Progression of monoaminergic dysfunction in Parkinson's disease: A longitudinal 18F-dopa PET study

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A B S T R A C T
Post-mortem and neuroimaging studies in Parkinson’s disease (PD) have shown involvement of the brain serotonergic, noradrenergic and cholinergic pathways alongside the characteristic degeneration of nigrostriatal dopamine neurons. The rate of progression of the degenerative process in these extrastriatal areas is still unclear.

We used 18F-dopa PET, a marker of aromatic aminoacid decarboxylase activity in monoaminergic neurons, to assess longitudinal changes in tracer uptake in brain noradrenergic, serotoninergic and extrastriatal dopaminergic structures over a 3-year period in a group of early PD patients.

Ten PD patients had 18F-dopa PET twice: at baseline and again after 37.1 ± 21.5 months follow up. A standard object map was used to extract tracer influx constants (Ki) in 11 striatal and extrastriatal regions.

Progressive decreases in 18F-dopa Ki occurred over the follow-up period in the majority of the investigated areas, the fastest annual declines occurring in putamen (8.1%), locus coeruleus (7.8%), and globus pallidus interna (7.7%). Caudate and hypothalamus showed 6.3% and 6.1% annual Ki declines, respectively. At baseline, some structures showed increased levels of 18F-dopa uptake in PD compared to controls (internal pallidum, 7.7%). Caudate and hypothalamus showed 6.3% and 6.1% annual Ki declines, respectively. At baseline, some structures showed increased levels of 18F-dopa uptake in PD compared to controls (internal pallidum, 7.7%). Caudate and hypothalamus showed 6.3% and 6.1% annual Ki declines, respectively. At baseline, some structures showed increased levels of 18F-dopa uptake in PD compared to controls (internal pallidum, 7.7%). Caudate and hypothalamus showed 6.3% and 6.1% annual Ki declines, respectively. At baseline, some structures showed increased levels of 18F-dopa uptake in PD compared to controls (internal pallidum, 7.7%). Caudate and hypothalamus showed 6.3% and 6.1% annual Ki declines, respectively. At baseline, some structures showed increased levels of 18F-dopa uptake in PD compared to controls (internal pallidum, 7.7%).

loss of raphe serotonin HT1A binding is reported to be associated with parkinsonian tremor ([Doder et al., 2003]) and also plays a significant role in the development of non-motor features such as sleep disorders, fatigue, dementia, and depression, so providing possible targets for pharmacological interventions to treat these symptoms.

Current knowledge concerning rates of disease progression in non-dopaminergic structure is limited. Based on patterns of abnormal immunostaining for α-synuclein, it has been suggested that Lewy bodies and Lewy neurites first appear in the medullary dorsal nucleus of the vagus and the pathology then ascends to involve non-dopaminergic brainstem structures in the pons, such as the locus coeruleus and median raphe, antedating by several years the involvement of the substantia nigra in the midbrain and the appearance of the classical motor signs. Lewy body pathology then progressively extends in a rostral direction to involve the nucleus basalis, the forebrain, and, in the final stages, the neocortex ([Braak et al., 2004]). However, while the pathology of PD may be ascending in nature, the associated dysfunction is highly variable from structure to structure and the rate of disease progression in individual non-dopaminergic regions and in extrastriatal dopaminergic structures remains unclear. Additionally, the relationship between decline in

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striatal function in PD and dysfunction in extra-striatal areas remains to be clarified.

18F-dopa PET, a marker of monoaminergic nerve terminal function, has been extensively used to evaluate severity and progression of presynaptic nigrostriatal dysfunction in PD. Striatal uptake of 18F-dopa, which reflects aromatic amino acid decarboxylase activity (AADC), correlates well with nigral cell counts and striatal tyrosine hydroxylase activity in both human cases and in primates with MPTP induced parkinsonism (Snow et al, 1993, Pate et al, 1993). Longitudinal studies with serial 18F-dopa PET have shown that the mean annual rate of 18F-dopa uptake decline in PD patients ranges from 8% to 12% of the baseline value in the putamen and 4% to 6% in the caudate compared with an annual decline less than 1% in normal volunteers (Vingerhoets et al., 1994, Morrish et al., 1996, 1998, Nurmi et al., 2001, 2003).

In non-dopaminergic structures, 18F-dopa is taken up by the large neutral aminoacid transporter and decarboxylated by AADC in serotonin and noradrenaline terminals so providing an index of function of these terminals (Brown et al. 1999; Moore et al., 2003). In this report, we have used serial 18F-dopa PET to assess rates of progression of serotonergic, noradrenergic, and extrastratal dopaminergic dysfunction in patients with early PD. Changes over time in 18F-dopa uptake in extra-striatal structures were then compared with the rates of progression of striatal dysfunction in the same patients in order to better elucidate the time-course of the different aspects of the neurodegenerative process in PD.

Methods

Subjects

Ten patients (6 male and 4 female; mean age ± SD = 57.4 ± 7.2 years) with early stage PD (mean disease duration ± SD = 25.5 ± 7.6 months, mean Unified Parkinson’s Disease Rating Scale (UPDRS) motor score in “off” condition ± SD = 17.2 ± 4.8) were enrolled in this study. A clinical diagnosis of probable idiopathic PD was made according to the UK Parkinson’s Disease Society Brain Bank diagnostic criteria for Parkinson’s disease. None of the patients had significant comorbidity, current or previous history of other neurological conditions, including dementia and depression, or were taking any medication acting on serotonergic and noradrenergic systems. Table 1 summarises the demographics of all patients investigated.

Six patients were scanned with 18F-dopa PET twice, at baseline and again at follow-up 37.1 ± 21.5 months later (range of 21 months – 72 months). All patients were studied prospectively with the intent to assess disease progression. However, to speed up recruitment we also invited a few patients who had previously had an 18F-dopa PET during the first 2 years of their disease to have a follow-up scan. Four such patients agreed to have a repeat scan. In these four patients, the interval between scans was 22, 65, 67, and 72 months, respectively. In the remaining six patients, the follow-up scan was planned 24 ± 3 months after the baseline scan to accommodate for patients’ availability and PET scanning schedule at the PET Unit.

All patients had their levodopa medication stopped for at least 12 h before PET while dopamine agonists were stopped 3 days before scanning. On the day of each scan, disease severity in an “off” state was assessed by UPDRS evaluation, which was performed half an hour before PET scanning.

Brain 18F-dopa uptake values in PD patients at both baseline and follow-up were compared with those of 11 healthy volunteers retrospectively selected from our database (6 males and 5 females; mean age ± SD = 66.6 ± 5.5 years). None of these healthy volunteers had any significant medical history of current or previous neurological or psychiatric disorders.

All subjects gave their written informed consent to be scanned (approved by the Ethics Committee of Hammersmith, Queen Charlotte’s & Chelsea and Acton Hospitals Trust), according to the declaration of Helsinki. Permission to administer 18F-dopa was obtained from the Administration of Radioactive Substances Advisory Committee (ARSAC), UK.

PET procedure

All patients and healthy volunteers were scanned at the Cyclotron Building, Hammersmith Hospital, using an ECAT EXACT HR+ (CTI/Siemens 966) PET scanner, which covers an axial field of view of 23.4 cm and provides 95 transaxial planes. The mean spatial resolution of the tomograph is 4.8 ± 0.2 mm full width at half maximum (transaxial, 1 cm off axis) and 5.6 ± 0.5 mm (axial, on axis) after image reconstruction (Spinks et al., 2000).

All subjects received 150 mg oral carbidopa 1 h prior to scanning, in order to improve 18F-dopa availability to the brain (Hoffman et al., 1992). Subjects were then positioned in the scanners such that their orbitomeatal plane was parallel to the transaxial plane of the tomograph. Head position was carefully monitored with a video camera and by direct observation throughout.

The scanning protocol involved list mode (event-by-event) 3D acquisition over 95 min following a bolus injection of 110 MBq of 18F-dopa, which was supplied by Hammersmith Imanet.

PET analysis

The analysis was performed using an a priori defined region of interest (ROI) approach. Parametric images of specific 18F-dopa uptake (Ki maps) were created at a voxel level for the whole brain using the Patlak graphical approach to calculate Ki, influx rate constant values [ml min⁻¹ g⁻¹] (Patlak et al., 1983), as previously described (Whone et al., 2004). A reference region input function representing non-specific tissue uptake was used to generate Ki values. This was obtained by sampling occipital cortex which has been previously validated as a reliable reference region (Brooks et al. 1990). Additionally, all 26 frames of the dynamic 18F-dopa time series were integrated to form a summed image reflecting both tracer delivery and specific uptake.

In order to optimise image quality, the quality of the reference region input function time activity curves, alignment of Ki maps and corresponding summed images were all audited. The summed images were then normalised into standard stereotaxic Montreal Neurological Institute (MNI) space using Statistical Parametric Mapping (SPM) software (www.fil.ion.ucl.ac.uk/spm) and a normal 18F-dopa PET template already in MNI space created in-house. Individual Ki maps were subsequently spatially normalised by applying the transformation parameters obtained during normalisation of the corresponding summed images. This technique standardises brain position and shape allowing the use of standard object maps in MNI space to quantify tracer uptake in pre-selected ROIs.

Table 1

<table>
<thead>
<tr>
<th>Healthy subjects (n = 11)</th>
<th>Parkinson’s disease patients (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At baseline</td>
<td>At follow-up (37.1 ± 21.5 months)</td>
</tr>
<tr>
<td>M/F</td>
<td>6/5</td>
</tr>
<tr>
<td>Age (years, mean ± SD)</td>
<td>66.6 ± 5.5</td>
</tr>
<tr>
<td>Disease duration (months, mean ± SD)</td>
<td>=</td>
</tr>
<tr>
<td>Hoehn and Yahr</td>
<td>=</td>
</tr>
<tr>
<td>UPDRS in “off”</td>
<td>=</td>
</tr>
</tbody>
</table>
Percentage individual changes in $^{18}$F-dopa uptake from baseline in PD patients were calculated for each structure as follows

$$100 \times \left( \frac{\text{baseline}^{18}\text{F-dopa Ki}}{\text{follow-up}^{18}\text{F-dopa Ki}} - 1 \right) \div \text{baseline}^{18}\text{F-dopa Ki}$$

Percentage changes per annum were then calculated as follows

$$12 \times \left( \frac{\% \text{change}^{18}\text{F-dopa Ki}}{\text{from baseline}} - 1 \right) \div \text{months from baseline to follow-up}$$

Finally, individual patient’s values were averaged for each structure.

We used the Mann–Whitney U-statistic to compare PD patients and healthy volunteers and Wilcoxon matched-pairs to compare baseline and follow-up $^{18}$F-dopa Ki values within the PD group. The relationship between the annual $^{18}$F-dopa Ki decline in putamen and that in each of the other ROIs was investigated with the Spearman Rank Correlation statistic.

**Results**

Regional mean $^{18}$F-dopa Ki values (ml min$^{-1}$ g$^{-1}$) in healthy volunteers and PD patients are shown in Table 2 and Fig. 1.

**PD patients and healthy volunteers’ comparison**

**Baseline**

When comparing PD patients at baseline with control subjects, we found significant decreases in $^{18}$F-dopa uptake in the PD group in putamen (41.1% below the averaged mean of the healthy volunteers, $p \leq 0.01$) and ventral anterior thalamus (21.5% below the averaged mean of the healthy volunteers, $p \leq 0.05$). Conversely, the globus pallidus interna and midbrain raphe showed raised $^{18}$F-dopa uptake in the PD group compared to healthy volunteers (19.8% and 16.9%, respectively; $p \leq 0.05$). The p values refer to a comparison between $^{18}$F-dopa Ki values in healthy volunteers and PD patients with the Mann–Whitney U statistic.

Non-significant reductions in $^{18}$F-dopa uptake were also seen in globus pallidus externa (10.8%), hypothalamus (10%), caudate (6.7%), subthalamic nucleus (6.5%), and ventral striatum (5.8%) in the PD group, whereas the locus coeruleus showed a mildly raised $^{18}$F-dopa uptake compared to healthy volunteers (2.8%).

**Follow-up**

At follow-up, PD patients showed $^{18}$F-dopa uptake declines in all the regions sampled. Putamen Ki was most affected showing a 55.9% mean reduction below healthy volunteers ($p \leq 0.001$), followed by caudate (25.9%, $p \leq 0.001$), hypothalamus (24.5%, $p \leq 0.001$), ventral anterior thalamus (21.2%, $p \leq 0.05$), globus pallidus externa (19.6%, $p \leq 0.001$), locus coeruleus (18%, $p \leq 0.05$), ventral striatum (17.8%, $p \leq 0.001$), subthalamic nucleus (15.3%), red nucleus (13%), globus pallidus interna (2.9%), and median raphe (1.9%). The p values refer to comparisons with the Mann–Whitney U-statistic between $^{18}$F-dopa Ki values in healthy volunteers and PD patients.

**Baseline versus follow-up comparison in PD patients**

The most rapid annual decline in $^{18}$F-dopa Ki was observed in putamen (8.1%, $p \leq 0.01$) followed by locus coeruleus (7.8%, $p \leq 0.01$), globus pallidus interna (7.7%, $p \leq 0.01$), caudate (6.3%, $p \leq 0.05$), and hypothalamus (6.1%, $p \leq 0.01$). In remaining structures, the annual decline in $^{18}$F-dopa uptake was less than 5% (Table 2). The p values
refer to comparisons between baseline and follow-up 18F-dopa Ki values with the Wilcoxon matched-pair statistic.

We found no correlations between the rate of annual decline in 18F-dopa uptake in putamen and that in other structures. However, there was a trend towards a correlation between the rate of 18F-dopa decline in putamen and globus pallidus interna (r = 0.60, p = 0.073).

**Discussion**

This is the first longitudinal, prospective, in vivo study to report the time course and the rate of disease progression in extrastriatal monoaminergic structures in early stages of PD. Using serial 18F-dopa PET imaging, a marker of AADC activity in monoaminergic neurons, we found that dysfunction in extrastriatal monoaminergic structures is delayed and occurs at a later stage of the disease compared to loss of function of nigrostriatal projections to the putamen. Indeed, when comparing PD patients at baseline with control subjects, we only found significant decreases in 18F-dopa uptake in putamen and ventral anterior thalamus. However, it should be acknowledged that in early stages of the disease, 18F-dopa PET may underestimate the extent of the degenerative process due to compensatory upregulation of AADC in remaining functioning terminals (Ribeiro et al., 2002).

In agreement with previous studies (Rakshi et al., 1999; Whone et al., 2003a; Moore et al., 2008), baseline mean 18F-dopa uptake in globus pallidus interna and midbrain raphe was significantly raised in our early PD patients. Increases in 18F-dopa uptake in these structures are likely to reflect upregulation of AADC activity and dopamine turnover in surviving terminals and could represent a compensatory adaptive mechanism to preserve functionality. The longevity of these compensatory mechanisms is unknown. In cross-sectional studies, advanced PD patients showed significant reductions in globus pallidus interna and raphe 18F-dopa uptake compared to both controls and PD patients with early disease, suggesting that compensatory mechanisms involving these structures eventually fail during the time course of the disease. In our longitudinal study, tracer uptake in these two nuclei fell slightly below the control mean value at follow up, suggesting that compensatory hyperactivity reverses within the first years of the disease. The annual declines observed in 18F-dopa uptake in globus pallidus interna and midbrain raphe could, therefore, simply reflect the loss of their compensatory upregulation rather than cellular loss. Longer follow-ups with three or more imaging assessments are required to assess the effective rate of disease progression in these structures once the compensatory mechanisms have disappeared.

When assessing percentage changes per annum in 18F-dopa uptake in individual monoaminergic structures, we found that putamen had the fastest annual decline in 18F-dopa uptake (8.1%) followed by locus coeruleus (7.8%), and globus pallidus interna (7.7%). Caudate and hypothalamus showed a 6.3% and a 6.2% decline per annum respectively, whereas the remaining structures showed less than 5% annual decline in 18F-dopa uptake (Table 2). Additionally, we found no significant correlations between the rate of annual decline in 18F-dopa uptake in putamen and that in other structures. These findings suggest that the degeneration in extrastriatal monoaminergic structures in PD occurs independently from nigrostriatal degeneration and at a slower rate. These results are in line with several post-mortem studies, which have shown that in advanced PD cases, the cell loss in non-dopaminergic nuclei ranges between 30 and 50%, whereas it is close to 80% in the nigral region (Jellinger, 1991; Zarow et al., 2003; Thannickal et al., 2007).

The locus coeruleus showed the second highest mean annual 18F-dopa decline in the PD group. At follow-up, our patients had significantly lower 18F-dopa uptake in the locus coeruleus than controls (p<0.05) with a mean 18% reduction below the averaged mean of the healthy volunteers. Reduced 18F-dopa Ki in this nucleus most likely reflects the progressive loss of noradrenergic terminal function. Interestingly, at baseline, our PD patients had higher locus coeruleus 18F-dopa uptake than the healthy volunteers, although the difference between the two groups was not statistically significant. Lewy body pathology in the locus coeruleus is a well-documented post-mortem finding in PD (Zarow et al., 2003) and appears in stage 2 of the disease (Braak et al., 2004). The preservation of 18F-dopa uptake in the locus coeruleus of our PD patients at baseline could indicate that AADC upregulation also occurs in this nucleus. Alternatively, it could imply that Lewy body pathology is not necessarily associated with neuronal dysfunction in this area in the early phases of the disease.

The hypothalamus is commonly affected in PD. Lewy body inclusions have been demonstrated in every nucleus of the hypothalamus, particularly the tuberomammillary nucleus and the lateral and posterior hypothalamic nuclei (Langston and Forno, 1978; Sandyk et al., 1987; Wakabayashi and Takahashi, 1997). Reduced hypothalamic 18F-dopa uptake has previously been reported in PD patients (Moore et al., 2008; Pavese et al., 2010). Moreover, our group has recently reported a significant reduction in dopamine D2 receptor availability, as measured by 11C-raclopride PET, in the hypothalamus of PD patients compared with age-matched healthy volunteers.

**Table 2**

Regional mean 18F-dopa Ki values (ml min⁻¹ g⁻¹) ± Standard Deviation in the normal subjects and in the Parkinson’s disease patients at Baseline and Follow-up.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Healthy subjects (n=11)</th>
<th>Parkison’s disease patients (n=10)</th>
<th>% changes annum mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>Caudate</td>
<td>0.0114 ± 0.0006</td>
<td>0.0106 ± 0.0016</td>
<td>0.0084 ± 0.0022</td>
</tr>
<tr>
<td>Putamen</td>
<td>0.0124 ± 0.0010</td>
<td>0.0073 ± 0.0023</td>
<td>0.0055 ± 0.0009</td>
</tr>
<tr>
<td>Ventral striatum</td>
<td>0.0117 ± 0.0009</td>
<td>0.0110 ± 0.0014</td>
<td>0.0096 ± 0.0011</td>
</tr>
<tr>
<td>Globus pallidus interna</td>
<td>0.0052 ± 0.0010</td>
<td>0.0062 ± 0.0059</td>
<td>0.0051 ± 0.0007</td>
</tr>
<tr>
<td>Globus pallidus externa</td>
<td>0.0059 ± 0.0008</td>
<td>0.0053 ± 0.0007</td>
<td>0.0047 ± 0.0007</td>
</tr>
<tr>
<td>Ventral ant. thalamus</td>
<td>0.0033 ± 0.0002</td>
<td>0.0026 ± 0.0006</td>
<td>0.0026 ± 0.0006</td>
</tr>
<tr>
<td>Subthalamic nucleus</td>
<td>0.0043 ± 0.0015</td>
<td>0.0040 ± 0.0009</td>
<td>0.0036 ± 0.0007</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>0.0048 ± 0.0007</td>
<td>0.0044 ± 0.0003</td>
<td>0.0037 ± 0.0004</td>
</tr>
<tr>
<td>Locus coeruleus</td>
<td>0.0050 ± 0.0009</td>
<td>0.0051 ± 0.0007</td>
<td>0.0041 ± 0.0006</td>
</tr>
<tr>
<td>Midbrain raphe</td>
<td>0.0068 ± 0.0015</td>
<td>0.0080 ± 0.0009</td>
<td>0.0067 ± 0.0013</td>
</tr>
<tr>
<td>Red nucleus</td>
<td>0.0057 ± 0.0010</td>
<td>0.0057 ± 0.0012</td>
<td>0.0050 ± 0.0009</td>
</tr>
</tbody>
</table>

† indicates a significant increase compared to healthy subjects, and ○ indicates a significant decrease compared to healthy subjects. § indicates a significant decrease in the follow-up 18F-dopa Ki values compared to baseline.

*** Mann–Whitney test: p<0.001.

** Mann–Whitney test: p<0.01.

* Mann–Whitney test: p<0.05.

§ Wilcoxon matched-pairs signed-rank test: p<0.05.

Wilcoxon matched-pairs signed-rank test: p<0.001.
In this study, we found no significant difference in mean $^{18}$F-dopa uptake in the hypothalamus between PD patients and healthy volunteers at baseline although it was reduced by 10%. At follow-up, our PD patients showed a significant 20.2% reduction ($p<0.05$) below the controls’ mean value in $^{18}$F-dopa uptake with an annual 6.2% decline from baseline. These findings confirm that hypothalamic involvement is common in PD and suggest that this structure could be targeted at very early stages of the disease with a fast progression rate once degeneration has started.

The hypothalamus has a complex internal structure including intrinsic dopaminergic neurons and a dense innervation from serotonergic midbrain raphe and lateral medullary noradrenergic neurons. In PD patients, the reduction of $^{18}$F-dopa uptake in this region could reflect dysfunction in any or all of these pathways. Further post-mortem and in vivo studies, preferably with PET ligands specific for each of these neurotransmitter systems, are required to better understand the pathogenesis of hypothalamic involvement in PD.

The mean annual decline in putamen and caudate $^{18}$F-dopa Ki noted in this study is comparable with data from previous studies (Morris et al., 1996, 1998). The rate of progression of dopaminergic dysfunction in the ventral striatum has not been assessed previously. The ventral striatum, which encompasses the nucleus accumbens and the ventromedial parts of putamen and caudate, is generally considered a limbic center and has widespread connections with other limbic structures including the amygdala, hippocampus, and the prefrontal cortex (Groenewegen and Trimble, 2007). The ventral striatum is strongly innervated by dopaminergic fibers from the midbrain ventral tegmental area. In PD, the ventral tegmental area shows a less pronounced loss of dopaminergic neurons than the contiguous substantia nigra pars compacta. In line with these observations, we found a relatively slow mean annual decline (4.9%) in $^{18}$F-dopa uptake in ventral striatum compared to both putamen (8.1%) and caudate (6.3%).

Annual $^{18}$F-dopa Ki decline in the red nucleus and other remaining extrastriatal monoaminergic structures was less than 5%, suggesting that degeneration occurs at a slow rate in these structures. Alternatively, prolonged AADC upregulation in surviving monoaminergic terminals could be masking the effects of neural loss in these areas.

In our patients the interval between baseline and follow-up scans ranged from 21 to 72 months. However, seven out of the ten patients had their follow-up scan 21–27 months after the baseline. Additionally, there were no indications that the three patients with a longer scan interval had a different rate of progression in extrastriatal areas compared to the remaining patients. To obtain precise percentage changes per annum for each patient, the percentage of change in $^{18}$F-dopa from baseline was divided by the months of follow-up and the resulting value was multiplied by twelve. No other corrections were applied to the data.

$^{18}$F-dopa PET and the dopamine transporter marker $^{123}$I-f-CIT SPECT have been used as surrogate markers of nigrostriatal degeneration in clinical trials of putative neuroprotective drugs in PD (Oertel et al., 2001; Rakhi et al., 2002; Parkinson Study Group, 2002; Whone et al., 2003b; Pavese et al., 2005). Unfortunately, no unequivocal evidence of neuroprotection has been demonstrated for any drugs tested so far. Interpretation of data generated by these trials has also been limited by adaptive compensatory effects upregulating dopamine turnover and downregulating transporter binding over time, direct effects on receptor availability and enzyme activities by the drug itself, and placebo effects. All these confounding factors potentially can interfere with the imaging outcome and must be addressed when designing new clinical trials of neuroprotective agents in PD patients.

In this paper, we have shown that $^{18}$F-dopa PET can be successfully used to assess disease progression in serotonergic and noradrenergic extrastriatal areas along with nigrostriatal degeneration. We acknowledge that confounding factors such as adaptive upregulation may influence $^{18}$F-dopa uptake in extrastriatal structures. However, once these factors have been addressed, $^{18}$F-dopa PET could provide supplementary information on the progression of the degenerative process in extrastriatal monoaminergic structures when assessing the effects of novel neuroprotective agents in PD.

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**References**


