Lateralisation of striatal function: evidence from ^{18}F -dopa PET in Parkinson's disease

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Objectives: The aetiology of the cognitive changes seen in Parkinson's disease (PD) is multifactorial but it is likely that a significant contribution arises from the disruption of dopaminergic pathways. This study aimed to investigate the contribution of the dopaminergic system to performance on two executive tasks using ^{18}F -6-fluorodopa positron emission tomography (^{18}F -dopa PET) in PD subjects with early cognitive changes.

Methods: 16 non-demented, non-depressed PD subjects were evaluated with the Tower of London (TOL) spatial planning task, a verbal working memory task (VWMT) and ^{18}F -dopa PET, all known to be affected in early PD. Statistical parametric mapping (SPM) localised brain regions in which ^{18}F -dopa uptake covaried with performance scores. Frontal cortical resting glucose metabolism was assessed with ^{18}F -fluoro-2-deoxy-D-glucose (^{18}F -FDG) PET.

Results: SPM localised significant covariation between right caudate ^{18}F -dopa uptake (Ki) and TOL scores and between left anterior putamen Ki and VWMT performance. No significant covariation was found between task scores and ^{18}F -dopa Ki values in either limbic or cortical regions. Frontal cortical glucose metabolism was preserved in all cases.

Conclusions: These findings support a causative role of striatal dopaminergic depletion in the early impairment of executive functions seen in PD. They suggest that spatial and verbal executive tasks require integrity of the right and left striatum, respectively, and imply that the pattern of cognitive changes manifest by a patient with PD may reflect differential dopamine loss in the two striatal complexes.

The earliest cognitive changes evident in patients with Parkinson's disease (PD) involve executive functions and probably arise as a consequence of brainstem pathology disrupting projections to subcortical and cortical targets. Braak and colleagues¹ have shown that Lewy inclusion body pathology initially affects the medulla and pons and subsequently involves not only midbrain dopaminergic neurones but also extensive extranigral sites including the cholinergic, noradrenergic, and serotonergic systems with potentially far-reaching effects on cerebral function. Executive processes affected include working memory, temporal sequencing, planning, problem solving, and decision making.^{2,3} With progression of PD, local cortical pathology, comprising Lewy bodies and/or Alzheimer-type changes, may become clinically relevant; the spectrum of cognitive impairment broadens and may extend to frank dementia.

In the early stages of PD, the effect of dopaminergic depletion on cognitive function is not clear. However, many lines of research, including neurophysiological evidence from animal models,^{4,5} the behavioural effects of dopaminergic drugs,^{6,7} and neuroimaging studies^{8–11} support a role for dopaminergic involvement in specific cognitive functions. Dopaminergic projections modulate neuronal activity at several levels in the system of parallel corticostriato-thalamo-cortical loops described by Alexander *et al*^{12,13} influencing the function of the striatum, globus pallidus, limbic regions, and cortex both directly and indirectly. The relative contributions from individual dopaminergic projections are likely to depend on the task involved, the clinical stage of PD, and the genetic makeup of the patient.¹⁴

In early disease the loss of dopaminergic neurones from the nigrostriatal pathway is associated with upregulation of nigropallidal¹⁵ and mesocortical^{16,17} dopaminergic function. Indeed, the existence of a hyperdopaminergic state in the prefrontal cortex relative to the striatum in early disease may help explain some of the findings of psychometric studies in

PD^{6,14}—that is, higher levels of dopaminergic activity are associated with impaired executive function. Withdrawal of dopaminergic medication from patients with PD, although not necessarily affecting executive task performance, can produce less efficient prefrontal cortical functioning as evidenced by increased levels of activation.^{18,19} Whether the cognitive changes resulting from alterations in dopamine levels are primarily due to a direct cortical effect via mesocortical pathways, an indirect effect via altered corticostriato-thalamo-cortical loop function, or a combination of the two remains uncertain.

In order to address this, we used ^{18}F -6-fluorodopa positron emission tomography (^{18}F -dopa PET), a marker of presynaptic dopamine storage capacity, to correlate the functional integrity of the dopaminergic system with executive function in PD. The organisation of the corticostriatal loops suggests that the lateralisation of function displayed by the cortex might also apply to subcortical structures. By analysing data with right and left hemispheres aligned and, then, with primarily and secondarily affected hemispheres aligned, we addressed the question of whether performance on these tasks shows lateralisation or simply relates to the greater dopamine changes present on the primarily affected side. (The primarily affected hemisphere is that which is contralateral to the side of symptom onset.) In order to minimise the possibility of clinically significant cortical pathology confounding our data, we selected non-demented PD patients with cognitive deficits confined to executive tasks known to be affected in PD (see Methods). In addition, the integrity of local frontal cortical function was assessed with ^{18}F -fluoro-2-deoxy-D-glucose (^{18}F -FDG) PET.

Abbreviations: CMRGlc, cerebral metabolic rate for glucose; ^{18}F -dopa PET, ^{18}F -6-fluorodopa positron emission tomography; ^{18}F -FDG, ^{18}F -fluoro-2-deoxy-D-glucose; Ki, ^{18}F -dopa storage capacity; PD, Parkinson's disease; SPM, statistical parametric mapping; TOL, Tower of London; VWMT, verbal working memory task

MATERIALS AND METHODS

Subject evaluation

A total of 16 patients (eight women and eight men) with PD were recruited from a longitudinal epidemiological study being undertaken at the Parkinson's Disease Research Clinic at the Cambridge Centre for Brain Repair, Cambridge, UK. All patients satisfied the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank clinical criteria,²⁰ were right handed, non-demented (Folstein Mini Mental State Examination ≥ 29 in all) and non-depressed (Beck's Depression Inventory score < 9).²¹ Subjects underwent the following psychometric testing on medication: the National Adult Reading Test, Verbal Phonological Fluency (letter cues: F, A, and S), Verbal Semantic Fluency (category: animals), pattern and spatial recognition subtests of the Cambridge Neuropsychological Test Automated Battery (CANTAB),²² and the one-touch Tower of London (TOL) task.²³ This last task requires mental manipulation of an arrangement of coloured balls in three wells to deduce the minimum number of moves required to achieve a target arrangement. The same motor demands apply for all levels of cognitive difficulty with a maximum score of 14.

Subjects were chosen who either performed normally on the above tests or who showed selective deficits on the spatial recognition test or TOL task only which can be affected in early PD. Eight (three women, five men) had right side predominant and eight (five women, three men) left side predominant motor symptoms. Hoehn and Yahr scores ranged from 1.0 to 2.5.²⁴ Demographic details of the patients are given in table 1. In those who had performed the TOL on several occasions, the score nearest the time of ¹⁸F-dopa PET scanning was taken. The mean time between TOL evaluation and ¹⁸F-dopa PET was 34 weeks (range 7–65). The 65 week interval occurred in a subject too fatigued to complete the TOL on the assessment nearest their scan date.

In addition, 12/16 of the subjects were involved separately in a study of a novel verbal working memory task (VWMT).²⁵ Seven of these 12 patients (three women, four men) had right side predominant and five (three women, two men) left side predominant motor symptoms. The VWMT involves presentation of a sequence of four consonants that is rehearsed subvocally until a cue word is presented. This directs the subject either to simply retain or to retain and perform one of two manipulations on the sequence. Once the subject indicates that they are ready by pressing a button, two letter sequences are presented and the subject chooses one as correct. The VWMT task parameter we chose for use in the current study was the accuracy score (maximum value 30) for the manipulation involving retention and reversal of the middle letters of the sequence (BQNR becomes BNQR) as this measure has been shown to differentiate most effectively in absolute terms between PD subgroups with and without executive dysfunction.²⁵

PET and MRI acquisition

PET scanning and analysis were performed at the Cyclotron Building, MRC Clinical Sciences Centre, Hammersmith Hospital, London, UK. ¹⁸F-dopa PET and ¹⁸F-FDG were performed within four months of each other (mean 7 weeks) and, before scanning, patients were withdrawn from their medication for at least 12 hours.

¹⁸F-dopa PET was performed using an ECAT EXACT HR++ (CTI/Siemens 966; CTI, Knoxville, TN) camera with a 23.4 cm axial field of view. Entacapone 400 mg and carbidopa 150 mg were given orally 60 minutes before injection time to increase ¹⁸F-dopa bioavailability to the brain. A 10 minute transmission scan, to enable a subsequent correction for tissue attenuation of 511 keV radiation, was followed by 94 minutes of emission acquisition: 26 time frames ranging from

Table 1 Demographic details of subjects

Subject	M/F	Age	Duration	H and Y	UPDRS OFF	Primarily affected hemisphere	MMSE	TOL	VWMT	Medication
1	F	52	3	2	15	L	30	12	22	200*†
2	M	60	5	2	30	R	30	14		1000*‡
3	M	69	20	2	51.5	L	30	11	18	450*‡
4	F	66	7	2.5	41	L	30	11	14	300*
5	M	56	5	2	29.5	R	30	14	25	400*¶§
6	F	46	3	1.5	36	R	30	14	29	Nil
7	F	69	6	2	29.5	L	30	8	24	600*†¶
8	F	54	4	2	38.5	R	30	11	29	Nil
9	F	65	10	2	28	R	30	6	28	500*†
10	M	65	5	2.5	41.5	R	30	8	19	†**
11	F	57	6	2	31.5	R	30	9		400*¶
12	M	56	3	2	31.5	L	30	14		†‡
13	F	69	7	2.5	48.5	R	30	12		300*
14	M	65	6	1.0	22.5	L	30	12	26	600*†
15	M	67	5	2.5	51.5	L	30	13	23	300*†¶
16	M	64	3	2	30	L	29	13	27	500*
Mean (SD)		61.3 (7.0)	6.1 (4.1)	2.0 (0.4)	34.8 (10.2)					

M/F: male/female.
 Age: at time of ¹⁸F-dopa PET.
 Duration: time since first symptoms in years at time of ¹⁸F-dopa PET.
 H and Y: Hoehn and Yahr score off medication.²⁴
 UPDRS: Total Unified Parkinson's Disease Rating Scale off medication on day of ¹⁸F-dopa PET.
 Primarily affected hemisphere: primarily affected cerebral hemisphere (contralateral to the side of symptom onset).
 MMSE: Mini Mental State Examination (maximum 30).
 TOL: Tower of London task score (maximum 14).
 VWMT: Verbal Working Memory Task score (maximum 30).
 Medication: medication at time of ¹⁸F-dopa PET.
 *Daily L-dopa dose in mg (in combination with a dopa decarboxylase inhibitor).
 †Dopamine agonist.
 ‡Monoamine oxidase inhibitor selegiline.
 ¶β blocker.
 §Anticholinergic medication.
 **Selective serotonin reuptake inhibitor (one subject. Not taken at time of psychometric testing and subject not clinically depressed).

30 seconds to 5 minutes. Thirty seconds after the start of emission acquisition, a mean (SD) of 111 (5.6) MBq ^{18}F -dopa was injected intravenously.

^{18}F -FDG PET was performed after an overnight fast using a Siemens 953B/CTI camera (CTI, Knoxville, TN) with a 10.8 cm axial field of view. A 10 minute transmission scan was followed by 60 minutes of emission acquisition with 21 time frames ranging from 10 seconds to 5 minutes. Thirty seconds after the start of emission acquisition, a mean (SD) of 181 (7) MBq ^{18}F -FDG was injected intravenously. Arterial blood samples were taken at baseline, 5, 10, 20, and 50 minutes to generate a brain arterial input function.

PET images were reconstructed using filtered back projection (Ramp filter) resulting in a final spatial resolution (full width at half maximum) of 5 mm.^{26, 27} A T1-weighted volumetric magnetic resonance image (MRI) was obtained for each subject either at the Wolfson Brain Imaging Unit, Cambridge, UK or at Hammersmith Hospital, London, UK for coregistration purposes. Normal control data for ^{18}F -FDG PET were obtained from eight non-demented subjects previously reported by Hu and colleagues²⁸ who were age matched (mean (SD) age 61.0 (5.5) years) to our PD subjects (61.3 (7.0) years). The subjects in our current study were scanned in the same scanner using an identical protocol.

Hammersmith Hospitals NHS Trust Ethics Committee and the Cambridge Local Research Ethics Committee gave ethical approval for the study, with additional approval for the administration of radioactive ligands given by the Administration of Radioactive Substances Advisory Committee of the United Kingdom.

Data analysis

We used IDL image analysis software (Research Systems Inc, Boulder, CO) and an in-house programme (Kronos), which applies Patlak linear graphical analysis to reconstructed images, to create ^{18}F -dopa PET add-images and parametric images of ^{18}F -dopa storage capacity (Ki) from the raw dynamic images.²⁹ A reference occipital tissue input function was used to generate Ki values using time frames from 30 minutes after ligand injection.³⁰ The add-image was transformed into standard Montreal Neurological Institute (MNI) space by normalisation to a smoothed ^{18}F -dopa template created from a normal subject database¹⁵ and the transformation matrix was then applied to the Ki image. Smoothing was applied with a Gaussian kernel of $6 \times 6 \times 6$ mm for interrogation of smaller structures such as the basal ganglia and limbic system and $10 \times 10 \times 10$ mm for cortical regions to allow for inter-individual anatomical variability. We applied statistical parametric mapping software (SPM99, Wellcome Department of Cognitive Neurology, London, UK) to the smoothed Ki images to localise voxel clusters throughout the whole brain volume where ^{18}F -dopa Ki covaried with TOL or VWM scores. PET images were not flipped when first transformed into MNI space. The analysis was then repeated, flipping the scans of those with primarily affected left hemispheres (initial right motor symptoms) to have all primarily affected sides coincident. SPM was performed using absolute threshold masking with Ki thresholds of 0.0015/min and 0.0008/min for smaller structures and cortical regions, respectively. These thresholds were chosen to be lower than minimum values in these regions to provide an appropriate search volume for the SPM.

We then used region of interest (ROI) analysis to quantify the degree of correlation in the structures identified which were drawn on the single subject T1 MRI in MNI space and applied to the normalised Ki images. Alignment correction was applied, while preserving the volume of interest, in the few cases where the Ki and add-images were not in exact register (head movement during the scan can give a degree of

misregistration as the Ki image is more affected by later timeframes). Spearman's non-parametric rank correlations were performed between regional Ki values obtained and TOL and VWM scores.

We reanalysed the raw ^{18}F -FDG scan data from the normal controls in parallel with our new PD data. Parametric PET images of cerebral metabolic rate for glucose (CMRGlC) were created using spectral analysis with the lumped constant set at 0.48. An anatomical volume of interest (VOI) MRI template was created in MNI space by combining a maximum probability atlas based on the MRIs of 20 normal subjects³¹ with more detailed frontal regions from a separate probabilistic atlas drawn on 10 MRIs.³² The final template included 34 cortical regions, 17 in each hemisphere. This VOI template was transformed into the subject's own MRI space using SPM99. We then coregistered the subject's MRI to their PET image using Matlab (Mathworks Inc., Sherborn, MA) and applied the transforming matrix to the normalised VOI template such that it could be applied to the parametric PET image and regional values of CMRGlC (rCMRGlC) computed. Coefficients of variation (standard deviation/mean) can be high within groups for the absolute rCMRGlC datasets due to the range of global CMRGlC and this can mask differences between groups. To reduce this variation, relative rCMRGlC (rrCMRGlC) values were derived, normalised to the global value for each scan. This global value was defined as $\Sigma(\text{rCMRGlC} \times \text{VOI volume}) / \Sigma(\text{VOI volume})$ summed over all regions. Mean values of rCMRGlC and rrCMRGlC for the PD patients were compared with those for the control group region by region using Student's two tailed *t* test assuming different variances in the two datasets. We chose $p < 0.05$ as the threshold for significance.

RESULTS

^{18}F -dopa PET SPM

All *p* values quoted are at the cluster level with significance taken as a corrected cluster *p* value < 0.05 . Using 6 mm of smoothing, we found a positive covariation of TOL score with ^{18}F -dopa Ki in the right head of caudate (peak voxel -10 12 4 , *Z* score 3.82, corrected $p = 0.031$) extending to the border with the ventral striatum (fig 1, table 2). There was no

Figure 1 Cluster of covariation between right caudate ^{18}F -dopa storage capacity (Ki) and Tower of London (TOL) scores. Statistical parametric mapping clusters displayed on Montreal Neurological Institute (MNI) single subject T1 magnetic resonance image. $Z = 3.82$; height threshold = 0.005; cluster corrected $p = 0.031$.

Table 2 Statistical parametric mapping (SPM) analysis: coordinates (mm) of all SPM clusters with uncorrected $p < 0.05$

	MNI			Talairach and Tournoux						
Hemisphere	x	y	z	x	y	z	Z	No of voxels in cluster	Corrected p	Structure
Tower of London										
R	−10	12	4	−10	12	3	3.82	69	0.031	Caudate
R	−16	6	−8	−16	5	−7	3.57	26	0.756	Putamen
L	26	−4	−6	26	−4	−5	3.68	28	0.682	Putamen
L	14	−2	−24	14	−3	−20	3.31	20	0.936	Amygdala
1 off	−10	12	2	−10	12	1	2.86	33	0.913	Caudate
1 off	−20	2	−8	−20	2	−7	3.63	48	0.547	Putamen
1 off	−10	−4	−24	−10	−5	−20	4.21	68	0.188	Amygdala
2 off	16	4	−8	16	4	−7	3.04	65	0.223	Putamen
Verbal working memory task										
L	34	10	2	34	10	1	3.63	77	0.012	Putamen/caudate
L	22	24	2	22	23	1	3.54	24	0.818	Caudate
	18	18	−6	18	17	−6				

MNI: Montreal Neurological Institute coordinates.

Talairach and Tournoux coordinates³³ derived from MNI coordinates using Matthew Brett's transformation (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html).

1 off: primarily affected cerebral hemisphere (contralateral to the side of symptom onset).

2 off: secondarily affected cerebral hemisphere.

Figures in **bold**: corrected cluster $p < 0.05$.

covariation between TOL score and left caudate Ki even when the height threshold was reduced from $p = 0.005$ to $p = 0.01$. A cluster was evident in the left amygdala (table 2) but did not survive cluster correction. We repeated the analysis with the primarily affected sides (eight right, eight left) aligned, and no clusters identified survived cluster correction. There were no significant clusters of negative covariation between Ki and TOL scores to suggest dopaminergic upregulation. No significant additional positive or negative covariations were found with 10 mm of smoothing to suggest direct meso-cortical involvement.

Using 6 mm of smoothing, there was a positive covariation of VWMT score with Ki in the left anterior putamen, the focus extending into the claustrum (peak voxel 34 10 2, Z score 3.63, corrected $p = 0.012$) (fig 2, table 2). There was also a cluster in the left caudate which did not survive cluster correction. Lowering the height threshold for significance from $p = 0.005$ to $p = 0.01$ revealed no clusters in the right striatum. With primarily affected hemispheres aligned, no clusters reached our threshold for significance. There were no significant clusters of negative covariation with VWMT scores and no additional significant positive or negative covariations with 10 mm of smoothing.

¹⁸F-dopa PET ROI analysis

The Spearman correlation coefficient between the right caudate Ki and TOL score was $r_s = +0.61$ ($p = 0.012$) (fig 3). VWMT accuracy correlated with left putamen Ki with a coefficient $r_s = +0.66$ ($p = 0.021$) (fig 4).

Cortical ¹⁸F-FDG PET analysis

There was no significant difference between the mean global CMRGlc of the PD patients and controls (table 3). The mean

coefficient of variation (standard deviation/mean) for the absolute rCMRGlc datasets over the 34 cortical regions was 18% in controls and 11% in the PD patients, providing 80% power to detect an effect size of 20%, $p = 0.05$, so smaller differences could have been masked. No values in the PD

Figure 2 Cluster of covariation between left putamen ¹⁸F-dopa storage capacity (Ki) and verbal working memory task scores. Statistical parametric mapping clusters displayed on Montreal Neurological Institute (MNI) single subject T1 MRI. Z = 3.63; height threshold = 0.005; cluster corrected $p = 0.012$.

Table 3 ¹⁸F-FDG PET: Parkinson's disease (PD) versus controls, including regions of significant reduction in relative regional cerebral metabolic rate for glucose (rrCMRGlc)

	PD	Controls	Two tailed p
Mean age (SD)	61.3 (7.0)	61.0 (5.5)	
Folstein Mini Mental State Examination (SD)	29.9 (0.3)	29.2 (1.3)	
FDG dose mCi (SD)	4.89 (0.19)	5.01 (0.41)	
Global CMRGlc (SD) (mg/100 ml/min)	4.82 (0.37)	4.77 (0.76)	0.87
Right parietal lobe rrCMRGlc (SD)	0.977 (0.071)	1.063 (0.031)	0.001
Right occipital lobe rrCMRGlc (SD)	1.030 (0.096)	1.110 (0.068)	0.028

Figure 3 Tower of London (TOL) score versus right caudate ^{18}F -dopa storage capacity (Ki) from region of interest analysis. Spearman $r_s = +0.61$, $p = 0.012$.

group lay more than two standard deviations below the regional control mean. The coefficient of variation in the globally normalised relative rCMRGlC (rrCMRGlC) datasets was 8% in both controls and PD patients providing 80% power to detect an effect size of 10%, $p = 0.05$. Comparing PD and control mean regional rrCMRGlC values, significant relative metabolic decreases in the PD group were found in the right parietal lobe and right occipital lobe (table 3). The values of rrCMRGlC in these regions did not correlate significantly with the TOL or VWMT scores, using the Spearman rank statistic. Importantly, there were *no* significant frontal reductions in rrCMRGlC in any of the PD cases.

DISCUSSION

This ^{18}F -dopa PET study has shown that, in PD patients with cognitive deficits confined to the executive domain, levels of striatal dopamine storage capacity correlate with performance on the TOL and VWMT tasks. These results support the view that dopaminergic loss in the nigrostriatal pathway contributes to the early cognitive changes in PD. In addition, there was evidence for lateralisation of striatal involvement in that right caudate dopa uptake correlated with TOL and left anterior putamen uptake with VWMT performance. Lowering the thresholds for significance did not reveal additional contralateral striatal clusters. There was no evidence of correlation between pallidal or cortical dopaminergic function and executive performance in the SPM analysis. Regarding mesolimbic projections, clusters of correlation were identified in the amygdala (see table 2) but these did not survive cluster correction.

There were no significant frontal decreases in rrCMRGlC in our subjects with PD compared with controls. As it is here that one might expect local cortical pathology to affect executive functioning, we may conclude that this was not a major confounding factor in this study. There were decreases in mean values of parieto-occipital rrCMRGlC in our non-demented PD subjects, a finding previously reported,³⁴ but these changes did not correlate with TOL or VWMT performance.

Some PD patients involved in this study had performed the TOL on two or three occasions as part of regular assessments. Therefore there is the possibility of visual habit formation allowing these subjects to recall a previous response related to a given visual stimulus. Such visual habit processing is believed to involve networks which include the caudate and therefore could theoretically influence our findings. Beauchamp *et al*, however, have established that the caudate is activated during early as well as later phases of TOL performance suggesting that its involvement is not using visual habit processes.³⁵

Figure 4 Verbal working memory task (VWMT) score versus left putamen ^{18}F -dopa storage capacity (Ki) from region of interest analysis. Spearman $r_s = +0.66$, $p = 0.021$.

The striatum and executive tasks

The striatum has been implicated in cognitive processing since the 1950s³⁶ with Divac demonstrating the topographic nature of the segregation of function within the caudate nucleus in the following decade.³⁷ A specific role for the caudate nucleus in the TOL task employed in this study is supported by functional imaging findings in normal subjects.^{38–40} Although involvement of the putamen in cognition is less well established, it has been recognised^{41–42} and diffusion tensor fibre tracking has demonstrated direct connections between the prefrontal cortex and the anterior putamen in humans.⁴³ Indeed, the putamen has been implicated in human executive functioning^{9–44} with putamenal activation being seen in a task of time estimation,⁴⁵ suggesting a role in temporal sequencing. In addition and of particular relevance to this study, a recent event related functional magnetic resonance imaging (fMRI) study using the VWMT paradigm has shown both caudate and putamenal hypoactivation during cognitive manipulation in a group of PD subjects with selective executive impairment.⁴⁶

Lateralisation of subcortical function

Although corresponding neural networks in the two cerebral hemispheres may both be engaged in performing a task, they may be differentially involved in distinct aspects of cognitive processing.⁴⁷ There has been debate about whether the side of symptom onset in PD is predictive of subsequent cognitive decline with verbal impairments being associated with right sided motor symptoms^{48–49} and spatial with left.⁴⁸ Other studies, however, have suggested a more global cognitive impairment with left sided motor symptoms^{50–51} and some have found no evidence of functional asymmetry.⁵² Interpretation of these studies is complicated by the differing stages of disease of the patients involved. To minimise bias towards lateralisation, we recruited eight PD patients with right and eight with left predominant motor symptoms for the TOL analysis. The 12 PD subjects who performed the VWMT comprised five left and seven right predominant motor symptoms.

We found TOL performance to correlate with right caudate and VWMT with left putamenal ^{18}F -dopa uptake. Although there are studies in normal subjects in which the left caudate has been activated by the TOL task,³⁵ activation of right cerebral structures has been the more typical finding including the right caudate and dorsolateral prefrontal cortex³⁸ and right globus pallidus.⁵³ In particular, those studies interrogating task complexity have found positive correlations with right caudate activation.^{39–40} PD patients performing the TOL have demonstrated an altered pattern of activation with an apparent shift from right caudate to right

hippocampal systems.⁵⁴ In the case of the VWMT, the combined retrieval and retrieval + manipulation conditions in PD patients and controls resulted in bilateral activation of the striatum and frontal cortex.⁴⁶ However, those regions activated by manipulation alone or where activation covaries with task accuracy were not determined.

Case reports have given evidence of disorientation for place and constructional apraxia in a subject with a right capsulo-putaminal haematoma⁵⁵ and contralateral neglect in subjects with right caudate infarcts.⁵⁶ The right caudate has shown increased activation in neuroimaging studies using tasks felt to use predominantly visuospatial skills: mental rotation,⁵⁷ a mirror reading task in English,⁵⁸ and Japanese *kana* mirror reading.⁵⁹ The right caudate has also been implicated in performance during probabilistic classification,⁶⁰ set-shifting/inhibition,⁸ and suppression of cognitive interference.¹¹

In contrast, the left striatum has associations with language: subjects with left caudate infarcts display language abnormalities⁵⁶ and there was increased activation in the left caudate during a task completing three word stems when many completions were possible.⁶¹ The left putamen has been activated during processing of sentences with errors in syntax.⁴⁴

Asymmetry has occurred in the cognitive deficits appearing after surgery to the globus pallidus interna: visuospatial construction declining after right and verbal fluency after left pallidotomy.^{62–63} Finally, lesions in the left thalamus can give rise to a selective verbal working memory impairment,⁶⁴ suggesting that loop function can be affected by lesions at any point in the circuit.

Mesocortical dopaminergic pathways

In this study we found no evidence for the involvement of mesocortical dopaminergic projections in the two tasks employed. However, ¹⁸F-dopa uptake in the frontal regions of normal subjects is only 15% of striatal levels and only two to three times greater than the standard deviation of the measurements.⁶⁵ We, therefore, cannot discount the possibility that subtle changes in these mesocortical projections are affecting cognitive performance. Against a contributing role for cortical dopamine depletion is the recent demonstration by Piccini *et al* that frontal dopamine release following an amphetamine challenge is preserved even in advanced PD⁶⁶ and that significant *increases* in prefrontal cortical dopa uptake (Ki) have been demonstrated in early drug naïve PD patients.¹⁶ Rinne *et al* have demonstrated a positive correlation between frontal cortical Ki and performance on tasks involving working memory, suggesting a causative role for mesocortical dopamine depletion.¹⁰ However, their findings may have been confounded by local cortical pathology as 6/28 patients were demented.

Although cortical dopamine per se may not be critical to performance accuracy, recent functional imaging studies have given evidence of greater activation in PD patients in the dopamine depleted (OFF) than the dopamine replete (ON) state, suggesting that dopamine may influence the *efficiency* of cortical function.^{18–19} The normalisation of cortical activation by dopaminergic medication may reflect as much an action in the striatum as in the cortex given the nature of the frontostriatal networks.

In summary, this is the first study to correlate dopamine terminal function with performance on executive tasks in non-demented PD patients in whom frontal cortical resting metabolism is shown to be preserved. Our study supports the hypothesis that cognitive deficits in PD relate to striatal dopamine depletion, which in turn disrupts corticostriato-cortical loop function. In addition, there is evidence for lateralisation of dopaminergic function in that

right caudate ¹⁸F-dopa uptake selectively covaries with performance on the TOL spatial planning task and left putaminal ¹⁸F-dopa uptake with performance on the VWMT. The implication of these findings for PD patients is that the side of disease onset may determine the earliest cognitive deficits, although cognitive profiles may become less distinguishable as the secondarily affected hemisphere becomes significantly involved. The lateralisation found is broadly consistent with the results of activation studies and indicates that subcortical structures may be important mediators of lateralised hemispheric functions.

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