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Regional changes in [^{18}F]dopa metabolism in the striatum in Parkinson's disease

P. K. Morrish,[1] G. V. Sawle[3] and D. J. Brooks[1,2]

[1]*MRC Cyclotron Unit, Hammersmith Hospital and* [2]*Institute of Neurology, London, and* [3]*Division of Clinical Neurology, Queens Medical Centre, Nottingham, UK*

Correspondence to: Dr P. K. Morrish, MRC Cyclotron Unit, Hammersmith Hospital, DuCane Road, London, W12 0HS, UK

Summary

We have investigated regional changes in dopamine metabolism within the basal ganglia with clinical progression of idiopathic Parkinson's disease, using coregistration of [^{18}F]dopa-PET and MRI images and comparing six normal subjects with 15 Parkinson's disease patients in a cross-sectional study. We have demonstrated that [^{18}F]dopa metabolism in the dorsal putamen is reduced to almost 50% of normal both caudally and rostrally early in the disease whilst the ventral putamen is not significantly affected. With progression of symptoms there is loss of dopa metabolism from the ventral putamen, the ventrocaudal putamen in advance of the ventrorostral putamen. Throughout the disease the ventrorostral putamen is relatively preserved; even in the most advanced group [^{18}F]dopa uptake is reduced here by only 30%. We conclude that the progression of Parkinson's disease is associated with a focal process affecting only the dorsal putamen in its early (and preclinical) phase then affecting the ventral putamen with increasing disease severity.

Keywords: Parkinson's disease; [^{18}F]dopa; progression; intrastriatal

Abbreviations: AC–PC = anterior commissure to posterior commissure; K_i = [^{18}F]dopa influx constant; REML = restricted maximum likelihood estimation; ROI = region(s) of interest; UPDRS = unified Parkinson's disease rating scale

Introduction

The [^{18}F]dopa-PET technique allows the study of striatal dopa metabolism *in vivo*, and it is well established that putamen [^{18}F]dopa uptake deteriorates with advancing disability in Parkinson's disease (Brooks *et al.*, 1990*a*, Takikawa *et al.*, 1994). A post mortem study (Kish *et al.*, 1988) has suggested that reductions in dopamine levels in the striatum are not uniform in Parkinson's disease but that there are gradients, the greatest reductions occurring dorsally in both the putamen and the caudate nucleus, with rostral caudate nucleus and caudal putamen most affected. An important advantage of [^{18}F]dopa-PET over post-mortem studies is that patients with early disease can be studied. We have estimated that the onset of symptoms in Parkinson's disease is associated with a mean putamen [^{18}F]dopa uptake of ~80% of normal (Morrish *et al.*, 1996) but technical limitations have not allowed us to examine the topography of this deficit.

In order to investigate the regional changes in dopamine storage within the caudate nucleus and putamen that are associated with preclinical disease and with the progression of symptomatic Parkinson's disease we have used a method of analysis that combines MRI and [^{18}F]dopa-PET imaging (Morrish *et al.*, 1995) in a cross-sectional study.

Methods

Recruitment and clinical assessment

Fifteen patients fulfilling the UK Brain Bank criteria for Parkinson's disease (Gibb and Lees, 1988) were recruited from neurological centres throughout the UK (mean age 57.2±13.4 years, mean disease duration 43±36 months: ±SD here and throughout text). All were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn *et al.*, 1987) after at least 12 h off medication; their mean total score was 38.5±22.7. The patients and a group of six unrelated healthy controls (mean age 72.8±9.4 years) then underwent [^{18}F]dopa-PET and MRI scanning (on separate days). All subjects gave written informed consent prior to PET and MRI scanning. Permission to perform these studies was obtained from the Ethical committee of the Hammersmith Hospital, London, UK, and from the Administration of Radioactive Substances Advisory Committee, UK.

Scanning procedures

The [^{18}F]dopa-PET scans were performed using the CTI 931/08/12 tomograph (CTI, Knoxville, Tenn., USA) yielding 15 simultaneous planes with an axial full-width half maximum resolution of 7 mm and an inplane resolution of 8.5×8.5 mm^2. All subjects were given carbidopa 1 h before (100 mg) and 5 min before (50 mg) scanning. Correction for tissue attenuation of 511 KeV gamma radiation was measured using an external ^{68}Ge ring. 80–180 MBq of [^{18}F]dopa in 10 ml normal saline solution was infused i.v. over a period of 30 s. An arterial line was inserted into the radial artery and blood was drawn continuously throughout the scan, giving plasma counts and samples for metabolite analysis using the alumina extraction method (Boyes *et al.*, 1986). Scanning began at the start of the tracer infusion with a protocol of 31 time frames over 93 min. The MRI scans were performed using a 1.0 Tesla Picker Vista MRI scanner with a T_1 weighted spoiled gradient sequence, giving an axial resolution of 1.3 mm and a transaxial resolution of 1 mm.

Data analysis

Analysis of data was performed on SUN Sparc workstations (Sun Microsystems, Silicon Valley, Calif., US) using ANALYZE (ANALYZE 7.5, Mayo Foundation, Baltimore, Md., USA) image analysis software (Robb and Hanson, 1991). An [^{18}F]dopa influx constant (K_i) image (voxel size 2.1×2.1×6.4 mm^3) was created from each dynamic image by applying the metabolite corrected plasma input function, with subtraction of background derived from four cerebellar regions of interest (ROI), each 32.8 mm in diameter, from two planes, on a pixel by pixel basis (Bloomfield *et al.*, 1991). An aggregate image of each dynamic scan was aligned to the subject's MRI scan, which was aligned to the anterior commissure to posterior commissure (AC–PC) line using automated image alignment software (Woods *et al.*, 1992). The parameters of this coregistration were then applied to the individual's plasma K_i image. A 1×1×3 voxel smoothing function was applied to each resliced K_i image. The ROI were traced from each individual's MRI scan at 3 mm intervals from the AC–PC line to 12 mm dorsal to the AC–PC line. A single region was traced around the head of each caudate nucleus and two regions were traced around each putamen at each level, dividing the putamen at its midpoint into rostral and caudal sections. There was no significant difference in traced ROI size between the Parkinson's disease and normal groups. These ROI were then applied to the smoothed and resliced K_i image from which mean within-region K_i values were measured. We follow the terminology of Kish *et al.* (1988) referring to rostral, caudal, ventral and dorsal putamen and caudate nucleus (*see* Fig. 1).

In the normal subjects all caudate nucleus and putamen K_i values were averaged to create a normal range. In the Parkinson's disease patients results from the putamen and head of caudate were grouped according to the subject's contralateral motor UPDRS scores. Those putamen and head of caudate nucleus results contralateral to a motor UPDRS score of zero were grouped together (Group I, n = 6), as were those contralateral to motor UPDRS scores between zero and 10 (Group II, n = 13), and those >10 (Group III, n = 11). Mean values for the head of the caudate nucleus and rostral and caudal putamen K_i were calculated at each level for each group. The K_i values for each group at each level in each structure were compared with the K_i values obtained from the normal group with an unbalanced analysis of variance using the REML (restricted maximum likelihood estimation) procedure in Genstat (*see* Genstat 5 Committee, 1993). Three fixed factors, group, structure and level, were included in the analysis of variance. This analysis makes the assumption that there is no effect due specifically to right or left side. From this analysis predicted mean values were derived for each combination of area, level and group, and the standard error of the difference between pairs of mean values was calculated.

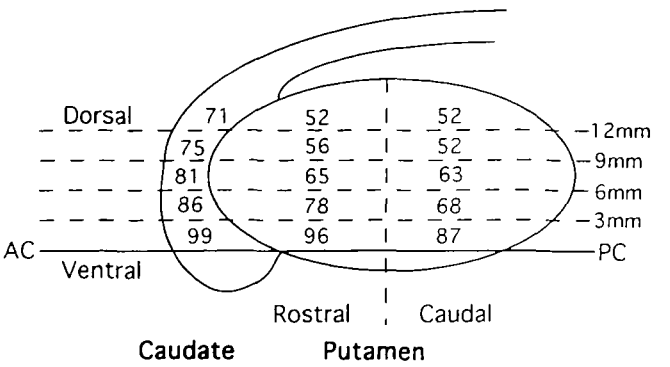

Fig. 1 A diagram showing the percentage of normal [^{18}F]dopa metabolism in subdivisions of the striatum in Parkinson's disease contralateral to a motor UPDRS score of zero (Group I).

Results

The mean K_i values in each group at each level in each structure are shown in Table 1. In the normal subjects the rostral putamen [^{18}F]dopa uptake was higher than that caudally at each level. There were three significant (P < 0.001) two-factor interactions, between structure and level, between structure and group, and between level and group. In all three groups in each region there was a gradient (decrease) in [^{18}F]dopa metabolism from ventral to dorsal. Figure 1 shows the mean values in Group I (contralateral to a motor UPDRS of zero) as a percentage of the respective normal mean. In the caudate nucleus the [^{18}F]dopa metabolism declined from 99% ventrally to 71% dorsally, in the rostral putamen from 96% ventrally to 52% dorsally and in the caudal putamen from 87% ventrally to 52% dorsally. In Group II (with a contralateral motor UPDRS of 1–10), caudate nucleus [^{18}F]dopa metabolism declined from 90% ventrally to 71% dorsally, rostral putamen [^{18}F]dopa metabolism from 89% ventrally to 55% dorsally, and caudal

Table 1 *Values of the [^{18}F]dopa influx constant (K_i) in the caudate nucleus, and rostral and caudal putamen in normal subjects and the three groups of Parkinson's disease patients*

Level (mm)	K_1 values (min^{-1})			
	Normals (n = 12)	Group I (n = 6)	Group II (n = 13)	Group III (n = 11)
Caudate nucleus				
0	0.0105±0.0026	0.0104±0.0029	0.0094±0.0027	0.0096±0.0031
3	0.0111±0.0031	0.0096±0.0023	0.0091±0.0020	0.0091±0.0030
6	0.0113±0.0022	0.0092±0.0026	0.0090±0.0012	0.0087±0.0027
9	0.0110±0.0019	0.0083±0.0028	0.0082±0.0014	0.0078±0.0020
12	0.0104±0.0019	0.0074±0.0030	0.0074±0.0019	0.0068±0.0017
Rostral putamen				
0	0.0131±0.0031	0.0126±0.0036	0.0116±0.0021	0.0091±0.0036
3	0.0147±0.0030	0.0115±0.0023	0.0109±0.0022	0.0088±0.0034
6	0.0151±0.0025	0.0098±0.0026	0.0093±0.0021	0.0079±0.0021
9	0.0140±0.0023	0.0079±0.0033	0.0071±0.0022	0.0063±0.0012
12	0.0110±0.0020	0.0057±0.0030	0.0056±0.0020	0.0046±0.0012
Caudal putamen				
0	0.0107±0.0031	0.0093±0.0023	0.0073±0.0028	0.0052±0.0009
3	0.0132±0.0033	0.0090±0.0027	0.0066±0.0026	0.0048±0.0008
6	0.0126±0.0025	0.0079±0.0028	0.0057±0.0024	0.0042±0.0013
9	0.0115±0.0022	0.0060±0.0032	0.0039±0.0022	0.0034±0.0009
12	0.0090±0.0028	0.0047±0.0040	0.0027±0.0017	0.0028±0.0008

The K_1 values (±SD) were measured at the AC–PC line and at 3 mm increments dorsal to it in each structure.

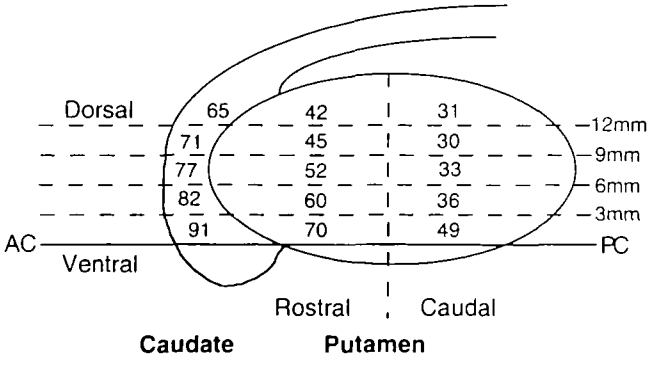

Fig. 2 A diagram showing the percentage of normal [^{18}F]dopa metabolism in subdivisions of the striatum in Parkinson's disease contralateral to a motor UPDRS score ≥10 (Group III).

putamen [^{18}F]dopa metabolism from 68% ventrally to 30% dorsally. The mean K_1 values in the most severely affected group (Group III with contralateral motor UPDRS >10) are shown in Fig. 2.

The predicted mean values arising from the REML analysis are given in Table 2 which enables the identification of significant change in mean [^{18}F]dopa uptake (Ki) between groups and levels. A significant change between groups at any one level is indicated by the difference (in predicted mean) exceeding twice the average SE of differences for the group (0.0008 min^{-1}). A significant change between levels in any group is indicated by the difference exceeding twice the average SE of differences for the level (0.0010 min^{-1}). In the caudate nucleus there was a significant difference from normal in all three groups at 6 mm dorsal to the AC–PC line. In both rostral and caudal putamen there was a significant difference from normal in Group I at 3 mm dorsal to the AC–PC line, and in Groups II and III at the AC–PC line.

Figure 3 demonstrates the regional loss of [^{18}F]dopa metabolism in a patient with hemiparkinsonism and a motor UPDRS score on the left of zero, and on the right of 11. On the right (contralateral to the less affected limb) [^{18}F]dopa metabolism has fallen below the threshold value in the dorsal and caudal putamen (35% of image maximum) whilst on the left only the ventral rostral putamen has retained [^{18}F]dopa metabolism above this value.

Discussion

This study demonstrates the focal onset and sub regional progression of [^{18}F]dopa metabolism with clinical progression in Parkinson's disease. The earliest identifiable stage of disease is found in Group I, contralateral to a motor UPDRS score of zero. Here severe loss (almost 50%) of [^{18}F]dopa uptake is confined to the dorsum of the putamen, whilst at the AC–PC line [^{18}F]dopa uptake is normal. Groups II and III, in whom clinical signs and symptoms are more advanced, show deterioration of the ventral putamen, both caudally and rostrally, with continuing loss in the already depleted dorsal putamen. The head of the caudate nucleus is less affected by increasing disease severity (measured by motor UPDRS) and even in Group III [^{18}F]dopa uptake in the ventral head of the caudate nucleus is not significantly different from normal.

These [^{18}F]dopa PET findings confirm observations from pathological and biochemical studies. Fearnley and Lees (1991) studied nigral cell counts at post-mortem and demonstrated a cell loss in Parkinson's disease beginning in the lateral ventral nigra. Lateral ventral nigral cells project

Table 2 *The predicted mean* K_i *values from the REML analysis for each combination of structure, level and group*

Level (mm)	Predicted mean K_i values (min^{-1})			
	Normals (n = 12)	Group I (n = 6)	Group II (n = 13)	Group III (n = 11)
Caudate nucleus				
0	0.0106	0.0105	0.0093	0.0097
3	0.0111	0.0098	0.0090	0.0092
6	0.0113	0.0094	0.0089	0.0088
9	0.0110	0.0085	0.0081	0.0079
12	0.0104	0.0076	0.0072	0.0069
Rostral putamen				
0	0.0131	0.0127	0.0114	0.0092
3	0.0147	0.0116	0.0108	0.0095
6	0.0151	0.0100	0.0091	0.0079
9	0.0140	0.0080	0.0070	0.0064
12	0.0110	0.0059	0.0054	0.0047
Caudal putamen				
0	0.0107	0.0094	0.0072	0.0053
3	0.0132	0.0091	0.0064	0.0049
6	0.0126	0.0081	0.0056	0.0043
9	0.0115	0.0061	0.0037	0.0035
12	0.0090	0.0048	0.0026	0.0029

These predicted mean K_i values enable the identification of significant changes in mean [^{18}F]dopa uptake (K_i) between groups of subjects and levels in the brain. A significant change between groups at any one level is indicated by the difference (in predicted mean) exceeding twice the average SE of differences for group (0.0008 min^{-1}). A significant change between levels in any group is indicated by the difference exceeding twice the average SE of differences for level (0.0010 min^{-1}).

to the dorsal putamen so the findings of this PET study are entirely compatible with their data. The pattern of functional deterioration identified here is also very similar to that identified by the postmortem biochemical study of Kish *et al.* (1988). However, there is a very important difference; where Kish *et al.* (1988) found severe loss of dopamine throughout the putamen with the best preserved area, the ventrorostral putamen, retaining only 10.9% of the control value, our study shows that [^{18}F]dopa metabolism in the best preserved area (also the ventrorostral putamen) is 70% of normal even in the most severely affected group. Dorsal to this there is a greater loss but even in the most depleted area (the dorsocaudal putamen) in the most severely affected group [^{18}F]dopa metabolism has only fallen to 30% of normal. Kish *et al.* (1988) measured post mortem dopamine concentration whereas K_i, measured by [^{18}F]dopa-PET, is an *in vivo* measurement of dopa decarboxylase activity and vesicular storage capacity. It has been suggested that dopa decarboxylase might be upregulated in response to the loss of dopaminergic terminals with ageing or disease progression (Kish *et al.*, 1995) so that [^{18}F]dopa-PET might overestimate the surviving terminal density. However, animal and human PET studies (Pate *et al.*, 1993, Snow *et al.*, 1993) have suggested a good correlation between PET measurements of [^{18}F]dopa metabolism and surviving nigrostriatal cell numbers. An alternative explanation for the discrepancy between the two studies is that the group studied by Kish *et al.* (1988) had more severe disease than even the most severely affected patients studied here. It has also been suggested that post-mortem estimates of dopamine concentration might underestimate *in vivo* dopamine levels (Scherman *et al.*, 1989).

Our data suggest that dopaminergic function is significantly depleted in the dorsal putamen and dorsal head of the caudate nucleus at the earliest stage of the disease, when contralateral limb function is normal (*see* Fig. 1). The difference in dopamine metabolism in the ventral putamen between Group I and Group III suggests that it is the loss of dopa metabolism here that is most critical to the progression of symptoms and signs in clinical Parkinson's disease. Loss of dopa metabolism from the dorsal putamen is still continuing (to a lesser degree) so of course may still be important. Caudate nucleus [^{18}F]dopa metabolism appears less affected by disease progression but categorization with the motor UPDRS score may be inappropriate to demonstrate progression of disease in this structure.

A focal onset and spreading loss of dopaminergic function in the putamen could explain the typical pattern of symptom progression in Parkinson's disease. The motor and somatosensory cortex are represented somatotopically in the putamen with the foot most dorsal and the hand and face most ventral (Flaherty and Graybiel, 1994). However, the clinical pattern of progression that our study and the post-mortem studies (Kish *et al.*, 1988; Fearnley and Lees, 1991) predict would be the initial involvement of the leg, rather than the typical clinical presentation of upper limb tremor and bradykinesia. Fearnley and Lees (1991) offered a possible explanation for this paradox, namely that deficits in upper limb function may be noted sooner by the patient.

This is not the first demonstration of gradients in dopa

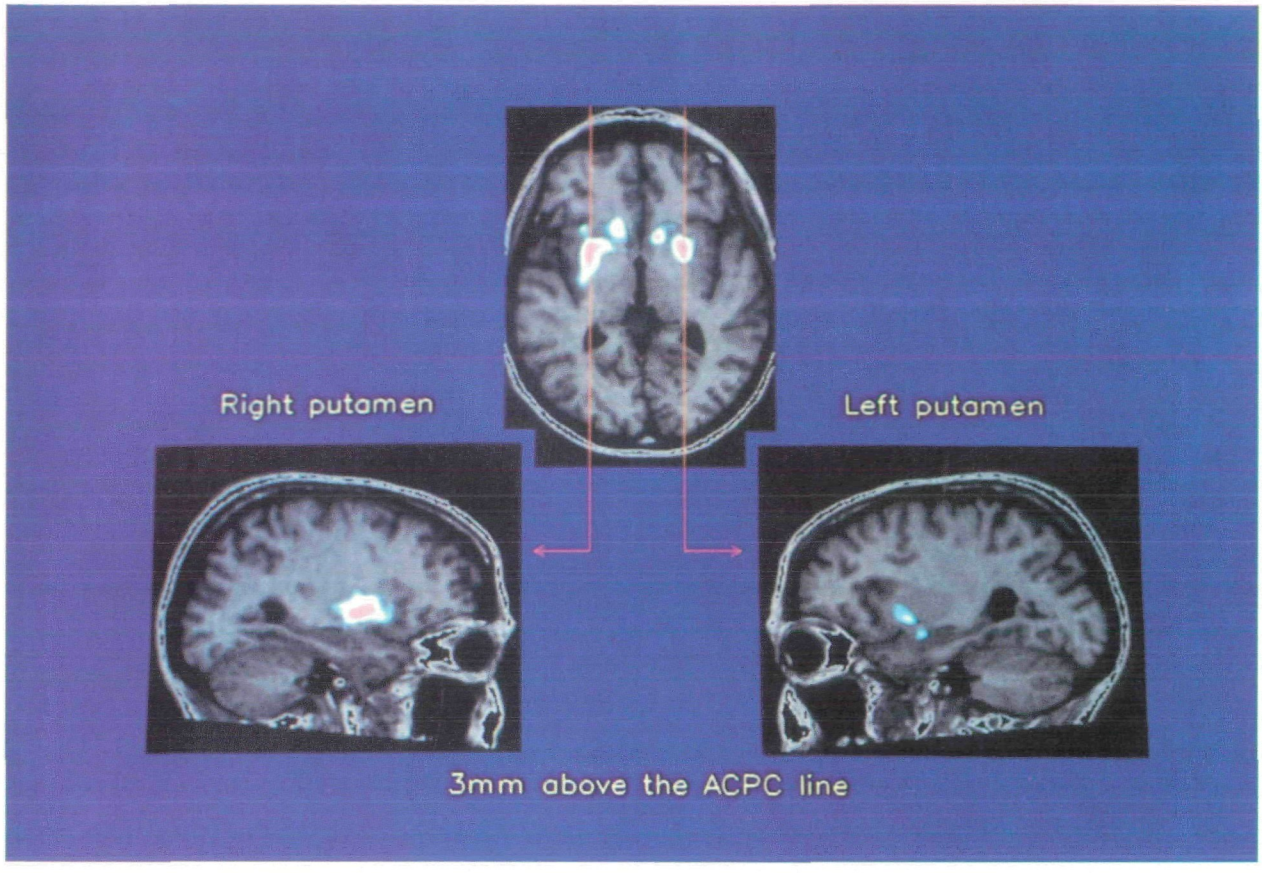

Fig. 3 This image shows transverse and sagittal sections of a K_i image from a patient with hemiparkinsonism, overlaid on the same individual's MRI after coregistration. The colour scale of the Ki image has a threshold at 35% of the image maximum K_i value (blue = 35–45%; white = 45–60%; pink is ≥60%). On the right, K_i has fallen below the threshold in dorsal and caudal putamen. The ventral rostral putamen only retains a K_i above the threshold on the left.

metabolism within the Parkinson's disease striatum using [^{18}F]dopa-PET. Brooks *et al.* (1990*b*) showed a significant difference between rostral and caudal putamen Ki values in a group of Parkinson's disease patients with early to severe disease but they were unable to separate dorsal and ventral change or to correlate change in rostral and caudal putamen with disease severity. Sawle *et al.* (1994) used discriminant analysis to separate Parkinson's disease from normals on the basis of a low putamen Ki value relative to its pair and the accompanying caudate nucleus Ki values. The separation achieved by this method supports the suggestion that the disease (at least when measured by [^{18}F]dopa metabolism) may begin focally, affecting one putamen more than either the caudate nucleus or the contralateral putamen.

Holthoff *et al* (1994) used putamen rostro-caudal gradients to identify subclinical dysfunction in at-risk Parkinson's disease co-twins, and a number of other studies have identified suspected preclinical disease [in Parkinson's disease co-twins (Burn *et al.*, 1992) and in subjects exposed to MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine) (Calne *et al.*, 1985)] on the basis of low putamen or whole striatal [^{18}F]dopa metabolism identified using standard ROI. The present study indicates that the measurement of a ventral–dorsal gradient may offer a more sensitive and specific method of identifying preclinical disease than either total putamen K_i or rostrocaudal gradient. It would clearly be of great interest to study those subjects previously suspected to have preclinical disease with the methodology used in this study. If these subjects truly have preclinical Parkinson's disease they might be expected to show a similar focal pattern of dysfunction to that of Group I. The alternative, that the low putamen *Ki* values in these subjects is the result of a global reduction in [^{18}F]dopa uptake throughout the putamen, would suggest that their pathology is different from that of early idiopathic Parkinson's disease; extrapolation from PET studies in these subjects to the pathogenesis of idiopathic Parkinson's disease might then be inappropriate.

There is a need to identify the optimal site for therapeutic implantation of embryonic mesencephalic tissue. Lindvall *et al.* (1992) have previously reported implanting embryonic tissue throughout the putamen whilst Freeman *et al.* (1995) have implanted embryonic tissue into the post-commissural putamen alone and Remy *et al.* (1995) implanted tissue into both the caudate nucleus and putamen. Whilst our study demonstrates the pattern of decreased dopaminergic function in the striatum in Parkinson's disease it should not be

interpreted as evidence for any one surgical approach. The most affected area early in the disease is the dorsal putamen but the progression of contralateral clinical signs is associated with greater loss of dopaminergic function from the ventral putamen. It follows that the demonstration of a more severe deficit in one area of the striatum does not imply that implanting tissue into that area is the best way to restore clinical function. Our assessment of caudate nucleus function does suggest that evidence of caudate nucleus dysfunction either clinically or with [^{18}F]dopa-PET should be present before implantation into the caudate nucleus; the ventral caudate nucleus appears to be functionally intact late in the disease.

We make the assumption that in our group of normal subjects there were no preclinical patients. We also assume that there is no ageing effect on gradients of dopamine metabolism. The normal group in the current study is too small to investigate such an effect. In cross-sectional studies striatal K_i values do not decrease with age (Sawle *et al.*, 1990, Eidelberg *et al.*, 1993), and in a longitudinal study we have demonstrated rapid change in the putamen in Parkinson's disease (7% of the normal mean per year) but no change in normal volunteers, suggesting that ageing and progression in Parkinson's disease are distinct processes. Our normal group are older than our patient group so such an effect would increase the differences between normals and patients. We have separated left and right striatal structures and placed them in groups according to contralateral motor scores. The wide range of clinical disease severity at any duration of Parkinson's disease (Di Rocco *et al.*, 1996) justifies grouping by disease severity rather than by duration of symptoms, and dopamine terminal loss is likely to be more closely related to clinical severity than it is to duration of symptoms. However, we accept that this analysis remains a simplification of the function of these structures, and it assumes that the effect of pathology within them is exclusively on the contralateral limbs.

The present study demonstrates the advantages that this method of PET analysis gives over studies using a conventional ROI approach without MRI co-localization. It allows accurate assessment of [^{18}F]dopa uptake in areas of low dopa metabolism such as the diseased dorsal putamen which has previously proved difficult to assess (Vingerhoets *et al.*, 1996). It can also be used to study extrastriatal [^{18}F]dopa metabolism. In this study we chose to use metabolite-corrected plasma counts as the input function; this provides compensation for any change in peripheral [^{18}F]dopa metabolism with disease progression. The method can equally be applied using reference tissue counts as the input function in a graphical analysis or in a ratio analysis. We are aware however that the PET camera has a relatively low resolution and that the coregistration and reslicing processes reduce resolution further; this method is not a substitute for the development of higher resolution PET imaging.

This study has demonstrated the pattern of Parkinson's disease progression within the striatum, beginning focally in the dorsal putamen and sparing ventral putamen and the caudate nucleus early in the disease when subjects may be presymptomatic or mildly affected. The PET–MRI coregistration approach demonstrated here offers significant advantages over conventional [^{18}F]dopa analysis, potentially providing more sensitive and specific identification of preclinical disease and permitting study of regions low in specific dopa uptake.

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