Brain (2001), **124,** 1020–1032

The role of the striatum and hippocampus in planning
A PET activation study in Parkinson's disease

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Summary
Previous work has identified the prefrontal cortex (PFC) and striatum as participating in the planning and selection of movements. We compared the brain activation patterns during planning in Parkinson's disease patients and age-matched controls using $H_2{}^{15}O$-PET and the Tower of London (TOL) task. In this study, our mildly affected Parkinson's disease group performed as well as the control group but showed a different pattern of neuronal activation. In the two groups, overlapping areas of the PFC were activated but, whereas the right caudate nucleus was activated in the control group, this was not evident in the Parkinson's disease patients. This suggests that normal normal frontal lobe activation can occur in Parkinson's disease despite abnormal processing within the basal ganglia. Moreover, right hippocampus activity was suppressed in the controls and enhanced in the Parkinson's disease patients. This could represent a shift to the declarative memory system in Parkinson's disease during performance of the TOL task, possibly resulting from insufficient working memory capacity within the frontostriatal system.

Key words: Parkinson's disease; positron emission tomography; Tower of London task; caudate nucleus; hippocampus

Abbreviations: ACC = anterior cingulate cortex; BA = Brodmann area; GPi = internal segment of globus pallidus; PFC = prefrontal cortex; rCBF = regional cerebral blood flow; TOL = Tower of London

Introduction
The basal ganglia and prefrontal cortex (PFC) form a distributed neuronal system involved in cognitive tasks that require the selection of actions in a particular context (Passingham, 1993; Rolls, 1994; Wise *et al*., 1996). Cognitive tasks involving frontostriatal circuits, such as planning (Shallice, 1982; Morris *et al*., 1988; Owen *et al*., 1990) and skill and habit learning (Mishkin *et al*., 1984; Squire and Zola-Morgan, 1996; White, 1997), have in common the need for evaluation of outcomes and improvements in performance by trial and error. On the other hand, the hippocampus and surrounding cortical structures are thought to mediate declarative memory, which is more rapid and flexible (Mishkin *et al*., 1984; Squire and Zola-Morgan, 1996). Several studies in humans and animals have shown a dissociation between hippocampal and striatal contributions to learning and memory (Packard *et al*., 1989; McDonald and White, 1993; Knowlton *et al*., 1996; Packard and McGaugh, 1996). Some studies even suggest antagonism between the two systems, in that lesions of the hippocampus or fornix are associated with improved performance on procedural learning tasks known to involve the striatum (Packard *et al*., 1989).

Patients with Parkinson's disease are impaired on a variety of cognitive tasks that depend on frontal lobe function. These include tests of planning (Morris *et al*., 1988; Owen *et al*., 1990), attentional set-shifting (Downes et al., 1989; Owen *et al*., 1993), skill learning (Harrington *et al*., 1990; Ferraro *et al*., 1993) and habit learning (Knowlton *et al*., 1996). It has been suggested that frontal dopamine deficiency and/or frontal neuronal pathology are the underlying causes of these cognitive deficits (Cooper *et al*., 1991). However, we have previously provided evidence that the impairment could be attributed to abnormal processing within the basal ganglia in the face of normal frontal lobe function (Owen *et al*., 1998).

Using $H_2{}^{15}O$-PET with the Tower of London (TOL) planning task, a test that is sensitive to both frontal lobe lesions (Shallice, 1982; Owen *et al*., 1990) and Parkinson's disease (Morris *et al*., 1988; Owen *et al*., 1995*a*), we compared Parkinson's disease patients with controls and found similar levels of task-related regional cerebral blood flow (rCBF) changes in the PFC in the two groups, but a significant difference between the groups in the right globus pallidus (Owen *et al*., 1998). In that study, the Parkinson's disease patients were at a more advanced stage than those reported in the present study and performed significantly less well than the controls. Also, the study used a yoked visuomotor control condition to differentiate the cognitive from the motor effects of the disease. This may not be an adequate way of accounting for differences in rCBF resulting from differences in motor function, because visually cued movements activate different brain areas than internally generated ones (Deiber *et al*., 1996), as discussed by Dagher and colleagues (Dagher *et al*., 1999). Moreover, the areas that are differentially activated in the two situations include those that have been associated, in PET activation studies, with the presence of bradykinesia in Parkinson's disease: the dorsolateral PFC, anterior cingulate cortex (ACC) and supplementary motor area (Playford *et al*., 1992).

To overcome this problem, we developed a correlational version of the TOL task in which subjects solved problems of different difficulty levels while undergoing $H_2{}^{15}O$-PET scanning (Dagher *et al*., 1999). By searching for brain areas where rCBF correlated with task complexity, we were able to identify a brain network of areas involved in planning. This network included the PFC, ACC, posterior parietal cortex and caudate nucleus, thus providing an explanation for previously identified impairments in planning in patients with frontal lobe lesions or Parkinson's disease. In the present study we used this correlational approach, along with a categorical comparison, to study the functional anatomy underlying planning in Parkinson's disease.

Methods

Subjects

Six Parkinson's disease patients (three females, three males, age range 50–71 years, mean ± SD 60.6 ± 8.8 years) and six healthy subjects (four females, two males, age range 49–70 years, mean ± SD 58.6 ± 9.7 years) participated. All were right-handed and none had a history of psychiatric or cardiovascular disease or drug or alcohol abuse. None of the control subjects had a history of neurological disease and they all had normal neurological examinations. The Parkinson's disease patients were Hoehn and Yahr stage 2 or 3 (Hoehn and Yahr, 1967) when off medication and all were taking levodopa. The patients were scanned off all antiparkinsonian medications for at least 12 h. All subjects gave informed consent prior to taking part in the study, which was approved by the Research Ethics Committee of the Hammersmith Hospital.

PET scanning

PET scanning was performed with a CTI/Siemens 953B PET camera (CTI, Knoxville, Tenn., USA) with lead septa retracted (Spinks *et al*., 1992). All scans were performed to include the vertex of the brain in the 10.65 cm field of view. The subjects were placed in a vacuum-operated head-holder with line markings drawn on their orbitomeatal lines and forehead. These lines were aligned with two perpendicular lasers located on the gantry so that subject's position could be verified before each scan. At the start of each scanning session, a transmission scan was performed using a 68a/68e rotating rod source for the purpose of attenuation correction. Each emission scan was performed after intravenous injection of 11 mCi of $H_2{}^{15}O$ into the left antecubital vein over 20 s. Data were acquired over 90 s and patients started solving problems 10 s before the start of data acquisition (except for the two rest conditions). Emission scans were performed 10 min apart to allow radioactive decay of the injected tracer. The PET data were reconstructed using a Hanning filter with a cut-off frequency of 0.5 cycles per voxel to produce 31 image planes with a resolution of 8.5 × 8.5 × 6.0 mm FWHM (full width at half maximum) and 128 × 128 pixels of dimensions 2.05 × 2.05 mm.

Cognitive task

Each TOL problem starts with the presentation of two sets of three coloured balls (red, green or blue) on a touch-sensitive computer monitor (Owen *et al*., 1996*a*). The three balls are distributed among three pockets that can hold one, two or three balls. Subjects are instructed to rearrange the balls in the bottom half of the screen to match the distribution in the top half of the screen. They move a ball by touching it with the right index finger and then touching the empty position where they want to move it. Task complexity was defined as the number of moves required to solve each problem (from one to five). The paradigm was identical to that used by Dagher and colleagues (Dagher *et al*., 1999).

All subjects underwent 12 $H_2{}^{15}O$-PET scans after a 30 min training session during which the task was taught to them. Scans were performed in a darkened room, with a touch-sensitive computer monitor suspended ~18–24 inches above the subject's face so that it could be touched comfortably with the right index finger. During 10 of these scans, they performed the TOL task at one of five complexity levels. Problems were presented in succession during each 90 s scan without pause. All problems during a scan were of the same complexity (i.e. they required the same number of moves for a solution). Two scans were performed with the subjects at rest staring at a blank computer screen. The order of the scans was the same for all subjects: rest, 1 move, 2, 3, 4, 5, 5, 4, 3, 2, 1, rest. For each trial, the number of moves and number of mistakes were recorded and a performance index consisting of the percentage of perfect solutions for each trial was calculated. In addition, the time taken to solve the

problems was recorded: the 'initial thinking time' was defined as the time between the presentation of each problem and the first touch of a ball, and the 'subsequent thinking time' as the time between the first touch of a ball and the final solution of the problem. These estimates of performance are similar to those used previously, except for the fact that we did not attempt to differentiate movement execution time from thinking time (Owen *et al*., 1990, 1992).

Data analysis

PET data were analysed using Statistical Parametric Mapping (SPM96, Wellcome Department of Cognitive Neurology, London, UK) and MATLAB (Mathworks, Natick, Mass., USA). Each individual's scan was realigned to their first scan using a six-parameter rigid-body transformation with least-squares optimization (Friston *et al*., 1995). A mean image of the 12 realigned scans was created and used to perform non-linear transformation into stereotaxic space (Talairach and Tournoux, 1988) using the SPM96 MNI template. Finally, each normalized image was smoothed using an isotropic Gaussian kernel of 12 mm FWHM to increase signal-to-noise ratio and allow for inter-individual anatomical differences. The effect of variance due to global blood flow was removed by using analysis of covariance with global activity as the confounding variable (Friston *et al*., 1990), and all scans were normalized to a mean of 50. A correlational analysis was carried out by specifying task difficulty as a covariate of interest for the 10 planning scans. The covariate was set equal to the difficulty level of the problems for each scan (defined as the number of moves required to solve each problem). This correlational analysis, by looking for brain regions where rCBF varied with task complexity, was designed to identify structures involved in planning. Thus we generated *t* statistical maps of brain regions activated in each group separately, as well as maps of group differences. We also used conjunction analysis (Price and Friston, 1997) to identify brain regions where rCBF correlated with complexity level in both groups and a categorical analysis (all task levels minus rest) to identify all areas involved in the TOL. All activated regions at a level of $P < 0.001$ are reported with their Z scores. Task performance data were analysed by repeated measures analysis of variance.

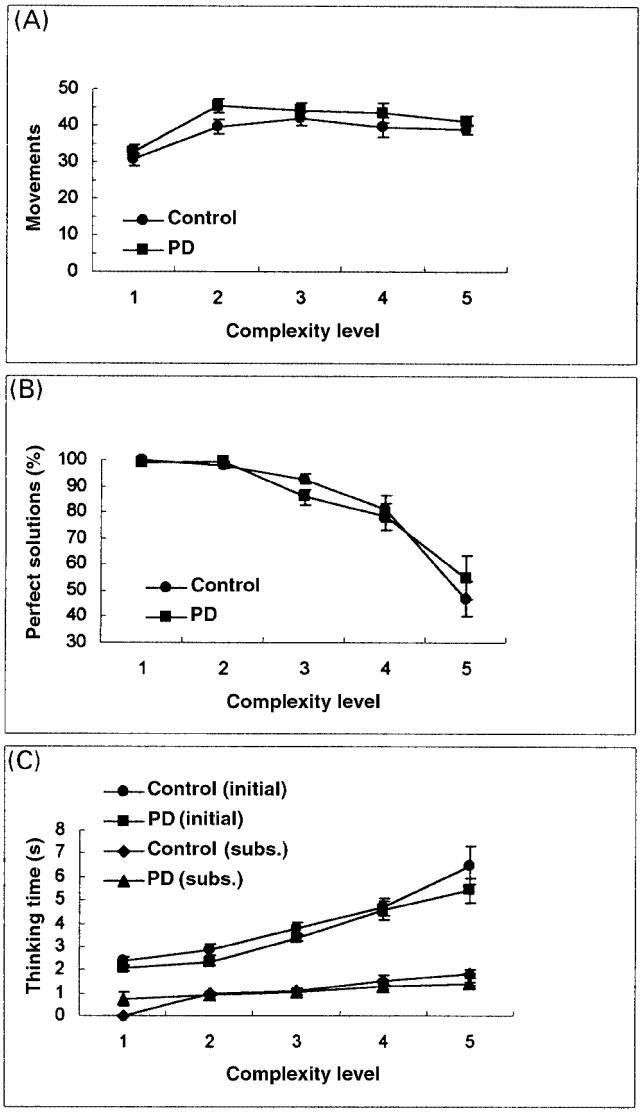

Fig. 1 Performance on the TOL task during scanning. (**A**) Arm movements. Mean number of touches made on the computer screen during each 90 s scan. (**B**) Percentage of correct solutions at each complexity level. A correct solution is one in which the subject arrives at the solution in the minimum number of moves. (**C**) Mean thinking time at each level. The initial thinking time is defined as the time elapsed between presentation of the problem and the subject's first touch on the computer screen. The subsequent thinking time is defined as the remaining time until achievement of the correct solution. Error bars represent the standard error of the mean.

Results

Task performance

There were no differences between the groups in the number of movements made during the scan ($F = 0.983$, $P = 0.35$) (Fig. 1A), the percentage of perfect solutions made at each complexity level ($F = 0.004$, $P = 0.95$) (Fig. 1B) or the thinking time per problem (initial thinking time, $F = 1.031$, $P = 0.33$; subsequent thinking time, $F = 0.01$, $P = 0.93$) (Fig. 1C).

As expected, there was a reduction in the fraction of perfect solutions as complexity increased ($F = 46.57$, $P < 0.0001$), as well as an increase in thinking time (initial thinking time, $F = 38.51$, $P < 0.0001$; subsequent thinking time, $F = 20.79$, $P < 0.0001$). These results are in keeping with previously published data on the TOL in Parkinson's disease (Owen *et al*., 1992), in which only more severely affected patients were impaired, whereas mildly affected Parkinson's disease patients performed as well as healthy controls.

Table 1 *Categorical analysis: differences between the two groups in the categorical analysis comparing task performance with rest*

Brain region	BA	Coordinates (mm)			*Z* score
		x	*y*	*z*	
Normal subjects greater than Parkinson's disease					
Left hemisphere					
Inferior frontal gyrus	45	–58	32	14	3.82
Inferior frontal gyrus	45	–56	24	24	3.75
Medial frontal gyrus	8	–34	20	52	3.44
Anterior cingulate gyrus	32	–18	4	42	3.25
Superior temporal gyrus	41	–44	–24	12	3.52
Postcentral gyrus	2	–42	–30	56	3.60
Medial temporal gyrus	37	–46	–58	–2	3.43
Right hemisphere					
Medial frontal gyrus	10	34	44	–2	3.14
Parkinson's disease greater than normal subjects					
Left hemisphere					
Superior frontal gyrus	8	–20	26	60	3.26
Lingual gyrus	19	–14	–54	8	4.90
Inferior parietal lobule	40	–44	–60	44	3.82
Midline					
Superior frontal gyrus	6	–4	6	70	3.22
Lingual gyrus	17	2	–64	12	5.26
Cuneus	18	2	–72	20	5.24
Right hemisphere					
Medial frontal gyrus	8	48	14	40	3.55
Precentral gyrus	6	52	–2	42	3.34
Precentral gyrus (arm)	4	44	–10	56	3.37
Superior temporal gyrus	22	30	–38	24	3.69
Superior temporal gyrus	22	50	–40	18	4.68
Superior parietal lobule	7	42	–40	58	3.14

All peaks with $P < 0.001$ (uncorrected) are listed.

Cerebral blood flow

We performed a categorical comparison of the difference in rCBF between task and rest in the two groups (Table 1). This task-minus-rest difference was relatively greater in the control group in areas of the inferior frontal and prefrontal cortex and the anterior cingulate gyrus. The difference was relatively greater in the Parkinson's disease group in the anterior supplementary motor area, the inferior and superior parietal and temporal areas, the cuneus and the lingual gyrus.

Correlational analyses were performed to identify brain regions where rCBF correlated with task complexity during TOL performance (Tables 2–4). The brain areas with positive correlations for each group are shown in Table 2 and Figs 2–4. Several areas in the PFC demonstrated a correlation between rCBF and task complexity bilaterally in both Parkinson's disease patients and controls: the mid-dorsolateral PFC, Brodmann area (BA) 9/46 (Petrides and Pandya, 1994), the frontopolar cortex (BA 10) and the lateral premotor cortex (BA 6). The rostral ACC (BA 32) was activated on the left in both groups and on the right in the controls only (Fig. 5). There were also activated areas mesially and laterally in the superior parietal lobule (BA 7) in both groups. Areas where rCBF correlated with TOL complexity in the normal controls but not in the Parkinson's disease patients were the right rostral ACC (BA 24 and 32) and right caudate nucleus, as well as the right inferior parietal lobule (BA 40). Areas where rCBF correlated with TOL complexity only in the Parkinson's disease patients were the left ventrolateral PFC (BA 44) and the left and right supplementary motor area (Table 2).

The conjunction analysis confirmed this pattern (Table 3). Brain areas where rCBF independently correlated with TOL complexity in both groups were the mid-dorsolateral PFC, frontopolar cortex and lateral premotor cortex bilaterally, the left rostral ACC, bilateral inferior and superior parietal lobules and the right precentral gyrus (BA 4).

The groups were also compared directly to generate a statistical parametric map of areas where the correlation between rCBF and task complexity was statistically different in the two groups (Table 4). There was a significantly stronger correlation of rCBF with complexity in the normal subjects than in the Parkinson's disease patients in the left lateral premotor cortex (BA 6), the right rostral ACC (BA 32) and several areas in the left temporal lobe and bilaterally in the occipital lobe. There was stronger correlation between rCBF and complexity in the Parkinson's disease group in a different part of the left premotor cortex (BA 6) and in the right hippocampus (Fig. 6). In the mid-dorsolateral PFC (BA 9/46, 10) there were no differences between the groups (Table 4 and Fig. 3). In the right caudate nucleus, there was a correlation between rCBF and complexity only in the control group; the *Z* score of the difference in activation between patients and controls ($Z = 2.19$) suggested a significant group difference for a directed search ($P = 0.03$ with 116 degrees of freedom) but fell below the threshold for statistical significance after correcting for multiple comparisons.

Discussion

This study confirms previous results showing that planning engages the PFC (mid-dorsolateral, frontopolar and lateral premotor cortices, BA 9/46, 10 and 6/8), the rostral ACC and posterior parietal areas. In overlapping areas of these regions rCBF correlated with task complexity in both healthy control subjects and Parkinson's disease patients (Table 2 and Figs 3 and 4). In addition, there was correlated activation in the right dorsal caudate nucleus in the normal subjects but not in the Parkinson's disease patients. These results suggest that planning remains mediated by frontostriatal circuitry in Parkinson's disease; however, the impairment in caudate function seen here provides a neuroanatomical explanation for deficiencies in planning when present in Parkinson's disease.

Frontal cortex and striatum

The group of brain regions activated in the present study (dorsolateral PFC, ACC, posterior parietal lobe and striatum) have also been implicated in functional neuroimaging studies

Table 2 *Correlations between rCBF and task complexity*

Brain	BA	Normal subjects				Parkinson's disease			
		x	*y*	*z*	*Z* score	*x*	*y*	*z*	*Z* score
Positive correlations									
Left hemisphere									
Prefrontal	10	–28	62	–2	3.03	–42	54	20	3.87
	46	–32	42	6	3.47				
	9/46	–24	28	34	3.15	–46	36	38	3.23
	9/46	–28	20	24	3.79				
	44					–62	20	24	3.34
Lateral premotor	6	–24	10	60	3.27	–24	4	64	3.71
	6					–26	14	62	3.27
Anterior cingulate	32	–10	38	20	3.03	–10	28	26	3.48
Precentral	6					–64	6	30	3.93
SMA	6					0	–20	82	3.71
M1	4					–8	–36	6	3.73
Posterior cingulate	23	–4	–30	18	3.67				
Medial parietal	7	–16	–68	58	3.50	–8	–66	54	3.77
Right hemisphere									
Prefrontal	10	32	54	6	3.50	28	54	10	3.12
	10	48	48	–6	3.26	40	54	2	3.04
	9/46	32	28	42	3.85	26	40	34	3.70
	9/46	58	18	36	3.49	48	24	34	3.59
Lateral premotor	8	28	24	56	3.71				
	6	26	16	62	3.59	28	16	66	3.16
	6	48	8	54	3.66				
	6					24	4	60	4.27
Anterior cingulate	32	8	24	38	3.07				
	24	10	18	28	3.34				
Pre-SMA	6					6	12	68	3.71
Caudate nucleus		8	–2	18	3.52				
Lateral parietal	40	66	–36	42	3.64				
	7	46	–68	42	3.24	40	–64	50	3.74
Negative correlations									
Left hemisphere									
Prefrontal	10	–2	66	6	3.14	–4	62	18	3.92
	44					–42	62	24	3.39
ACC (subcallosal)	32					–4	26	–6	4.40
SMA	6	–8	–12	56	3.32				
Temporal	22	–70	–28	4	3.56	–6	–40	12	3.93
	21					–60	–6	–4	3.62
	21					–54	–22	–8	4.97
	21					–66	–58	–8	4.23
	22					–70	–38	26	4.57
	39					–52	–58	26	4.14
Cerebellum		–26	–60	–24	3.17				
Right hemisphere									
Pre-SMA	8	6	28	58	3.15				
ACC (subcallosal)	32					4	22	–12	3.32
Temporal	21	48	–16	2	3.97				
	21					54	4	–10	3.32
Hippocampus		28	–18	–14	3.32				
Primary sensorimotor	1/2	40	–26	36	3.37				
	22	50	–50	12	3.16				
	37	54	–56	–2	4.30				
Occipital	18	6	–82	26	3.77				
Cerebellum		6	–74	–22	2.98	12	–60	–12	3.01

All peaks with $P < 0.001$ (uncorrected) are listed. SMA = supplementary motor area.

Table 3 *Conjunction analysis: brain areas where rCBF correlated with task complexity in both groups*

Brain region	BA	Left				Right			
		x	*y*	*z*	*Z* score	*x*	*y*	*z*	*Z* score
Prefrontal cortex									
Frontopolar	10	–40	50	18	4.04	30	54	8	4.33
Dorsolateral prefrontal	9/46	–44	36	34	3.67	52	24	34	4.18
Lateral premotor	6	–44	10	60	4.79	24	8	62	5.07
Anterior cingulate	32	–8	32	24	4.15				
Motor cortex									
Precentral gyrus	4					2	–24	84	3.88
Parietal cortex									
Inferior parietal lobule	40	–52	–48	48	3.81	54	–48	48	3.42
Precuneus	7	–8	–66	54	4.73	14	–64	56	3.57
Superior parietal lobule	40					36	–70	48	4.10

All peaks with $P < 0.001$ (uncorrected) are listed.

Table 4 *Differences between groups: regions where there was a statistically significant difference ($P < 0.001$ uncorrected) in the correlation between rCBF and complexity in the two groups*

Brain region	BA	Coordinates (mm)			*Z* score
		x	*y*	*z*	
Normals greater than Parkinson's disease					
Left hemisphere					
Lateral premotor cortex	6	–24	16	34	3.62
Inferior temporal gyrus	21	–54	–18	–12	3.50
Inferior parietal gyrus	7	–24	–54	52	3.32
Inferior temporal gyrus	37	–44	–60	–2	3.45
Medial temporal gyrus	39	–52	–62	26	4.80
Medial occipital gyrus	19	–30	–74	6	3.47
Right hemisphere					
Anterior cingulate cortex	32	16	42	2	3.31
Fusiform gyrus	18	40	–78	–18	3.62
Parkinson's disease greater than normals					
Left hemisphere					
Lateral premotor cortex	6	–64	6	30	3.53
Right hemisphere					
Hippocampus		28	–18	–10	3.41

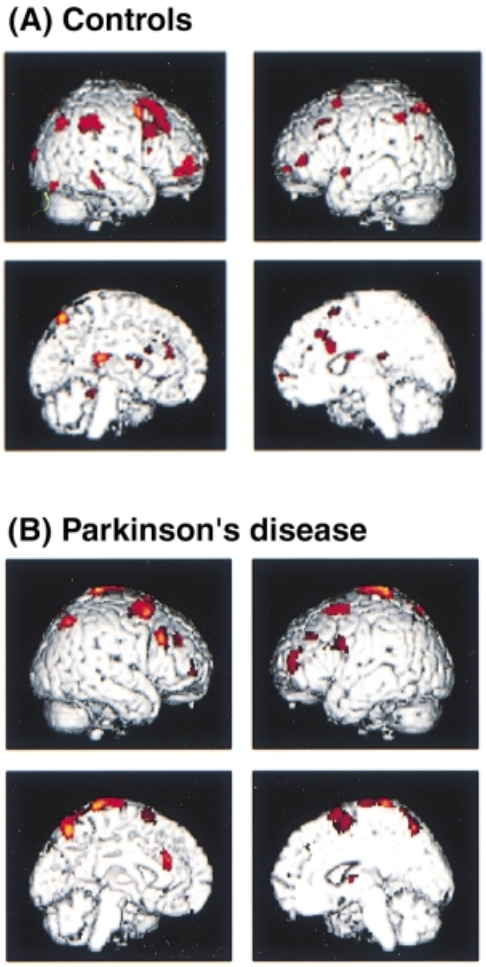

Fig. 2 Cortical activations in normal controls (**A**) and Parkinson's disease patients (**B**). Statistical parametric maps rendered upon a standard MRI in stereotaxic space. The coloured areas represent voxels where there was a positive correlation ($P < 0.005$) between rCBF and task complexity in the cerebral cortex. This figure corresponds to the data in Table 2. The patterns of activation in the prefrontal and posterior parietal cortexes are similar in the two groups.

of related cognitive tasks, such as attentional set-shifting (Rogers *et al*., 2000), *n*-back spatial working memory (Callicott *et al*., 1999) and habit learning (Poldrack *et al*., 1999). It has been argued that the involvement of the dorsolateral PFC in these types of task relates to the manipulation of information stored in working memory for the purpose of guiding behaviour (Petrides, 1994). Working memory could be a function of neuronal activity within networks linking the PFC with the parietal association areas, the striatum, or both (Petrides, 1994; Goldman-Rakic, 1995; Beiser and Houk, 1998). There are extensive connections between the dorsolateral PFC, posterior parietal cortex and dorsal caudate nucleus (Cavada and Goldman-Rakic, 1991;

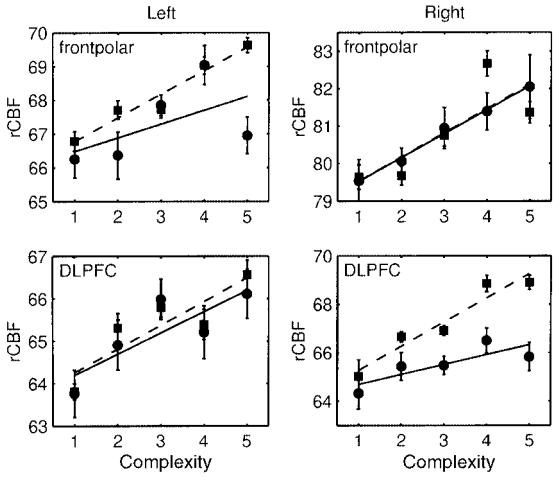

Fig. 3 rCBF in the prefrontal cortex. Comparison of rCBF with task complexity in four prefrontal areas in controls (circles, straight lines) and patients (squares, dashed lines). The rCBF values are extracted from the data points in Table 3. Error bars represent the standard error of the mean. DLPFC = dorsolateral prefrontal cortex.

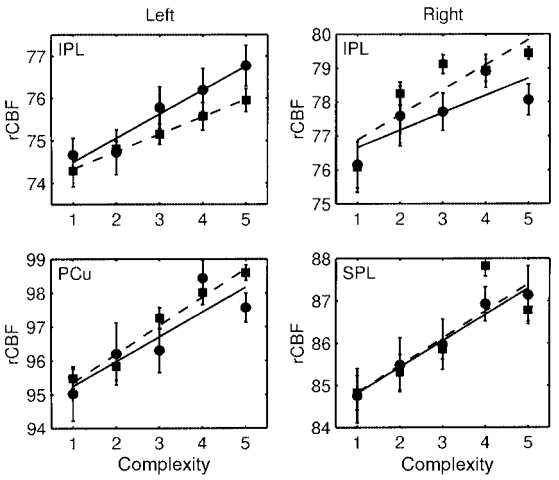

Fig. 4 rCBF in the parietal cortex. Comparison of rCBF with task complexity in four parietal regions in controls (circles, straight lines) and patients (squares, dashed lines). The rCBF values are extracted from the data points in Table 3. Error bars represent the standard error of the mean. IPL = inferior parietal lobule; PCu = precuneus; SPL = superior parietal lobule.

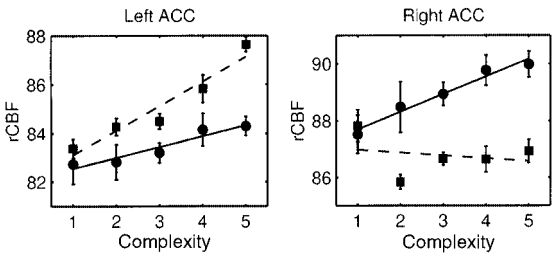

Fig. 5 rCBF in the rostral ACC. Comparison of rCBF with task complexity in the right and left rostral ACC (BA 32) in controls (circles, straight lines) and patients (squares, dashed lines). Error bars represent the standard error of the mean.

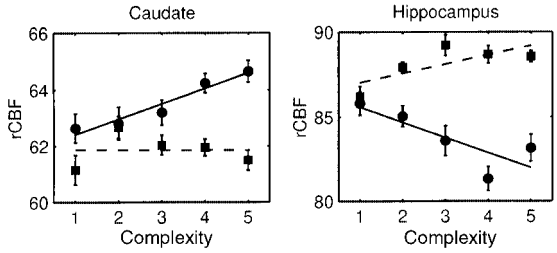

Fig. 6 rCBF in the right caudate and hippocampus. Comparison of rCBF with task complexity in the right caudate nucleus and right hippocampus in controls (circles, straight lines) and patients (squares, dashed lines). Error bars represent the standard error of the mean.

Yeterian and Pandya, 1991, 1993) and cognitive functions of the frontal cortex are thought to be mediated in part by processing occurring within corticostriatal loops (Alexander *et al*., 1986). One role of the PFC and striatum may be to encode the temporal order of sequences of events (Beiser and Houk, 1998), a function that could support the planning of a series of actions.

The patterns of activation in the frontal cortex were not identical for the two groups. While there were significant areas of correlation between rCBF and complexity level in BA 9/46 and 10 bilaterally in both groups, the precise location of the peaks did differ. Moreover, in the rostral ACC, while there was a correlation between complexity and rCBF in both groups, this was bilateral in the control group but only on the left in the Parkinson's disease group (Table 4 and Fig. 6). This may represent deficient activation in Parkinson's disease, as described previously with internally generated movements (Playford *et al*., 1992; Jahanshahi *et al*., 1995) and with an attentional task (Grossman *et al*., 1992). The rostral ACC tends to be activated by more complex motor tasks (Picard and Strick, 1996; Paus *et al*., 1998) and its function has been variously ascribed to attentional demands (Posner and Petersen, 1990), arousal (Hofle *et al*., 1997) and selecting between competing actions (Carter *et al*., 1998), all of which could play a role in the TOL task. Motor areas of the rostral ACC are anatomically connected to the dorsal caudate nucleus (Kunishio and Haber, 1994), which could explain why the right ACC and right caudate nucleus showed similarly deficient activation patterns in the Parkinson's disease patients (Figs 5 and 6).

We found that rCBF correlated with task complexity in the right dorsal caudate nucleus in normal subjects but not in Parkinson's disease patients (Fig. 6). Even though the Parkinson's disease patients in this study performed as well as the control subjects, this suggests that 'frontal lobe' deficits in Parkinson's disease could result from abnormal processing within the basal ganglia, at least in more advanced stages of the disease (Owen *et al*., 1998). This may be because the dopamine deficiency, in the earlier stages of Parkinson's disease, preferentially affects the striatum rather than the cerebral cortex. Degeneration of dopamine neurones in the midbrain is greater among neurones that project to the

striatum than among those projecting to cortical or limbic areas (German *et al*., 1989). This is reflected in the pattern of dopamine loss, which is greater in the striatum than in the PFC, ACC or hippocampus (Scatton *et al*., 1983; Agid *et al*., 1987). Post-mortem analyses in patients with long-standing Parkinson's disease (average illness duration 12.4 years) and age-matched controls showed a reduction in dopamine level to 17% of the normal value in the caudate nucleus, compared with 39% for the PFC, 48% for the ACC and 32% for the hippocampus (Scatton *et al*., 1983). Since dopamine levels probably need to fall to 20–30% of normal values before functional defects are experienced (Hornykiewicz and Kish, 1987), dysfunction may only occur late in the disease in areas other than the striatum. *In vivo* studies in humans using PET and [^{18}F]dopa (Rakshi *et al*., 1999) confirm that dopaminergic function in Parkinson's disease is most reduced in the striatum and may actually be upregulated in prefrontal areas in early disease, only becoming sufficiently reduced to cause functional impairments in the latest stages of the disease.

Further support for the theory that 'frontal' cognitive deficits in Parkinson's disease may not result from intrinsic frontal lobe dysfunction also comes from several studies by Owen and colleagues. They have shown that, while Parkinson's disease patients and patients with frontal lesions are impaired on the same cognitive tasks, the nature of the impairment is different in the two groups (Owen *et al*., 1993, 1995*a*; Rogers *et al*., 1998), frontal patients showing impaired use of strategy relative to Parkinson's disease, for example (Owen *et al*., 1997).

We argue that PFC neurones are not intrinsically dysfunctional in moderate Parkinson's disease. Nonetheless, the finding of normal rCBF activation in the PFC in this study may be surprising because several PET rCBF studies of voluntary movement have shown relatively less activation in motor, supplementary motor and dorsolateral prefrontal areas in Parkinson's disease patients than in control subjects (Playford *et al*., 1992; Jahanshahi *et al*., 1995). This is attributed to excessive inhibitory outflow from the internal segment of the globus pallidus (GPi) to these cortical areas (Albin *et al*., 1989; Wichmann and DeLong, 1993), which would explain why the rCBF hypoactivation reverses with administration of the dopamine agonist apomorphine (Jenkins *et al*., 1992) or after pallidotomy (Grafton *et al*., 1995; Samuel *et al*., 1997) or pallidal stimulation (Limousin *et al*., 1997). By analogy, one might therefore expect that the cognitive deficits in Parkinson's disease could also be the result of inhibition of PFC neurones due to GPi overactivity within the dorsolateral prefrontal corticostriatal loop. However, it is likely that the cognitive deficits arise from a neurophysiological abnormality that is qualitatively different from the motor deficits. Evidence for this comes from the different effects of pallidotomy on cognitive and motor function in Parkinson's disease. Posteroventral pallidotomy reliably reduces bradykinesia in Parkinson's disease patients (Fine *et al*., 2000) but does not improve cognitive deficits (reviewed by York *et al*., 1999). Indeed, pallidotomy may cause specific impairments in frontostriatal cognitive tasks (Stebbins *et al*., 2000; Trepanier *et al*., 2000), and these are more likely to occur if the lesion encroaches on the anteromedial GPi (Lombardi *et al*., 2000), which projects to the dorsolateral PFC (Middleton and Strick, 1994).

Therefore, bradykinesia in Parkinson's disease results from excess firing in the GPi, causing cortical inhibition, which explains the PET findings of cortical hypoactivation during movement and the beneficial effects of pallidotomy. On the other hand, cognitive deficits may result from an alteration in the pattern of activity rather than in the net output of basal ganglia circuits. This explains our PET findings of normal prefrontal activation during planning and the fact that pallidotomy produces either no benefit or deterioration in cognitive tests thought to depend on frontostriatal circuitry. Alternatively, the different patterns of PFC activation in Parkinson's disease in our study and in those of Playford and colleagues (Playford *et al*., 1992) and Jahanshahi and colleagues (Jahanshahi *et al*., 1995) could be explained by the fact that, in their tasks, the movements were not cued visually, and were thus perhaps more internally generated than in the TOL task.

Hippocampus

In the normal subjects, there was a task-related reduction in rCBF in the right hippocampus at coordinates 28, –18, –10 (Fig. 6). Patients with medial temporal lobe lesions are not impaired on the TOL task (Pantelis *et al*., 1997), suggesting that the hippocampus is not critical for the task. The right hippocampus and surrounding areas are activated by tasks that require explicit learning of non-verbal stimuli (Lepage *et al*., 1998; Martin, 1999; Schacter and Wagner, 1999), and anterior hippocampal activations ($y > -26$ mm; as in our current study) occur when the tasks involve remembering the relations between the stimuli (Schacter and Wagner, 1999). There is evidence that the hippocampus is engaged automatically whenever stimuli are attended to (Moscovitch, 1995) and that the amount of activation depends on the depth of encoding (Martin, 1999).

In a previous study with the TOL task, Owen and colleagues used a modified version of the task in which subjects had to explicitly remember and execute movement sequences that were taught to them (Owen *et al*., 1996*a*). There was increased right hippocampal rCBF when comparing long (four or five moves) with short (three moves) sequences in both normal subjects and Parkinson's disease patients. Therefore, declarative knowledge of movement sequences leading to solutions of TOL problems is associated with right hippocampal activation. It may thus seem surprising that we actually found right hippocampal deactivation in normal subjects in the present study. Perhaps this represents active suppression of right hippocampal activity. If the encoding of stimulus features, along with right hippocampal activation, occurred automatically as one solved the TOL task

(Moscovitch, 1995; Martin, 1999), remembered solutions from previous problems could cause interference with the solution of the current problem. Another PET study with the TOL task similarly found that right hippocampal rCBF was lower during the performance of difficult problems than easy problems in healthy subjects (Baker *et al*., 1996*b*). Other functional neuroimaging studies of frontostriatal tasks have also disclosed hippocampal deactivation. Baker and colleagues found hippocampal rCBF reductions during performance of a delayed matching-to-sample task with relatively short delays (Baker *et al*., 1996*a*). Poldrack and colleagues studied subjects with functional MRI while they performed a probabilistic classification task (Knowlton *et al*., 1996) and found reduced blood oxygen level-dependent signal in the hippocampus (coordinates –26, –18, –20) during task performance compared with an appropriate visuomotor control (Poldrack *et al*., 1999). This finding is relevant because, like the TOL task, the probabilistic classification task activates the dorsolateral PFC and the right caudate nucleus, and performance is impaired in Parkinson's disease but not in patients with medial temporal lobe lesions.

In the present study, Parkinson's disease patients failed to activate the right caudate nucleus during the TOL task but showed task-related rCBF increases in the right hippocampus (Fig. 6). This could represent recruitment of the hippocampus to overcome the striatal defect. Conversely, if hippocampal suppression is necessary for optimum performance, the absence of hippocampal deactivation could itself be contributing to impaired performance on the TOL task by Parkinson's disease patients.

Interactions between frontostriatal and hippocampal memory systems

Patients with severe amnesia secondary to bilateral hippocampal lesions are capable of learning certain skills (Milner, 1962; Corkin, 1968; Milner *et al*., 1998). The striatum is involved in non-declarative, or procedural, learning (Mishkin *et al*., 1984; Squire and Zola-Morgan, 1996; White, 1997) and forms, with the frontal cortex, an integrated system involved in the learning and potentiation of rules that guide behaviour (Passingham, 1993; Rolls, 1994; Wise *et al*., 1996). This explains why Parkinson's disease and frontal lobe lesions cause deficits on the same cognitive tasks. The type of learning mediated by the frontostriatal system occurs slowly, by trial and error, while that mediated by the hippocampal memory system is more rapid and flexible (Mishkin *et al*., 1984).

Experimental results showing a dissociation between the hippocampal and striatal systems suggest that they may be functionally separate (e.g. Packard *et al*., 1989; McDonald and White, 1993; Knowlton *et al*., 1996; reviewed by White, 1997). Packard and McGaugh studied rats in a cross-maze and found that hippocampal and striatal learning occurred simultaneously and independently, and that, under certain conditions, the two systems could lead to different behavioural responses (Packard and McGaugh, 1996). There is also evidence that hippocampal and striatal responses can interfere with each other. Several studies have shown improved performance on procedural tasks in rats with lesions of the hippocampus or fornix (Staubli *et al*., 1984; Eichenbaum *et al*., 1986; Packard *et al*., 1989; Shaw and Aggleton, 1993). It may be that the hippocampal lesion in these experiments reduces cognitive interference and thus improves the function of the striatal system for certain tasks. Similarly, if the hippocampus normally encodes the features of all stimuli to which subjects attend (Moscovitch, 1995; Martin, 1999), hippocampal suppression, as shown here and in other studies (Baker *et al*., 1996*a*, b; Klingberg, 1998; Poldrack *et al*., 1999), could reduce interference and improve striatal function.

Frontal, striatal and hippocampal lesions can all impair performance on certain spatial memory tasks. A series of studies of the relative contributions of the hippocampal and frontostriatal systems to spatial memory performance in humans (Owen *et al*., 1993, 1995*a*, *b*, 1996*b*, 1997) showed that the nature of the impairment is different in each group. They suggest that the PFC, striatum and hippocampus contribute differently to spatial memory tasks: executive functions, such as the development of a strategy, could be subsumed by PFC and short-term memory by the PFC and striatum. Only when the mnemonic components increase would the hippocampal system be recruited in task performance. This is in agreement with studies of delayed matching tasks in monkeys, in which lesions of the principal sulcus, corresponding to the human PFC, lead to impairments at all task levels, whereas hippocampal lesions only cause impairment at long delays (Goldman-Rakic, 1987). Hippocampal recruitment in Parkinson's disease patients performing a frontostriatal task, as shown in the present study, could therefore result from a normal response to striatal dysfunction.

We have reported elsewhere an analogous pattern in a PET study with an implicit learning task (Dagher *et al*., 1998). Parkinson's disease patients are impaired at implicit sequence learning, which is known to activate the striatum in normal subjects (Doyon *et al*., 1996). In our PET study, Parkinson's disease patients demonstrated abnormal right hippocampal activation during implicit sequence learning, as for the TOL task described here. Rauch and colleagues have also described a similar pattern in patients with obsessive compulsive disorder who underwent PET scanning during implicit learning (Rauch *et al*., 1997). Normal subjects activated the ventral striatum bilaterally during learning, whereas patients with obsessive compulsive disorder failed to activate this region but activated the hippocampus and parahippocampal cortex bilaterally.

It is also possible that hippocampal recruitment contributes to poor performance in Parkinson's disease patients. Indeed, in experiments in which Parkinson's disease patients must shift between sets of rules, they have been found to be especially vulnerable to a particular type of error that could

be the result of interference from declarative memory (Flowers and Robertson, 1985; Robertson and Flowers, 1990; Rogers *et al*., 1998). In these studies, the errors in switching did not appear to stem from perseveration or distractibility, as seen in frontal lobe patients, but from reversion to previously learned rules.

However, the Parkinson's disease patients in the present study performed normally on the TOL task, which suggests that hippocampal recruitment may serve to overcome partially the frontostriatal deficits. If this is the case, one might predict that involvement of the hippocampus in the disease process would lead to severe cognitive impairment in Parkinson's disease patients. Interestingly, Churchyard and Lees found a correlation between the degree of cognitive impairment in Parkinson's disease patients and the density of Lewy neurites in the hippocampus at post-mortem (Churchyard and Lees, 1997).

Conclusion

The frontostriatal system is involved in cognitive tasks such as planning, skill learning, set-shifting and habit learning. These tasks all involve the gradual learning of responses through trial and error. The hippocampal system mediates a different, more rapid and flexible type of learning. Experimental evidence suggests that the two systems may work independently, act together, or interfere with one another in different situations. In particular, when the short-term memory capacity of the frontostriatal system is exceeded, the hippocampal system may be recruited. On the basis of the data presented here and of previous studies, we draw the following conclusions. First, the 'frontal' cognitive deficits in moderate Parkinson's disease may be due to abnormal processing within the basal ganglia. Secondly, during the performance of frontostriatal tasks, normal subjects demonstrate hippocampal hypoactivation, which may represent suppression of interfering neuronal activity. Thirdly, in Parkinson's disease patients performing frontostriatal tasks there is abnormal hippocampal activation, which may represent the recruitment of a structure that is relatively spared by the degenerative process in Parkinson's disease. In different situations, this hippocampal activity may be either beneficial or deleterious.

Acknowledgements

We wish to thank Andrew Blythe and the staff of the MRC Cyclotron Unit for scanning the subjects. A.D. was supported by the Medical Research Council of Canada.

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Received October 19, 2000. Revised July 9, 2000.
Accepted January 23, 2001