

# Measuring the rate of progression and estimating the preclinical period of Parkinson's disease with [<sup>18</sup>F]dopa PET

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## Abstract

**Objectives**—To measure the rate of progression in striatal [<sup>18</sup>F]dopa metabolism in a large group (n=32) of patients with Parkinson's disease, to estimate the average duration of preclinical period, and to examine the influence of the PET method on the assessment of rate of progression and preclinical period.

**Methods**—Thirty two patients with Parkinson's disease (mean age 58 (SD 13) years, mean duration 39 (SD 33) months) were assessed with [<sup>18</sup>F]dopa PET and UPDRS scoring on two occasions a mean of 18 (SD 6) months apart. PET data were sampled with separate caudate and putamen and total striatal regions of interest, and both graphical (Ki) and ratio methods of analysis.

**Results**—The mean annual rate of deterioration in [<sup>18</sup>F]dopa uptake varied according to structure and method of analysis, with putamen Ki showing the most rapid mean rate of progression (4.7% of normal mean per year). The group showed a significant deterioration (p<0.0004, paired two tailed t test) in UPDRS and in the putamen (p=0.008) and total striatal (p=0.012) [<sup>18</sup>F]dopa uptake measured using a graphical analysis, but no significant change in caudate or putamen uptake measured by a ratio approach. A study of sensitivity confirmed that putamen Ki was the most sensitive measure of disease progression, caudate ratio the least. Symptom onset in Parkinson's disease was estimated at a mean putamen [<sup>18</sup>F]dopa uptake (Ki) of 75% of normal and a mean caudate [<sup>18</sup>F]dopa uptake (Ki) of 91% of normal.

**Conclusions**—Estimation of mean rate of progression varies according to the sensitivity of a functional imaging method to clinical severity. Sensitivity and reproducibility of method must be considered when designing studies of disease progression and neuroprotection. The mean preclinical period in Parkinson's disease is unlikely to be longer than seven years.

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Keywords: positron emission tomography; Parkinson's disease; preclinical period

Two longitudinal [<sup>18</sup>F]dopa PET studies<sup>1,2</sup> have shown that the rate of deterioration in striatal

dopaminergic metabolism associated with Parkinson's disease is faster than that associated with normal aging. These studies confirm that progression in Parkinson's disease is unlikely to be caused by age related cell attrition after an earlier insult and do not support the long latency hypothesis of Parkinson's disease proposed by Calne and Langston in 1983.<sup>3</sup> The two studies, however, gave very different estimates of the duration of the preclinical period and the mean rate of progression. Vingerhoets *et al*<sup>1</sup> estimated that the mean rate of deterioration in striatal [<sup>18</sup>F]dopa uptake in Parkinson's disease was 0.5% of the normal mean per year and that the duration of the preclinical period could be as long as 50 years. Our estimate<sup>2</sup> was a mean annual rate of progression of 7% of the normal mean putamen [<sup>18</sup>F]dopa uptake and a mean preclinical period of three years. These disparate estimates raise questions over the value of [<sup>18</sup>F]dopa PET in studying disease progression. [<sup>18</sup>F]dopa PET should provide an objective method of assessment of progression of disease that can be used in studies of progression and neuroprotection; at least two studies are already in progress using [<sup>18</sup>F]dopa PET to examine the effect of sparing levodopa (and substitution with a dopamine agonist) in early Parkinson's disease. We considered two explanations for the difference in the results of published studies; a difference in the clinical characteristics of the patients selected and a difference in PET methods.

The aim of the present study was to examine the influence of differing PET methods (specifically, larger total striatal regions of interest and quantification by ratio) on the measurement of the mean rate of progression and estimation of the preclinical period. We wished to examine the reproducibility and sensitivity of each method to establish the optimum method of assessing disease progression and duration of preclinical period with [<sup>18</sup>F]dopa PET. In doing so we hoped to establish guidelines for the use of [<sup>18</sup>F]dopa PET in therapeutic trials. By increasing our previous group of 17 patients to 32 we hoped to exclude the possibility that our previous group were atypical in their rate of progression. This larger group would also allow us to examine further the influence of duration, severity, and clinical presentation (with or without tremor) on the rate of progression of disease.

## Methods

### RECRUITMENT AND CLINICAL ASSESSMENT

Thirty two patients (mean age 58 (13) years, mean duration of symptoms 39 (SD 33)

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months) fulfilling the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank criteria<sup>1</sup> for the prospective diagnosis of Parkinson's disease were recruited by consultant neurologists in the United Kingdom. They were examined by clinical assessment and [<sup>18</sup>F]dopa PET on two occasions, an average of 18 (SD 6) months apart. Clinical assessment was by UPDRS assessment by one of two observers, carried out at least 12 hours after stopping medication.

All subjects were given carbidopa, 100 mg one hour before and 50 mg five minutes before PET. Thirteen of the patients with Parkinson's disease were also given the peripheral catechol-O-methyltransferase inhibitor entacapone (Orion Farnos pharmaceuticals, Espoo, Finland) at a dose of 400 mg one hour before each of their scans.

Two groups of normal volunteers took part in this study. One group of eight unrelated normal volunteers (mean age 72 (SD 9) years) was scanned on two occasions, an average of 39 (SD 28) months apart to assess reproducibility. A second group of eight normal volunteers (mean age 57 (SD 12) years) was also scanned, each on a single occasion after 400 mg entacapone, to determine the effect of this drug.

#### SCANNING PROCEDURES

All subjects gave written informed consent before PET. Permission to perform these studies was obtained from the ethics committee of the Hammersmith Hospital, London, United Kingdom, and from the Administration of Radioactive Substances Advisory Committee, United Kingdom. PET was performed using the CTI 931/08/12 tomograph (CTI, Knoxville, Tennessee, USA) yielding 15 simultaneous planes with an axial full width half maximum resolution of 7 mm and an in plane resolution of 8.5 by 8.5 mm. Tissue attenuation of 511KeV  $\gamma$ -radiation was measured using an external germanium ring. Scanning was carried out at least 12 hours after stopping medication. Between 80 and 180 MBq [<sup>18</sup>F]dopa in 10 ml normal saline solution was infused intravenously over 30 seconds. Scanning began at the start of the tracer infusion with a protocol of either 25 or 31 time frames over 93 minutes. For repeat scans the scan protocol and prescan medication were reproduced from the first scan.

#### DATA ANALYSIS

Analysis of data was performed on SUN Sparc 2 workstations (Sun Microsystems, Silicon Valley, CA, USA). To allow us to examine both the effect of size of region of interest (ROI) and the method of quantitation on [<sup>18</sup>F]dopa

uptake three approaches to PET analysis were employed:

(1) Using a method previously described<sup>5</sup> one square region of interest (ROI, each ROI 8.2 mm by 8.2 mm) was placed on each caudate and three similar ROIs were placed contiguously along the axis of each putamen on two adjacent planes of an aggregate image. Influx constants (Kis) were calculated using a multiple time graphical analysis (MTGA) approach with occipital counts as input function.<sup>6</sup>

(2) A single elliptical total striatal region 20.5 mm by 41 mm was placed on three adjacent planes of an aggregate image and the data averaged. Influx constants (Kis) were again analysed by the MTGA approach with occipital counts as input function.

(3) As with approach 1, four separate ROIs were placed over the caudate and putamen. The resulting time activity curves were analysed by applying a ratio method (region-occipital counts:occipital counts) to the data collected from 65 to 90 minutes after tracer injection.

For each approach the results from left and right hemispheres were averaged. A normal mean was calculated for each structure using each method, with and without entacapone. Entacapone changes Ki and the ratio calculated using occipital counts as input function<sup>7</sup> (and see below), and so the results of the 13 patients scanned with entacapone as premedication were normalised by multiplying them by the ratio of the normal mean with entacapone to normal mean without entacapone. Table 1 shows the normal means and normalising ratios. The normal mean of the non-entacapone group is used in subsequent calculations of rate of progression and sensitivity.

To examine the reliability of each approach the reliability coefficient (R), standard deviation between (SDB) and within (SDW) were calculated,<sup>8</sup> using the pairs of results from the group of healthy volunteers scanned twice.

In assessing progression, in the group of 32 patients with Parkinson's disease, change between baseline and follow up scan results was examined by paired two tailed *t* test. The mean annual rate of deterioration in [<sup>18</sup>F]dopa metabolism was calculated (by each method, for each structure) and is expressed in absolute units, and as a percentage of the normal mean and baseline scan mean per year. To examine the data for any influence of duration, clinical severity, or presence of tremor on the rate of progression, the group of patients with Parkinson's disease was subdivided at the median duration (26 months), the median severity (28 points), and the presence of tremor at recruitment, and the mean rate of progression in each subgroup compared (by unpaired two tailed *t* test). Correlation between rate of progression and duration of symptoms and clinical severity was also examined by Pearson product-moment correlation.

To examine the sensitivity of each PET method to increasing disability, a linear regression was applied to the mean of each patients' two UPDRS and PET assessments

Table 1 Mean (SD) [<sup>18</sup>F]dopa uptake in healthy volunteers scanned with and without entacapone

Structure (method of analysis)	Mean (n=8) without entacapone	Mean (n=8) with entacapone	Ratio
Mean putamen (Ki)	0.0101 (0.0014) min <sup>-1</sup>	0.0133 (0.0025) min <sup>-1</sup>	0.76
Mean caudate (Ki)	0.0114 (0.0016) min <sup>-1</sup>	0.0143 (0.0024) min <sup>-1</sup>	0.80
Mean total striatum (Ki)	0.0074 (0.0009) min <sup>-1</sup>	0.0101 (0.0012) min <sup>-1</sup>	0.73
Mean putamen (ratio)	2.38 (0.25)	2.75 (0.39)	0.87
Mean caudate (ratio)	2.40 (0.21)	2.72 (0.27)	0.88

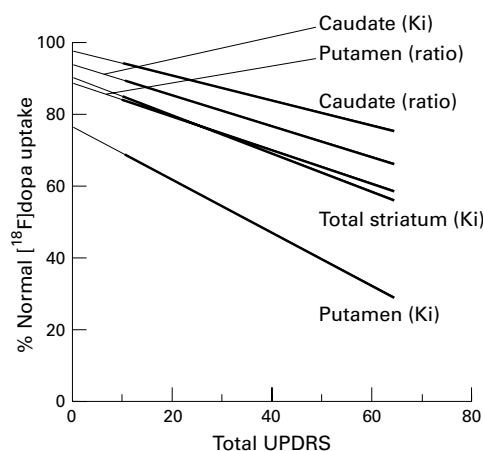


Figure 1 Regression lines of  $[^{18}\text{F}]$ dopa PET index against disease severity, with extrapolation to estimated symptom onset.

(to compensate for the presence of two pairs of measurements for each patient<sup>9</sup>). The gradient of the regression line indicates the sensitivity of the PET method to clinical progression and is expressed in absolute units and as a percentage change (of the normal mean  $[^{18}\text{F}]$ dopa uptake for each method) in the PET index for a change of 10 points in total UPDRS. This regression also allows an estimate of  $[^{18}\text{F}]$ dopa metabolism at symptom onset, the intercept of the regression line on the y axis, and is expressed in absolute units and as a percentage of the normal mean (fig 1).

The mean preclinical period was calculated in two ways (fig 2); firstly by extrapolation back from the estimated  $[^{18}\text{F}]$ dopa metabolism at symptom onset, calculated as above (method A); secondly, by extrapolation back from the mean  $[^{18}\text{F}]$ dopa uptake and mean duration in this group of patients at scan 1 (fig 2, method B).

## Results

The effect of entacapone was to significantly increase ( $p < 0.05$ , two tailed  $t$  test) the normal mean  $[^{18}\text{F}]$ dopa influx constants (Ki) and

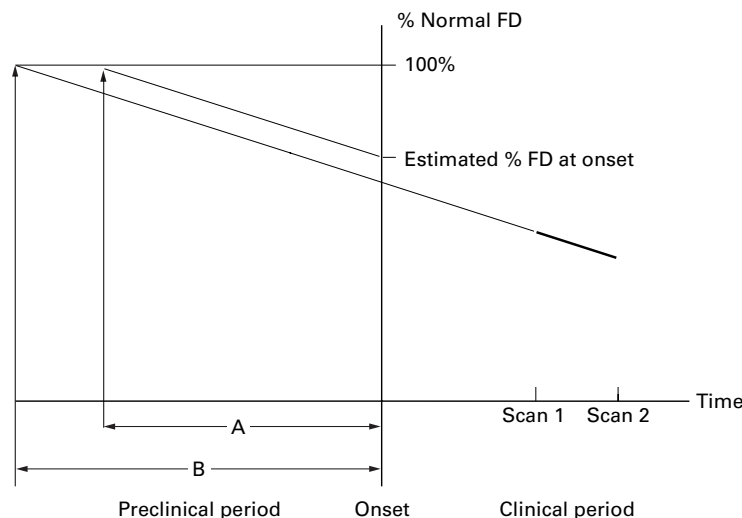


Figure 2 Two methods (A and B) of estimating the mean preclinical period in Parkinson's disease.

ratios (region-occipital counts:occipital counts) for each structure. Table 1 shows the normal mean Kis and ratios, with and without entacapone, calculated by each method. It was, therefore, necessary to introduce a compensation for the effect of entacapone to the results of the 13 patients scanned with entacapone (see methods). Table 1 also shows the compensating ratio.

Table 2 shows the reproducibility of each PET method. The ratio method of analysis gave better reproducibility, with a lower SDW, than the Ki methods for caudate and putamen assessment. Total striatal Ki did not give a more reproducible result than either putamen or caudate Ki. In this group of 32 patients, over the mean 18 months between the two assessments, there was a significant increase in mean total UPDRS, from 29 (SD 16) to 37 (SD 19) ( $p = 0.0004$ , paired two tailed  $t$  test), and a significant decrease in putamen Ki (from 0.0054 (SD 0.0022) to 0.0048 (SD 0.0021)  $\text{min}^{-1}$ ,  $p = 0.008$ ) and total striatal Ki (from 0.0055 (SD 0.0013) to 0.0051 (SD 0.0014)  $\text{min}^{-1}$ ,  $p = 0.012$ ). There was no significant change in putamen  $[^{18}\text{F}]$ dopa uptake measured by the ratio method (decreasing from 1.74 (SD 0.32) to 1.68 (SD 0.36)) nor caudate  $[^{18}\text{F}]$ dopa uptake measured by either Ki (decreasing from 0.0091 (SD 0.0018) to 0.0089 (SD 0.0018)  $\text{min}^{-1}$ ) or ratio (2.04 (0.30) to 2.04 (0.29)) methods. There was no significant correlation between change in UPDRS and change in any PET index. The measured annual rate varied (between 0.4% and 4.7% of the normal mean per year) according to both structure and PET method. Table 3 shows the mean annual rate of progression in  $[^{18}\text{F}]$ dopa storage calculated, for each structure, by each method.

The group of patients with Parkinson's disease was divided at the median duration of symptoms (26 months). The rate of deterioration in mean putamen Ki in the recent onset subgroup was 0.0008 (SD 0.0009)  $\text{min}^{-1}/\text{year}$ , significantly greater ( $p = 0.03$ , two tailed  $t$  test) than that in the more advanced group, 0.0001 (SD 0.0008)  $\text{min}^{-1}/\text{year}$ . The group of 32 patients was also divided at the median UPDRS score (28 points). There was no significant difference in the rate of progression between the more and less severely affected subgroups. There was no significant correlation between rate of progression and either duration or severity of illness. The group was divided into those with ( $n = 19$ , mean duration of illness 36 (SD 25) months) and without ( $n = 13$ , mean duration of illness 45 (SD 43) months) rest tremor at recruitment. Change in mean putamen Ki in the tremor group did not reach significance (from 0.0058 (SD 0.0025) to 0.0053 (SD 0.0021)  $\text{min}^{-1}$ ,  $p = 0.14$ ) whereas the decrease in the non-tremor group did (from 0.0049 (SD 0.0017) to 0.0040 (SD 0.0019)  $\text{min}^{-1}$ ,  $p = 0.017$ ). There was no significant difference in the rate of progression in putamen Ki between the tremor and non-tremor group.

Figure 1 shows the regression of mean (of baseline and follow up) Total UPDRS and the mean (of baseline and follow up) percentage of normal  $[^{18}\text{F}]$ dopa uptake for each method. Table 4 shows the regression equation for each

Table 2 Reproducibility in normal volunteers (n=8 pairs of scans, mean scanning interval 39 (28) months)

Structure (method of analysis)	SDB	SDW (% normal mean)	R (%)
Putamen (Ki)	0.0020	0.0009 (9)	82
Caudate (Ki)	0.0022	0.0011 (10)	80
Total striatum (Ki)	0.0016	0.0008 (11)	68
Putamen (ratio)	0.35	0.14 (6)	86
Caudate (ratio)	0.28	0.16 (7)	76

Table 3 The mean annual rate of progression and estimates of preclinical period according to each method of PET analysis and method of extrapolation in this group of 32 patients

Structure (method of analysis)	Annual rate of progression			Estimated duration of preclinical period (y)	
	Absolute	Normal mean (%)	Baseline mean (%)	Method A	Method B
Putamen (Ki)	0.00048 (0.0009)	4.7	8.9	5.2 years	6.5 years
Caudate (Ki)	0.00032 (0.0015)	2.8	3.5	3.1 years	4.2 years
Total striatum (Ki)	0.00029 (0.0005)	3.9	5.3	2.8 years	3.3 years
Putamen (ratio)	0.050 (0.14)	2.1	2.9	5.5 years	9.5 years
Caudate (ratio)	0.0089 (0.16)	0.4	0.4	8.9 years	37.2 years

Values in parentheses are SD.

Table 4 Regression equation and residual SD for each PET method

Structure (method of analysis)	r	Regression equation	Residual SD
Mean putamen (Ki)	-0.60*	y = 0.0076 + 0.000075 x	0.0017
Mean caudate (Ki)	-0.53†	y = 0.0105 + 0.000049 x	0.0013
Mean total striatum (Ki)	-0.54*	y = 0.0066 + 0.000041 x	0.0011
Mean putamen (ratio)	-0.58†	y = 2.09 + 0.011 x	0.272
Mean caudate (ratio)	-0.50†	y = 2.32 + 0.008 x	0.239

\* p < 0.0005; † p < 0.005 (Pearson product-moment correlation).

Table 5 Sensitivity to clinical deterioration (per 10 UPDRS points, (95% CIs)) and estimated point of symptom onset (95% CIs) for each PET method and structure

Structure (method of analysis)	Intercept as % normal mean	Sensitivity as % normal mean
Mean putamen (Ki)	75 (14) (80%)	7.4 (3.7) (7.2%)
Mean caudate (Ki)	91 (12) (93%)	4.3 (2.6) (3.6%)
Mean total striatum (Ki)	89 (12) (86%)	5.5 (3.2) (4.7%)
Mean putamen (ratio)	88 (9) (89%)	4.6 (2.5) (4.2%)
Mean caudate (ratio)	96 (8) (96%)	3.3 (1.8) (3.8%)

Results in italics exclude 13 patients given entacapone before PET scanning.

method and structure. The [<sup>18</sup>F]dopa uptake in each structure measured by each method showed a significant correlation with total UPDRS (Pearson product-moment correlation coefficients).

Table 5 shows the sensitivity of each method and estimated symptom onset (as a percentage of the normal mean). The Ki approach was more sensitive to increasing disability than the ratio approach. Putamen assessment alone was more sensitive to increasing disability than total striatal assessment which was, in turn, more sensitive than caudate assessment. The estimated [<sup>18</sup>F]dopa uptake at symptom onset (the y intercept) varied between 75% for putamen alone, measured using the MTGA approach, to 96% for caudate using the ratio approach. The results are given in table 4.

The calculated mean preclinical period varied between 2.8 and 37.2 years depending upon the method of analysis and extrapolation (fig 2 and table 3). The most sensitive approach, putamen Ki, showed a mean preclinical period of less than seven years.

## Discussion

In any longitudinal measurement of disease progression there are two indispensable re-

quirements. The first is reproducibility. The second is sensitivity, or the extent of change in the measured index with increasing disability. This longitudinal PET study gives a comparable estimate of the average rate of progression in striatal [<sup>18</sup>F]dopa uptake to our previous estimate,<sup>2</sup> with a larger group of patients. It has also allowed us to examine more closely the influence of different [<sup>18</sup>F]dopa PET methods on the measurement of rate of progression in Parkinson's disease. These data show that, not surprisingly, the most sensitive [<sup>18</sup>F]dopa PET method (the Ki approach applied to the putamen alone) gives the highest estimate of the rate of progression in Parkinson's disease. In our group of 32 patients the Ki approach yields an average annual rate of progression of 4.7% of the normal mean (and 8.9% of baseline) for the putamen, 3.9% of the normal mean for total striatum (5.3% of baseline), and 2.8% of the normal mean (3.5% of baseline) per year for the caudate. Extrapolation from these data suggests an average preclinical period between 2.8 and 6.5 years. If a less sensitive method, the ratio approach, is used and the structure showing the slowest progression, the caudate, is selected our estimate of the preclinical period approaches the 40 years estimated by Vingerhoets *et al*,<sup>1</sup> and hypothesised by Koller *et al*.<sup>10</sup>

Our reproducibility study has produced similar results to that of Vingerhoets *et al*.<sup>11</sup> We were unable to show their finding of improved reproducibility of single large total striatal regions over small separate caudate and putamen ROIs but we accept that a larger study might detect such a difference. The ratio method provides the most reproducible method of analysis. However, whereas the ratio method is more reproducible than the Ki method it is also less sensitive. The two factors are obviously closely linked; the ratio method distinguishes increasing disability with difficulty and is less likely to identify changes within a person.

Sensitivity of the PET method determines the annual change in PET index in Parkinson's disease, and so the significance of reproducibility can only be determined in the context of sensitivity. The importance of sensitivity of the [<sup>18</sup>F]dopa PET method in the study of disease progression is emphasised in this study by the lack of significant change between baseline and follow up results when less sensitive methods (putamen ratio) were used and the structure showing the least sensitivity to disease progression (caudate) was examined. The logical extension of the search for sensitivity to clinical deterioration in [<sup>18</sup>F]dopa PET measurement is, of course, that [<sup>18</sup>F]dopa PET is developed as a way to examine the dopaminergic deficits that underlie different clinical stages of disease<sup>12</sup> and different clinical phenotypes, rather than as a measurement of duration of disease. Application of the technique in this way avoids the increasingly controversial interpretation of [<sup>18</sup>F]dopa PET data as a measure of nigrostriatal cell count.<sup>13</sup>

We have presented one method of assessing the sensitivity of [<sup>18</sup>F]dopa PET approaches to

disease progression. A similar approach has been used extensively in [<sup>18</sup>F]dopa PET studies,<sup>6,14</sup> although strictly this should only be applied if there is a linear relation between PET index and clinical scale. We have chosen to use data from both patients' first and second assessments in our regression but this method can equally be applied to cross sectional data, when only a single PET and UPDRS assessment are available. Calculating the sensitivity of a PET method in this way allows an approximation of the expected progression in [<sup>18</sup>F]dopa uptake in a group in which the clinical deterioration is known (or can be estimated from other clinical studies). Over the mean 18 months between assessments this group deteriorated by a mean of eight UPDRS points, and so the calculated sensitivities would predict a change in mean putamen Ki of 5.9% of the normal mean (the measured change in this group was actually 6%), in mean total striatal Ki of 4.4% (actual change 5.4%), and in mean putamen ratio of 3.7% (actual change 2.5%).

The regression analysis has also allowed an estimate of the mean level of dopaminergic terminal function at the point of symptom onset. This was 75% of the normal mean putamen Ki, and 91% of the normal mean caudate Ki. The less sensitive ratio methods gave estimates of 88% for the putamen, 96% for the caudate. This is in accord with our previous estimates of the threshold for the development of symptoms. When we studied a group of patients with early hemiparkinsonism<sup>15</sup> we found the mean putamen Ki contralateral to the symptomatic limb to be 57% and that contralateral to the healthy limb to be 80% of normal, in a group in which duration of symptoms was a mean of 24 (SD 16) months. In our previous longitudinal study<sup>2</sup> we extrapolated a mean putamen Ki 79% of the normal mean at symptom onset. That study, of 17 patients, showed a trend towards rate of progression being more rapid in recent onset Parkinson's disease. In this larger group of 32 patients the shorter duration group again showed a significantly more rapid progression than the longer duration group but there was no correlation between duration of symptoms and rate of progression. Further, the tremor subgroup showed a significant deterioration over the course of the study, the non-tremor group did not (despite a longer mean duration of symptoms) but there was no significant difference between the two in the rate of progression. Larger patient numbers are required to establish the relation between rate of progression and duration, clinical severity, and phenotype.

This study confirms the findings from biochemical studies<sup>16</sup> and cross sectional PET studies<sup>6</sup> that caudate dopaminergic function is relatively preserved; the mean rate of progression in the caudate is lower than the mean rate of progression in the putamen (whether using the Ki or ratio approach). With increasing UPDRS there is less change in caudate [<sup>18</sup>F]dopa uptake suggesting that the UPDRS scale may not provide a good indicator of deficiency in caudate dopaminergic function.

We have used two methods to estimate the mean duration of the preclinical period in this group of patients (fig 2). Neither method is perfect. The first method (A) makes an extrapolation from the estimated point of symptom onset, and depends on the assumption of a linear relation between UPDRS and putamen Ki. The second method (B) makes an extrapolation from the mean [<sup>18</sup>F]dopa uptake and mean symptom duration at baseline and follow up. It also assumes a linear progression and extrapolates a preclinical window greater than the interval between the two PET time points. It is interesting to note that the estimated mean preclinical period is shorter using a total striatal approach (despite its lower sensitivity and measured rate of progression) than when using a putamen Ki approach. The explanation for this paradox is that total striatal Ki includes a contribution from the relatively preserved caudate and so the Ki at baseline scan and at estimated symptom onset are both relatively high. Were the methods of measuring progression perfect, it might be expected that the preclinical period predicted by each PET method would be identical. If progression is not linear<sup>2,17,18</sup> the average preclinical period is likely to be less than estimated here.

To summarise, when measured with our PET camera and the more sensitive PET methods, the mean annual rate of progression in Parkinson's disease is about 5% of the normal mean (and 9% of baseline) in the putamen and 3% (4% of baseline) in the caudate. Symptom onset occurs when [<sup>18</sup>F]dopa Ki is about 75% of normal in the putamen and 91% in the caudate. The preclinical period is less than seven years. We do, however, advise caution in the interpretation of these results in regard to their pathological relevance. Whereas one study has shown a correlation between postmortem cell count and striatal [<sup>18</sup>F]dopa uptake<sup>19</sup> we have shown that measurement of striatal [<sup>18</sup>F]dopa uptake varies according to the PET method. It may also vary according to the sensitivity of the PET machine (which might provide a further explanation for the discrepancy between the results of the two published longitudinal studies). We are also aware that our measurement is of dopaminergic terminal function and that preservation of dopa decarboxylase compared with tyrosine hydroxylase activity in Parkinson's disease could lead to overestimation of the nigrostriatal cell count as assessed by striatal [<sup>18</sup>F]dopa uptake. Our data, however, are supported by cross sectional [<sup>18</sup>F]dopa PET data from another group,<sup>18</sup> and a recent cross sectional study<sup>20</sup> that used the tracer [<sup>11</sup>C]RTI-32 to label the presynaptic dopamine transporter. These data are also supported by the pathological study of Fearnley and Lees<sup>17</sup> which estimated, after correction for aging effects, that symptom onset occurred after a 30% loss of nigral cells due to disease.

We have previously shown that entacapone enhances the striatal uptake of [<sup>18</sup>F]dopa by blocking peripheral methylation<sup>7</sup> and we have included in this study a group of 13 patients scanned on both occasions with entacapone as

premedication. At the outset of this study it was our intention to use metabolite corrected plasma counts as input function but, during the course of the study, it became apparent from our own work and that of others<sup>11, 21</sup> that this method was less reproducible than the use of an occipital reference as input function. Entacapone has the effect of increasing Ki and ratio when calculated using a reference tissue input function and so it was necessary to normalise for the presence of entacapone to allow us to examine data from all 32 patients. The gradients of the regression lines and estimated points of symptom onset including and excluding the entacapone treated cohort are in fact similar (table 5). We think that the gain in reproducibility through the use of an occipital input is likely to outweigh any detrimental effect of this approach, and the data are strengthened by the inclusion of both cohorts of patients in this study.

This study has allowed us to develop guidelines for the use of functional imaging techniques in studies of neuroprotection. All patients should fulfill recognised diagnostic criteria.<sup>4</sup> Ideally PET analysis should be performed blind to clinical state and medication. The method of PET analysis should be chosen at the outset of the study, based on knowledge of reproducibility and sensitivity. We have shown that the expected rate of progression measured by [<sup>18</sup>F]dopa PET can be approximated from the sensitivity of the chosen method to clinical progression. For any given intervention on the mean rate of progression the optimum scanning interval and size of group can be determined. It should be emphasised that the estimation of group size must, however, also include consideration of the variability in rate of progression within each group. For example, if we rescan patients at a five year interval in a trial in which a drug is 50% neuroprotective the expected mean change in putamen Ki in the untreated group would be 0.0025 min<sup>-1</sup>, and that in the treated group 0.0012 min<sup>-1</sup>. Clinical data suggest that there is a wide range in rate of progression in Parkinson's disease.<sup>22</sup> If it is assumed that there is no measurable progression in 2.5% of the patients (in keeping with clinical observation), the SD of the mean change in putamen Ki over five years would be 0.00125 min<sup>-1</sup>, and so 16 patients would be required in each group to show neuroprotection (80% power at p<0.05). We can see no reason to use different PET methods, with their differing sensitivities, for studies of progression and embryonic mesencephalic implantation.<sup>21</sup>

In conclusion we have shown that both reproducibility and sensitivity of the PET method are important in the estimation of the mean rate of progression of Parkinson's

disease, and that when these criteria are met the mean annual rate of loss of dopaminergic function in Parkinson's disease is about 5% (of the normal mean). We estimate that onset of symptoms occurs when mean putamen dopaminergic metabolism falls to 75% of normal and caudate function to 91% of normal. The mean preclinical period is unlikely to be longer than seven years.

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