025$]. There was a significant effect of task difficulty [$F(1,10) = 12.28, P < 0.01$], but the interaction between the group and task difficulty factors did not reach significance [$F(1,10) = 2.9, P = 0.12$].

The mean numbers of movements made by the two groups during the planning scans are shown in Fig. 3. There was no significant difference between the two groups in this respect [$F(1,10) = 0.00$], and no significant difference between the number of movements made during the two scans [$F(1,10) = 0.34$]. The interaction between the two factors did not reach significance [$F(1,10) = 1.07$]. Given the variability in these data and the importance of this result for interpreting group differences in the rCBF data, these results were reanalysed using a non-parametric Mann–Whitney statistic. There were no significant differences between the two groups with three moves ($U = 17.5, P = 0.937$), or with four or five moves ($U = 13.5, P = 0.49$).

The mean numbers (\pm SEM) of problems attempted by the two groups during the ‘difficult’ scans were 5.33 ± 1.63 and 4.33 ± 0.81 for the control subjects and Parkinson’s disease patients, respectively, and during the ‘simple’ scans, 8.50 ± 1.37 and 8.66 ± 2.42 , respectively. There was no significant difference between the two groups in this respect [$F(1,10) = 0.28$], although there was an overall significant difference between the number of movements made during the two types of planning problems [$F(1,10) = 46.77, P < 0.0001$]. The interaction between the two factors did not approach significance [$F(1,10) = 1.125$]. Thus, although

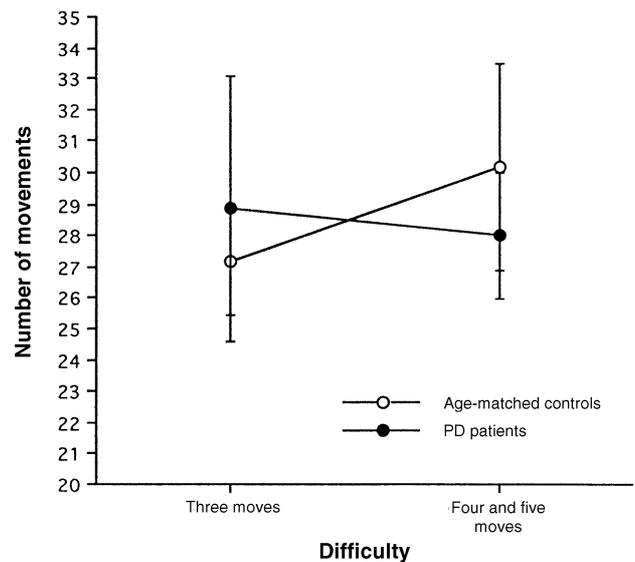


Fig. 3 Performance data from the Tower of London planning task. The total number of movements made as a function of task difficulty. Performance data shown are based on scores collected in the Simple Planning condition (three moves) and in the Difficult Planning condition (four or five moves). Bars represent standard error of the mean. PD = Parkinson’s disease.

the solution to each of the Difficult Planning problems required more moves (by definition) than each of the Simple Planning problems, subjects in both groups were able to complete more simple problems within the 90-s performance period, thereby accounting for the overall equivalence in the total number of moves between scans.

Blood flow

The experiment was designed to permit specific, previously defined comparisons, accomplished via subtractions between relevant conditions. The results of these subtractions, in terms of statistically significant changes in rCBF, are given in Tables 1–4, together with the corresponding stereotaxic (x, y, z) coordinates based on the system used in the brain atlas of Talairach and Tournoux (1988).

Difficult Planning minus Visuomotor Control

The first comparison, Difficult Planning minus Visuomotor Control, was designed to elucidate those cerebral regions involved in planning and executing the solutions to complex visual problems, and to ‘subtract out’ the visual and motor components of task performance which are common to both conditions. When the pattern of changes in rCBF observed in the age-matched control subjects was compared directly with that observed in the Parkinson’s disease patients, a significant difference was observed centred on the right internal segment of the globus pallidus (GPi), one of the main basal ganglia output nuclei (Fig. 4A). Other differences between the two groups were located in premotor and prestriate areas of the left hemisphere, but they failed to

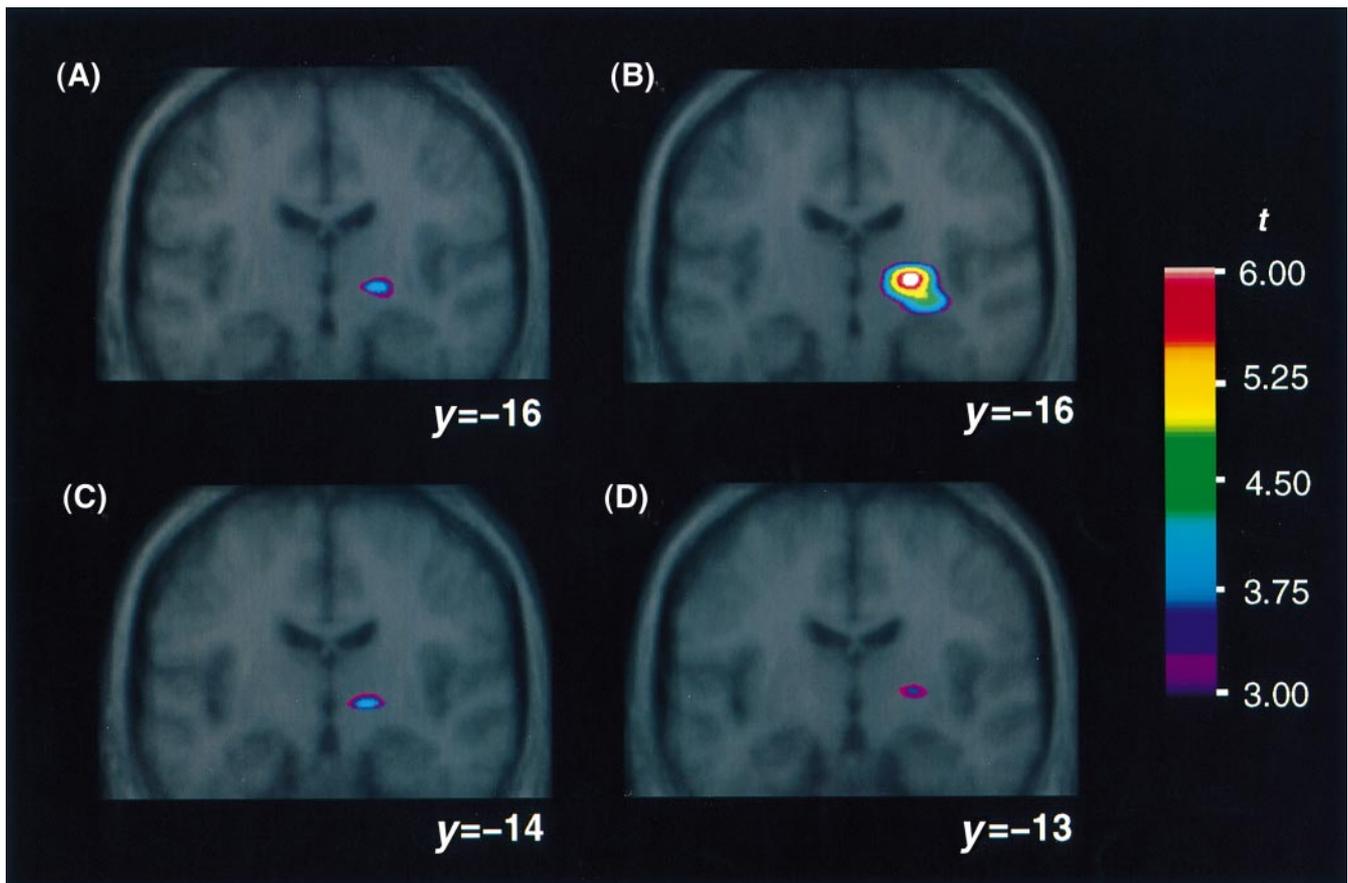


Fig. 4 The averaged PET subtraction images are shown superimposed upon the corresponding averaged MRI scan of all 12 subjects participating in the study. Direct comparisons between the six patients and the six control subjects yielded the focal differences in blood flow shown as a t -statistic image, whose range is coded by the colour scale on the right of the figure. In all four coronal sections, the y -coordinate represents the position of the section relative to the anterior commissure (anterior, positive) and has been chosen to illustrate the statistically significant difference in the region of the right GPi, between the control subjects and the Parkinson's disease patients when: (A) the Difficult Planning condition was compared with the Visuomotor Control condition (Difficult Planning minus Visuomotor Control); (B) the Difficult Planning condition was compared with the Simple Planning condition (Difficult Planning minus Simple Planning); (C) the Difficult Spatial Working Memory condition was compared with the Visuomotor Control condition (Difficult Spatial Working Memory minus Visuomotor Control); and (D) the Difficult Spatial Working Memory condition was compared with the Simple Spatial Working Memory condition (Difficult Spatial Working Memory minus Simple Spatial Working Memory). The subject's left is on the left of the figure.

reach significance by our criteria. No significant differences were observed in the prefrontal cortex (Table 1).

In the separate analysis of age-matched control subjects, significant increases in rCBF were observed in the dorsolateral, ventrolateral and premotor areas of the left frontal lobe, in the posterior parietal and prestriate cortices of the right frontal lobe and in the striate cortex at the midline. Significant negatives peaks (when the Difficult Planning condition was subtracted from the Visuomotor Control condition), were seen in the caudate nucleus, the frontal operculum and the ventral premotor area in the right hemisphere (Table 1).

In Parkinson's disease patients, significant changes in rCBF were observed in ventrolateral and premotor regions of the right frontal lobe when blood flow in the Visuomotor Control

condition was subtracted from that in the Difficult Planning condition. An increase in the right dorsolateral frontal cortex failed to reach significance according to our criteria ($t = 3.10$). An increase was also observed in the left mid-dorsolateral frontal region ($t = 2.80$ at $x, y, z = -46.9, 23.56, 27.0$), although, again, this failed to reach significance according to our criterion. A significant change was also seen in the left prestriate cortex. Negative peaks, which were only observed in the right hemisphere, were centred on the caudate nucleus, the putamen, the frontal operculum and the GPi (Table 1).

Difficult Planning minus Simple Planning

In order to assess whether any of the significant activation peaks observed in the Difficult Planning condition were

Table 1 Activation obtained when Difficult Planning and Visuomotor Control conditions were compared

Brain area	Coordinates			<i>t</i> -statistic	<i>P</i> -value (corrected)
	<i>x</i>	<i>y</i>	<i>z</i>		
Parkinson's disease patients versus age-matched control subjects					
Difficult Planning versus Visuomotor Control (left hemisphere)					
Premotor cortex (area 6)	-32.2	4.6	43.5	3.60	0.11
Prestriate cortex (area 19)	-17.4	-50.4	1.5	3.51	0.14
Difficult Planning versus Visuomotor Control (right hemisphere)					
Globus pallidus (internal segment)	18.8	-16.0	-3.0	4.00	0.004**
Age-matched control subjects					
Difficult Planning minus Visuomotor Control (left hemisphere)					
Ventrolateral frontal cortex (area 45)	-49.6	23.6	16.5	4.06	0.02*
Dorsolateral frontal cortex (area 9)	-40.2	18.4	31.5	3.81	0.05*
Premotor cortex (area 6)	-29.5	4.6	43.5	4.56	0.003**
Difficult Planning minus Visuomotor Control (right hemisphere)					
Ventrolateral frontal cortex (area 47)	29.5	13.2	-3.0	3.09	0.42
Premotor cortex (area 6)	32.2	15.0	49.5	3.29	0.26
Posterior parietal cortex (area 7/40)	38.9	-45.2	37.5	4.27	0.04*
Prestriate cortex (area 19)	22.8	-53.8	10.5	4.17	0.06
Difficult Planning minus Visuomotor Control (midline)					
Striate cortex (area 17)	0.0	-86.5	16.5	5.02	0.002**
Visuomotor Control minus Difficult Planning (left hemisphere)					
No significant peaks	-	-	-	-	-
Visuomotor Control minus Difficult Planning (right hemisphere)					
Caudate nucleus	10.7	8.1	1.5	3.79	0.009**
Premotor cortex (area 6)	45.6	2.9	3.0	3.99	0.03*
Frontal operculum (area 43)	44.2	-7.4	7.5	4.81	0.001***
Parkinson's disease patients					
Difficult Planning minus Visuomotor Control (left hemisphere)					
Prestriate cortex (area 19)	-16.1	-55.6	3.0	4.07	0.09
Prestriate cortex (area 18)	-9.4	-86.5	16.5	4.61	0.01*
Difficult Planning minus Visuomotor Control (right hemisphere)					
Dorsolateral frontal cortex (area 9)	45.6	39.0	22.5	3.10	0.41
Ventrolateral frontal cortex (area 47)	29.5	15.0	0.0	4.59	0.003**
Premotor cortex (area 6)	28.1	13.2	64.5	4.39	0.007**
Posterior parietal cortex (area 7)	30.8	-74.5	36.0	3.58	0.45
Visuomotor Control minus Difficult Planning (left hemisphere)					
No significant peaks	-	-	-	-	-
Visuomotor Control minus Difficult Planning (right hemisphere)					
Caudate nucleus	12.1	21.8	-6.0	3.79	0.009**
Putamen	32.2	-4.0	7.5	3.56	0.17
Frontal operculum (area 43)	50.9	-7.4	13.5	3.83	0.05*
Globus pallidus (internal segment)	20.1	-14.3	-3.0	3.62	0.15
Middle temporal gyrus (area 21)	54.9	-53.8	9.0	3.58	0.45

Activation foci in this and the other tables represent peaks of statistically significant (see text) changes in normalized CBF. The stereotaxic coordinates are expressed in millimetres (*x* = medial-to-lateral distance relative to the midline with right hemisphere, positive; *y* = posterior-to-anterior distance relative to the anterior commissure with anterior, positive; *z* = inferior-to-superior distance relative to the AC-PC line with superior positive). Significance level is given in *t*-test units. The corrected *P*-value is obtained using the formula $P = R/4\pi^2 \times (4 \log 2)^{1.5} \times e^{(-t^2/2)}$, where *t* = *t*-statistic, *R* = search volume in resels. The following search volumes are assumed: frontal cortex = 50 resels, basal ganglia = 7.23 resels, other areas (whole brain) = 200 resels (Worsley *et al.*, 1996). **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

specifically related to task difficulty, we subtracted the pattern of activation observed in the Simple Planning condition from that observed in the Difficult Planning condition and compared the resultant rCBF change in patients and control subjects directly. The two groups differed significantly only

at a location which was centred on the right GPi (Fig. 4B and Table 2).

In the age-matched control subjects, the only significant difference in rCBF between the two conditions was an increase in the right GPi (Table 2), during the Difficult

Table 2 Activation obtained when Difficult Planning and Simple Planning conditions were compared

Brain area	Coordinates			t-statistic	P-value (corrected)
	x	y	z		
Parkinson's disease patients versus age-matched control subjects					
Difficult Planning versus Simple Planning (left hemisphere) Prestriate cortex (area 19)	-17.4	-50.4	4.5	3.71	0.31
Difficult Planning versus Simple Planning (right hemisphere) Globus pallidus (internal segment)	21.4	-16.0	1.5	6.35	<0.001***
Age-matched control subjects					
Difficult Planning minus Simple Planning (left hemisphere) No significant peaks					
Difficult Planning minus Simple Planning (right hemisphere) Globus pallidus (internal segment)	17.4	-17.7	3.0	4.09	0.003**
Simple Planning minus Difficult Planning No significant peaks	-	-	-	-	-
Parkinson's disease patients					
Difficult Planning minus Simple Planning (left hemisphere) Dorsolateral frontal cortex (area 9)	-42.9	25.3	31.5	3.01	0.5
Difficult Planning minus Simple Planning (right hemisphere) Posterior cingulate	20.1	-55.0	12.0	3.54	0.51
Simple Planning minus Difficult Planning (left hemisphere) Striate cortex (area 17)	-1.3	-77.9	13.5	3.60	0.43
Simple Planning minus Difficult Planning (right hemisphere) Caudate nucleus	13.4	18.4	-1.5	3.55	0.18
Globus pallidus (internal segment)	24.1	-14.3	1.5	5.61	<0.001***

See footnote to Table 1 for details of coordinates and statistics. ** $P < 0.01$, *** $P < 0.001$.

Planning condition (relative to the Simple Planning condition). In the Parkinson's disease group, no significant rCBF increases were observed when the Simple Planning condition was subtracted from the Difficult Planning condition, whilst significant decreases were observed in the right caudate nucleus and in the right GPi.

Difficult Spatial Working Memory minus Visuomotor Control

The third comparison between the Difficult Spatial Working Memory condition and the Visuomotor Control condition, was designed to examine those blood flow changes associated with the monitoring and reproduction of complex four- and five-move problems and to 'subtract out' the visual and motor components of task performance which are common to both conditions. When the Parkinson's disease patients and the control subjects were compared directly, no significant differences were observed in the frontal cortex (Table 3). However, significant differences were observed in the caudate nucleus/accumbens and the precuneus in the right hemisphere. A significant difference between the two groups was also observed, again, in the region of the right globus pallidus, slightly more medially than during the planning conditions, and at the border of the GPi and the subthalamic nucleus (Fig. 4C).

As one would expect from recent patient, monkey and functional imaging studies (Goldman-Rakic, 1990; Owen *et al.*, 1990, 1995b, 1996b; Jonides *et al.*, 1993; McCarthy

et al., 1994), in the age-matched control group, rCBF changes were observed bilaterally, in the mid-dorsolateral frontal cortex (Table 3), although they failed to reach significance according to our criteria. In addition, significant changes were observed in the left ventrolateral frontal cortex in dorsal and ventral frontopolar regions of the right hemisphere and, bilaterally, in premotor cortex. A change was also observed in the left prestriate cortex. The reverse subtraction revealed three significant changes in blood flow: in the left putamen and in the right amygdala and supplementary motor area (area 6/8).

In the group of Parkinson's disease patients, subtracting the Visuomotor Control task from the Difficult Spatial Working Memory condition also produced several significant rCBF changes in fronto-cortical regions (Table 3). Thus, changes were observed bilaterally, in the frontopolar region and in the dorsolateral prefrontal cortex (reaching significance only on the right) and, in addition, in orbitofrontal and ventrolateral regions of the right frontal lobe. The reverse subtraction yielded three significant right hemisphere changes: in the caudate nucleus and the ventral frontopolar region, and in a location centred on the GPi.

Difficult Spatial Working Memory minus Simple Spatial Working Memory

The last subtraction, Difficult Spatial Working Memory minus Simple Spatial Working Memory, was performed to determine whether any of the rCBF changes observed during the Difficult Spatial Working Memory condition were specifically

Table 3 Activation obtained when Difficult Working Memory and Visuomotor Control conditions were compared

Brain area	Coordinates			<i>t</i> -statistic	<i>P</i> -value (corrected)
	<i>x</i>	<i>y</i>	<i>z</i>		
Parkinson's disease patients versus age-matched control subjects					
Difficult Working Memory versus Visuomotor Control (left hemisphere)					
Pulvinar	-9.4	-26.3	13.5	3.61	0.42
Superior temporal cortex	-45.6	-34.9	10.5	3.72	0.30
Prestriate cortex (area 18)	-33.5	-69.3	18.0	3.57	0.47
Mid cerebellum	-1.3	-55.6	-15.0	3.83	0.21
Difficult Working Memory versus Visuomotor Control (right hemisphere)					
Caudate nucleus/accumbens	10.7	21.8	-4.5	3.84	0.007**
Amygdala	29.5	-4.0	-19.5	3.78	0.25
Globus pallidus (internal segment)	14.7	-14.3	-1.5	4.05	0.004**
Sub-thalamic nucleus					
Precuneus (area 7)	2.7	-65.9	39.0	4.06	0.09
Age-matched control subjects					
Difficult Working Memory minus Visuomotor Control (left hemisphere)					
Supplementary motor area (area 6/8)	-4.0	23.6	49.5	3.55	0.12
Dorsolateral frontal cortex (area 9)	-45.6	23.6	33.0	3.13	0.38
Ventrolateral frontal cortex (area 45)	-53.6	23.5	18.0	4.50	0.004**
Premotor cortex (area 6)	-28.1	16.7	54.0	3.90	0.04*
Superior frontal cortex (area 8)	-41.5	15.0	39.0	3.86	0.05*
Prestriate cortex (area 19)	-33.5	-64.2	31.5	4.18	0.06
Prestriate cortex (area 18)	-20.1	-76.2	-3.0	3.58	0.45
Difficult Working Memory minus Visuomotor Control (right hemisphere)					
Dorsal frontopolar cortex (area 10)	34.8	56.2	6.0	4.09	0.02*
Ventral frontopolar cortex (area 10)	25.5	56.2	-7.5	4.42	0.006**
Dorsolateral frontal cortex (area 9/46)	36.2	27.0	36.0	3.16	0.36
Premotor cortex (area 6)	32.2	18.4	43.5	4.20	0.01**
Posterior parietal cortex (area 7)	29.5	-62.4	42.0	3.62	0.40
Striate cortex (area 17)	14.7	-84.8	9.0	3.72	0.30
Visuomotor Control minus Difficult Working Memory (left hemisphere)					
Putamen	-21.4	2.9	-1.5	3.71	0.11
Visuomotor Control minus Difficult Working Memory (right hemisphere)					
Amygdala	30.8	-2.2	19.5	5.00	0.002**
Supplementary motor area (area 6/8)	5.4	-5.7	54.0	4.04	0.02*
Parkinson's disease patients					
Difficult Working Memory minus Visuomotor Control (left hemisphere)					
Ventral frontopolar cortex (area 10)	-39.0	61.4	-13.5	3.62	0.10
Dorsolateral frontal cortex (area 9)	-45.6	21.8	25.5	3.61	0.10
Difficult Working Memory minus Visuomotor Control (right hemisphere)					
Dorsal frontopolar cortex (area 10)	30.8	58.0	9.0	3.63	0.10
Dorsolateral frontal cortex (area 9)	44.2	39.0	21.0	3.06	0.45
Ventrolateral frontal cortex (area 47/45)	38.9	25.3	0.0	4.59	0.003**
Orbitofrontal cortex (area 11)	17.4	25.3	-18.0	4.03	0.03*
Inferior parietal cortex (area 40)	43.0	-38.4	48.0	3.70	0.32
Posterior parietal cortex (area 7)	8.0	-67.6	57.0	3.70	0.32
Visuomotor Control minus Difficult Working Memory (left hemisphere)					
No significant peaks	-	-	-	-	-
Visuomotor Control minus Difficult Working Memory (right hemisphere)					
Ventral frontopolar cortex (area 10)	5.4	44.2	-16.5	4.17	0.02*
Caudate nucleus	5.4	16.7	-6.0	5.11	<0.001***
Globus pallidus (internal segment)	13.4	-10.8	-3.0	3.54	0.018*

See footnote to Table 1 for details of coordinates and statistics. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

associated with the difficulty of the task. When the patient and control groups were compared directly, a significant difference was observed in the right caudate nucleus/

accumbens. In addition, the two groups again differed significantly in a region centred on the right GPi (Fig. 4D).

In the separate analysis of age-matched control subjects,

Table 4 Activation obtained when Difficult Working Memory and Simple Working Memory conditions were compared

Brain area	Coordinates			<i>t</i> -statistic	<i>P</i> -value (corrected)
	<i>x</i>	<i>y</i>	<i>z</i>		
Parkinson's disease patients versus age-matched control subjects					
Difficult Working Memory versus Simple Working Memory (left hemisphere)					
Ventrolateral frontal cortex (area 45)	-29.5	21.8	7.5	3.56	0.012*
Difficult Working Memory versus Simple Working Memory (right hemisphere)					
Caudate nucleus/accumbens	4.0	15.0	-9.0	3.54	0.018*
Globus pallidus (internal segment)	22.8	-12.6	1.5	3.52	0.02*
Cerebellum	4.0	-59.0	-19.5	3.78	0.24
Age-matched control subjects					
Difficult Working Memory minus Simple Working Memory (left hemisphere)					
No significant peaks					
Difficult Working Memory minus Simple Working Memory (right hemisphere)					
Hippocampus	20.1	-26.3	-3.00	3.05	1.0
Simple Working Memory minus Difficult Working Memory (left hemisphere)					
Premotor cortex (area 6)	-21.4	13.2	40.5	3.69	0.08
Simple Working Memory minus Difficult Working Memory (right hemisphere)					
No significant peaks	-	-	-	-	-
Parkinson's disease patients					
Difficult Working Memory minus Simple Working Memory (left hemisphere)					
Orbitofrontal cortex (area 11)	-20.0	20.1	-19.5	3.77	0.06
Difficult Working Memory minus Simple Working Memory (right hemisphere)					
Hippocampus	30.8	-34.9	-15.0	4.09	0.08
Hippocampus	21.4	-10.8	-12.0	3.79	0.24
Simple Working Memory minus Difficult Working Memory (left hemisphere)					
Ventrolateral frontal cortex (area 47)	-33.5	21.8	7.5	3.77	0.06
Simple Working Memory minus Difficult Working Memory (right hemisphere)					
Globus pallidus (internal Segment)	16.1	-12.6	3.0	3.66	0.013*

See footnote to Table 1 for details of coordinates and statistics. * $P < 0.05$.

no significant rCBF changes were observed, according to our criteria (Table 4).

In the patients with Parkinson's disease, only the reverse subtraction yielded a significant change which was centred on the GPi in the right hemisphere. None of the cortical differences were statistically significant.

Across the four subtractions described above, significant differences between the control subjects and the Parkinson's disease patients were found only in the basal ganglia (Tables 1–4). Of these, only the right GPi emerged consistently, the difference between the two groups in this region reaching statistical significance in all four subtractions (Fig. 4). Given the intrinsic spatial resolution of the PET camera used in this study (~5 mm, full width half maximum), it is not possible to confirm, unequivocally, that these rCBF differences are actually within the GPi itself. The external segment of the globus pallidus and the sub-thalamic nucleus are both within 5 mm of the observed peaks. However, the peak difference in rCBF is consistently centred on the right GPi, even across subtractions that involve entirely independent data sets. Moreover, in order to confirm this finding, a further six right-handed Parkinson's disease patients were scanned (as part of

an unrelated study, to be published separately; A. M. Owen, A. Sadikot, J. Doyon, A. Dagher and A. C. Evans, unpublished observations) while performing four of the five tasks described in the current study. In all relevant subtractions, similar differences between the Parkinson's disease patients and control subjects were observed in the region of the right GPi (for Difficult Planning minus Simple Planning, $t = 4.8$ at $x, y, z = 21, -16, 2$; for Difficult Planning minus Visuomotor Control, $t = 3.5$ at $x, y, z = 21, -13, -2$; for Difficult Spatial Working Memory minus Visuomotor Control, $t = 3.3$ at $x, y, z = 16, -16, -2$). Thus, for the purposes of discussion, it will be assumed that the key difference in rCBF between patients and control subjects reflects an abnormal rCBF change in the region of the right GPi. To investigate the qualitative nature of this difference further, mean normalized blood flow values, measured in ml/100 g/min were extracted for each scanning condition, from the six patients, and separately, from the six control subjects, using a 5-mm diameter region-of-interest centred around the coordinates of the peak difference in the region of the right GPi. Difference scores were then extracted for each subtraction and the data are presented in Fig. 5.

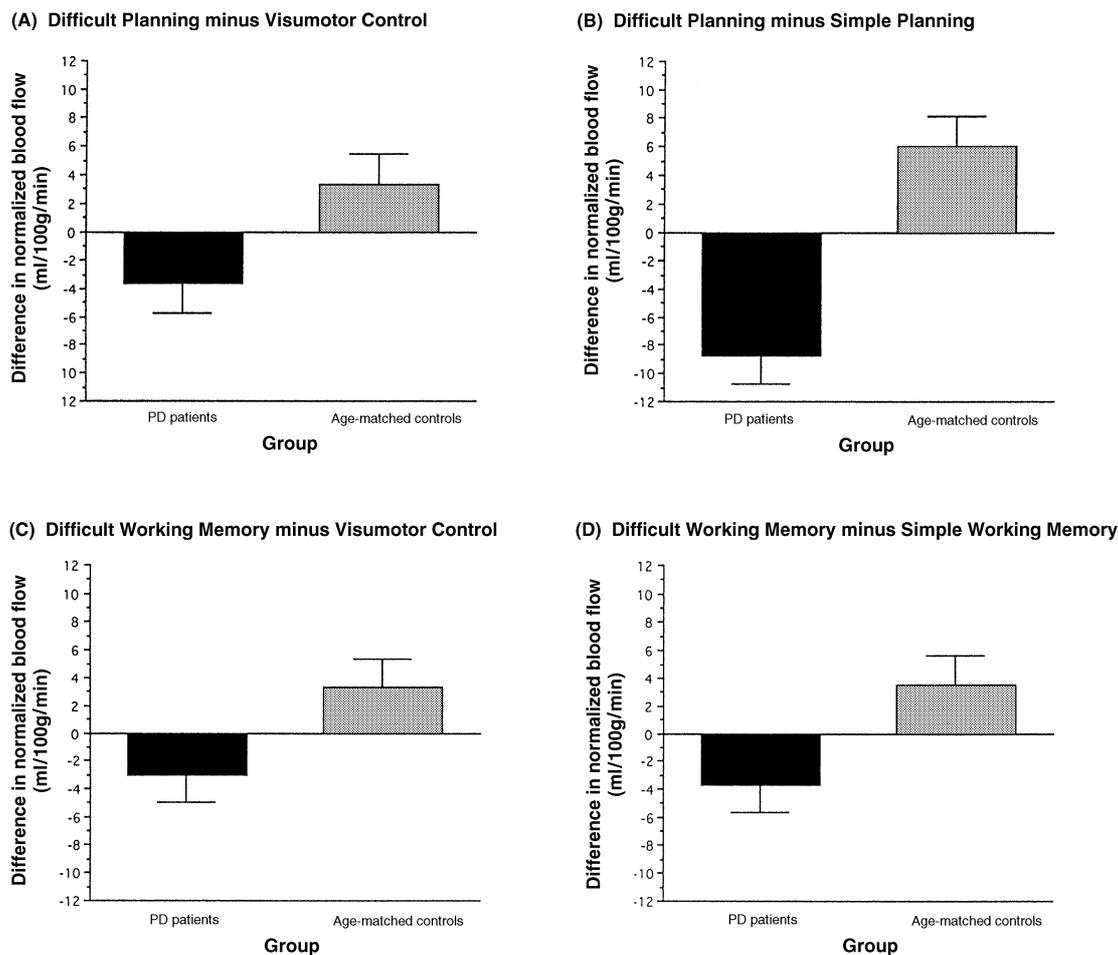


Fig. 5 Differences in mean blood flow (ml/100 g/min) for Parkinson’s disease (PD) patients and for control subjects at the peak coordinate in the region of the GPi for each of the four subtractions. Mean normalized blood flow values measured in ml/100 g/min were extracted for each scanning condition, from the six patients, and separately, from the six control subjects, using a 5-mm diameter region-of-interest centred around the coordinates of the peak difference between the two groups.

For all four comparisons between scanning conditions, the pattern of rCBF change observed in the region of the right GPi in the control subjects was opposite to, and approximately equal to, that observed in the patients with Parkinson’s disease (Fig. 5). Thus, blood flow increases centred on the right GPi were observed in the age-matched control subjects, whilst blood flow decreases were observed in the patients with Parkinson’s disease. In fact, regression of extracted blood flow values (ml/100 g/min) from the Parkinson’s disease group against those from the control group (Fig. 6) revealed a highly significant negative relationship between the two, across the five scanning tasks ($r^2 = 0.95$).

For comparison, the same qualitative assessment of group effects was conducted on the remaining 13 regions where any marginal differences between the two groups were observed (Tables 1–4). None of these analyses yielded difference patterns similar to those observed in the region around the right GPi.

Finally, although no significant differences were observed between the groups in the mid-dorsolateral frontal region, an exploratory qualitative analysis was conducted in this area,

given its strong involvement in both the planning and in the spatial working memory tasks (see Tables 1–4 and Owen *et al.*, 1990, 1995a, b, 1996a, b; Jonides *et al.*, 1993; McCarthy *et al.*, 1994). Mean normalized blood flow values (ml/100 g/min) were extracted for both left and right hemispheres, using 5-mm diameter regions-of-interest around the highest peak of activation identified for each subject group, before each main subtraction. The data for the Difficult Planning minus the Visumotor Control subtraction and for the Difficult Spatial Working Memory minus the Visumotor Control subtraction are presented in Fig. 7. Unlike the pattern of differences observed in the region of the GPi (Fig. 5), similar rCBF changes were observed in the mid-dorsolateral region of the frontal cortex in the control subjects and in the patients with Parkinson’s disease.

Discussion

In this study, no significant difference in activation was observed in the prefrontal cortex in patients with Parkinson’s disease when compared directly with normal control subjects

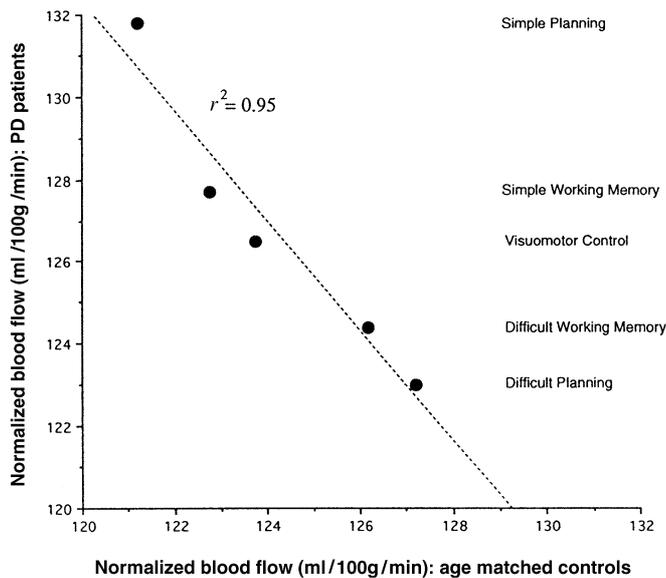


Fig. 6 Mean normalized blood flow values (ml/100 g/min) in the region of the right GPI for the Parkinson's disease (PD) patients and the control subjects. The data were sampled from each of the scanning conditions using a 5-mm diameter region-of-interest centred around the coordinates of the peak difference between the two groups in the region of the right GPI. The regression line reveals a highly significant negative relationship between rCBF in the control subjects and rCBF in the Parkinson's disease patients, across the five scanning tasks ($r^2 = 0.95$).

during the Tower of London planning test. Accordingly, the within-group analysis showed that, in Parkinson's disease, a change, albeit non-significant according to our criteria was observed in area 9 of the right mid-dorsolateral frontal cortex, while a significant increase was observed in ventrolateral area 47, when rCBF in the Visuomotor Control condition was subtracted from that in the Difficult Planning condition. Changes in both dorsolateral and ventrolateral frontal regions were also observed in the control subjects in this study and in the previous one by Owen *et al.* (1996a).

Similar results were obtained in the two related conditions which emphasized aspects of spatial working memory, but required minimal planning; when the patients and the control subjects were compared directly, no significant differences were observed in the prefrontal cortex. Once again, the within-group analysis revealed similar changes, which just failed to reach significance according to our criteria, in mid-dorsolateral frontal areas 9 and 46 in both the Parkinson's disease patients and the control subjects when comparing the Difficult Spatial Working Memory condition with the Visuomotor Control. Changes were also observed in both groups in the ventrolateral frontal region and in both dorsal and ventral frontopolar cortex. Although previous imaging studies in patients with Parkinson's disease have focused on motor tasks, rather than high-level cognitive functions, in some cases, abnormal prefrontal rCBF changes have been reported (e.g. Jenkins *et al.*, 1992; Playford *et al.*, 1992; Rascol *et al.*, 1992, 1993; Jahanshahi *et al.*, 1995). However, in most of these cases, no direct quantitative comparison

between the Parkinson's disease patients and control subjects are reported (Jenkins *et al.*, 1992; Playford *et al.*, 1992; Rascol *et al.*, 1992, 1993), and where they are, only tiny differences consisting of a few pixels are observed (Jahanshahi *et al.*, 1995).

In the current study, when the Difficult and Simple Spatial Working Memory conditions were compared, similar increases in rCBF were observed in the right hippocampus in both control subjects and Parkinson's disease patients, although these effects were rather small and just failed to reach significance according to our criteria. Nevertheless, this tentative evidence is consistent with related behavioural work in which spatial memory deficits have been demonstrated in rats (Olton *et al.*, 1978; Olton and Papas, 1979; Rawlins and Olton, 1982; Rawlins and Tsaltas, 1983; Aggleton *et al.*, 1986; Sziklas and Petrides, 1993), monkeys (e.g. Parkinson *et al.*, 1988) and patients (Owen *et al.*, 1990, 1995b), with damage to the hippocampus and related areas. More importantly, the result demonstrates that, like prefrontal activation, hippocampal activation is similar in patients with moderate Parkinson's disease and in age-matched control subjects during spatial working memory.

However, the groups did differ consistently in all comparisons, in one subcortical area centred on the right GPI. This region constitutes the main basal ganglia outflow nucleus by which descending corticostriatal inputs project back to discrete frontal regions, including the mid-dorsolateral frontal cortex (Middleton and Strick, 1994, 1995), via the thalamus, closing the so-called 'corticostriatal loops'. Extraction of mean normalized rCBF values in this region revealed that, relative to both the Visuomotor Control and the Simple Planning tasks, the Difficult Planning task was associated with an increase in control subjects, but a decrease in Parkinson's disease patients (Fig. 5). The same rCBF pattern (increase in control subjects, reduction in Parkinson's disease) was observed when subtracting either the Visuomotor Control or the Simple Spatial Working Memory tasks from Difficult Spatial Working Memory task. Indeed, when all the tasks were compared, there was a highly significant inverse correlation between patients and control subjects in rCBF in the region of the right GPI (Fig. 6). A similar inverse relationship was not found in any other cortical or subcortical area examined, including the mid-dorsolateral frontal cortex, which is known to be involved in these cognitive tasks.

The difference between Parkinson's disease patients and control subjects in the region of the right GPI is unlikely to reflect the movement requirements of the tasks and the motor deficits that characterize Parkinson's disease for several reasons. First, in the direct comparison between the Parkinson's disease patients and their age-matched control subjects, differences in the frequency and type of movements made during the Difficult Planning task were taken into account by subtracting the pattern of rCBF during the Visuomotor Control task, which required the same movements at the same relative moments in time. Although it was not possible to 'yoke' all the tasks in this way, there was no

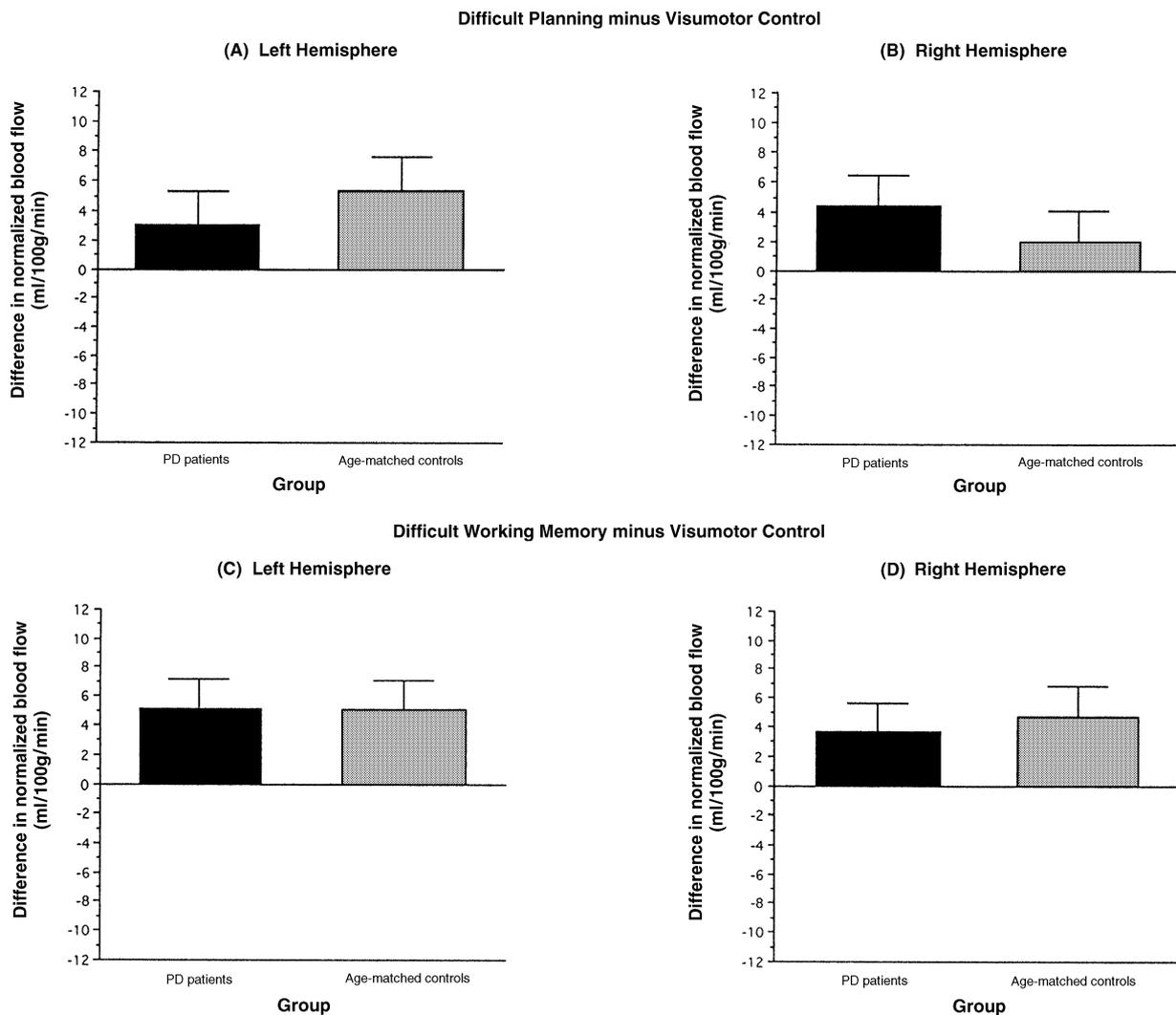


Fig. 7 Differences in mean blood flow (ml/100 g/min) for Parkinson's disease patients and for control subjects in the mid-dorsolateral frontal cortex. Mean normalized blood flow values measured in ml/100 g/min were extracted for both left and right hemispheres, using 5-mm diameter regions-of-interest centred around the highest peak of activation identified for each group, within each subtraction.

difference between the groups in the number of movements made during the experimental conditions, as shown in Fig. 3. Finally, the difference in the region of the GPi was only observed in the right hemisphere; i.e. ipsilateral to the side of movement, and is unlikely, therefore, to be related to motor factors in any direct way.

It seems likely, therefore, that the group difference in the right GPi is related to cognitive, rather than motor, aspects of performance on these tests of planning and spatial working memory and, presumably, to the deficits observed in Parkinson's disease patients (Fig. 2; see also, Owen *et al.*, 1992, 1995a), although the relatively small number of subjects precludes measuring direct correlations between performance and rCBF. This surprising result adds to the growing list of cognitive tasks in which basal ganglia structures have been shown to play a role by PET (e.g. Klein *et al.*, 1994; Doyon *et al.*, 1996). The fact that the GPi changes were strongly lateralized requires further investigation, but may suggest

that, like cortical regions (Milner, 1971, 1974), subcortical regions in the right hemisphere are preferentially involved in processing visuo-spatial material.

One possible interpretation of these results is that striatal dopamine depletion in Parkinson's disease disrupts the normal pattern of basal ganglia outflow through the GPi and, consequently, affects the expression of frontal cortical functions by interrupting normal transmission of information through frontostriatal circuitry.

In the motor system, studies in MPTP-treated monkeys show increased tonic discharge within the GPi (Filion *et al.*, 1988; Miller and DeLong, 1988). It is not possible to relate this phenomenon to the results of the present study directly, because a true resting condition was not included. It is interesting to note, however, the tendency for higher rCBF values in the region of the right GPi in Parkinson's disease relative to control subjects in the Visuomotor Control condition, as well as in the baseline memory and planning conditions (Fig. 6).

In control subjects, the relative increase in rCBF in the right GPi during the difficult planning and working memory conditions is similar to the bilateral increases found in this region in a PET study of increasingly complex sequential finger movements (H. Boecker, A. Dagher, A. Ceballos-Baumann, R. E. Passingham, M. Samuel, K. J. Friston, J.-B. Poline, C. Dettmers, B. Conrad and D. J. Brooks, unpublished results). As the influence of the GPi on cortex is inhibitory, a task-related increase in neuronal activity in the GPi probably reflects increasing inhibition of cortical areas not needed for the task in question, whilst a decrease probably reflects facilitation; the so-called 'focusing' function of the basal ganglia (Mink and Thach, 1991). Parent and Hazrati (1993) have shown that excitatory subthalamic inputs to the internal pallidum (the 'indirect pathway') can excite a large number of pallidal neurons, whereas the inhibitory striatal inputs (the 'direct pathway') exert a more narrowly focused inhibitory influence on these same neurons, thereby providing an anatomical substrate for this focusing mechanism. In this way the selection of cortical areas required for a particular task is associated with a large excitatory input and a smaller more focused inhibitory input onto the GPi. In the normal brain, this would produce an overall increase in synaptic activity in the GPi and, since rCBF is thought to reflect average local synaptic activity (Raichle, 1987), an increase in rCBF in this region.

The question arises how lack of dopamine in Parkinson's disease might disrupt this normal pattern of neuronal processing within the basal ganglia. The action of dopamine in the striatum is not fully understood, but it appears not to have a uniform effect on all striatal neurons (for review, see Groves *et al.*, 1995). Dopamine is released during conditioned learning tasks with a reward component (Schultz *et al.*, 1993), and, on this basis, it has been suggested that dopamine acts as an error signal to facilitate the selection of the necessary corticostriatal loops for the particular task being performed (Mireniewicz and Schultz, 1996). Depending on the activation state or the membrane potential of the target striatal neuron, dopamine may exert excitatory or inhibitory effects (West *et al.*, 1986; Haracz *et al.*, 1993; for review, see Groves *et al.*, 1995), which may drive the focusing mechanism described above. Absence of dopamine in Parkinson's disease may, therefore, alter the efficacy of the normal corticostriatal volley arising from the prefrontal cortex during performance of planning or spatial working memory tasks. Thus, inability to modulate the cortical excitatory input to striatal neurons may result in abnormal influence on the GPi via the direct or the indirect pathway, or both, and, consequently, abnormal processing of neuronal activity within the basal ganglia. The fact that this abnormality produces a reduction in right GPi activity during performance of the complex planning and working memory tasks is difficult to explain on the basis of known models of basal ganglia physiology. Such a reduction could reflect a decrease in excitation from the subthalamic nucleus or, perhaps, an increase in inhibition from the striatum.

Thus, on the basis of the results of the current study, one can postulate that the 'frontal' cognitive deficits in planning and spatial working memory seen in the early stages of Parkinson's disease are the result, not of intrinsic prefrontal dysfunction *per se*, but rather of abnormal processing of the prefrontal input through malfunctioning basal ganglia circuitry. This conjecture is entirely consistent with the fact that dopamine deficiency in the early stages of Parkinson's disease affects the striatum and not the frontal cortex, as demonstrated both pathologically (e.g. Agid *et al.*, 1987) and in a recent PET study using [¹⁸F]dopa (Rakshi *et al.*, 1996).

Acknowledgements

We wish to thank the staff of the McConnell Brain Imaging Centre and the Medical Cyclotron Unit for assistance with this study and P. Neelin, S. Milot and E. Meyer for technical expertise and advice. This work was supported by the McDonnell-Pew Program in Cognitive Neuroscience and by the Medical Research Council (Canada) Special Project Grant SP-30. During the preparation of the manuscript, A.M.O. was supported by a Pinsent-Darwin Research Scholarship at the University of Cambridge, UK.

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