

## **Clinical implications of early caudate dysfunction in Parkinson's disease**

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**Abbreviations:** CBD = Corticobasal degeneration; DAT = dopamine transporter; DLB = Dementia with Lewy bodies; GDS = Geriatric Depression Scale; GLM = General Linear Model; H&Y = Hoehn and Yahr; HC = healthy control; <sup>123</sup>I-FP-CIT = N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-[123I]iodophenyl)nortropane; MoCA = Montreal Cognitive Assessment; MSA = Multiple system atrophy; PD = Parkinson's disease; RBDSQ = Rapid eye movement Sleep Behavior Disorder Questionnaire; ROI = region of interest; SBR = Specific Binding Ratio; SPECT = Single Photon Emission Computed Tomography.

## **ABSTRACT**

### **Objective**

Although not typical of Parkinson's disease (PD), caudate dopaminergic dysfunction can occur in early stages of the disease. However, its frequency and longitudinal implications in large cohorts of recently diagnosed patients remain to be established. We investigated the occurrence of caudate dopaminergic dysfunction in the very early phases of PD (<2 years from diagnosis) using  $^{123}\text{I}$ -FP-CIT SPECT and determined whether it was associated with the presence or subsequent development of cognitive impairment, depression, sleep and gait problems.

### **Methods**

PD patients and healthy controls were identified from the Parkinson's Progression Markers Initiative database. We defined a clinically significant caudate dysfunction as  $^{123}\text{I}$ -FP-CIT binding <-2 standard deviations compared to the controls' mean and categorised three groups accordingly (no reduction, unilateral reduction, bilateral reduction). All statistical analyses were adjusted for mean putamen binding.

### **Results**

At baseline, 51.6% of 397 patients had normal caudate DAT binding, 26.0% had unilateral caudate involvement, 22.4% had bilaterally impaired caudate.

Compared to those with a baseline normal caudate function, at the four-year follow-up patients with a baseline bilateral caudate involvement showed a higher frequency of cognitive impairment ( $p<0.001$ ) and depression ( $p<0.001$ ), and worse cognitive ( $p<0.001$ ), depression ( $<0.05$ ) and gait ( $<0.001$ ) ratings. Significant caudate involvement was observed in 83.9% of the population after four years (unilateral 22.5%, bilateral 66.5%).

## **Conclusions**

Early significant caudate dopaminergic denervation was found in half of the cases in the PPMI series. Baseline bilateral caudate involvement was associated with increased risk of developing cognitive impairment, depression and gait problems over the next four years.

## **INTRODUCTION**

Caudate dopaminergic dysfunction is commonly seen in patients with established and advanced Parkinson's disease (PD) and plays a role in the pathophysiology of parkinsonian symptoms such as cognitive impairment,<sup>1-7</sup> depression,<sup>8</sup> REM sleep behaviour disorder (RBD),<sup>9</sup> and gait problems.<sup>10,11</sup> Conversely, both *post-mortem* and *in vivo* imaging studies suggest that caudate function is preserved in the early stages of PD. In fact, dopaminergic neurons of the substantia nigra pars compacta (SNc) degenerate in a selective pattern, with earliest and most severe loss occurring in the ventral tier projecting to the posterior putamen and tail of caudate, followed by the dorsal tier projecting to the head of caudate nucleus, the globus pallidus, and the neocortex.<sup>12,13</sup> Neuroimaging studies using SPECT and PET dopaminergic tracers<sup>14-16</sup> confirm that the dopaminergic deficit within the striatum is unevenly distributed with a more severe involvement of the posterior putamen and a relative sparing of the head of caudate nucleus. This asymmetrical posterior-to-anterior gradient of dopaminergic dysfunction is present from early disease stages and does not change substantially with disease progression.<sup>17,18</sup>

However, the occurrence of caudate involvement in the early stages of the disease and the clinical implications of such early caudate dysfunction (i.e. the current or subsequent manifestation of cognitive impairment, depression, RBD, gait problems) have not been fully investigated in large cohorts.

## **MATERIALS AND METHODS**

### **Study design and participants**

In this longitudinal study, we analysed clinical ratings and <sup>123</sup>I-FP-CIT SPECT data from a cohort of early stage PD patients and healthy controls (HCs) recruited in the Parkinson's Progression Marker Initiative (PPMI), an ongoing multicentre, longitudinal study aiming to identify biomarkers of PD progression. PD patients were required to have a clinical diagnosis for two years or less, be

untreated and show evidence of striatal dopamine transporter deficit on SPECT imaging (study protocol available at <https://www.ppmi-info.org/study-design/research-documents-and-sops/>).<sup>19</sup>

We performed three main analyses: (i) we evaluated caudate <sup>123</sup>I-FP-CIT binding at baseline and follow-up in PD patients and HCs. PD patients were categorised in three subgroups according to their baseline caudate binding compared to HCs (no reduction, unilateral reduction, bilateral reduction); (ii) we assessed whether these three PD subgroups showed different baseline manifestations in terms of cognitive impairment, depression, RBD, and gait problems; (iii) we investigated whether the initial pattern of caudate dopaminergic dysfunction was able to predict worse outcomes and increased risk of developing cognitive, mood, sleep and gait problems at four-year follow-up.

At the time of our analysis, we retrieved 405 PD patients and 177 HCs whose baseline assessments, including SPECT scan, motor and non-motor scores were available in the PPMI database (<http://www.ppmi-info.org/data>). At four-year follow-up, clinical assessments were available for 328 patients and SPECT imaging for 267. Four-year follow-up clinical assessments were available for 151 HCs; no follow-up SPECT imaging was provided for HCs in the PPMI.

<sup>123</sup>I-FP-CIT SPECT striatal specific binding ratios (SBRs) and demographics and clinical variables at baseline and four-year follow-up of all the study participants were downloaded from the PPMI database on the 15th May 2018.

## **Clinical Evaluations**

PD motor disability was assessed with the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and the Hoehn&Yahr scale. To assess differences in gait impairment between groups at baseline and four-year follow-up, we calculated an index of gait severity by using the product of the patient's self-reported walking and balance score (sub-item 2.12, MDS-UPDRS part II) and the freezing score (2.13, MDS-UPDRS part II) (Maximum score=16). All scores were collected in the OFF state.

Scores of the following non-motor scales were also obtained: Montreal Cognitive Assessment (MoCA), the 15-item Geriatric Depression Scale (GDS) and RBD Screening Questionnaire (RBDSQ). For each patient, one point was added to the MoCA unadjusted score of those who had twelve years of education or less, as indicated in the test original validation study<sup>20</sup> and in the PPMI protocol. A GDS score  $\geq 5$  was considered diagnostic for the presence of significant depressive features.<sup>21</sup>

Study participants were allocated to one of three cognitive categories (normal cognition, mild cognitive impairment, dementia) based on recommended criteria for dementia<sup>22</sup> and mild cognitive impairment (MCI)<sup>23</sup> and as outlined in the PPMI protocol (see **Supplementary Material-Section 1**)

Lastly, the final clinical diagnosis at four-year follow-up based on clinical judgment of the investigator was recorded to determine if the patient's diagnosis had changed compared to baseline. Eight patients initially diagnosed as idiopathic PD were re-diagnosed as a form of atypical parkinsonism: four had their diagnosis switched to Multiple system atrophy (MSA), three to Dementia with Lewy bodies (DLB), one to Corticobasal degeneration (CBD). These patients were excluded from the main analysis and their neuroimaging features analysed separately. Therefore, a total of 397 patients at baseline and 323 patients at follow-up were included in the main analysis.

### **<sup>123</sup>I-FP-CIT SPECT Imaging protocol**

A detailed description is provided in **Supplementary Material-Section 2**. Briefly, all subjects underwent <sup>123</sup>I-FP-CIT SPECT scans during the screening visit and at follow-ups (PD patients only) at their respective PPMI imaging centre, where standardized imaging protocols were used. Raw SPECT data were transferred back to the Institute for Neurodegenerative Disorders, New Haven, Connecticut (PPMI Imaging Core), for processing and calculations of SBRs. Upon transfer to the PPMI imaging core, images were processed and normalized to standard Montreal Neurologic Institute (MNI) space so that all scans were in the same anatomical alignment. Next, the transaxial

slice with the highest striatal binding was identified and the eight contiguous slices with highest striatal signal were then averaged to generate a single transaxial image. Regions of interest (ROI) were then placed to sample the left (area 240 mm<sup>2</sup>) and right caudate (area 244 mm<sup>2</sup>), the left (area 412 mm<sup>2</sup>) and right putamen (area 408 mm<sup>2</sup>), and the occipital cortex (reference tissue, area 4500 mm<sup>2</sup>).

Count densities for each region were extracted and used to calculate SBRs for each of the four striatal subregions.

$$SBR = (target\ region/reference\ region) - 1.$$

SBRs of caudate and putamen of each participant were downloaded from the PPMI database. SBR measures were rounded to the first two decimals. Mean caudate DAT SBR $\pm$ SD (95% CI) in controls was 2.96 $\pm$ 0.60 (2.88–3.06). The caudate signal was considered to be significantly abnormal in PD patients if its level of <sup>123</sup>I-FP-CIT binding fell two standard deviations or more below the mean caudate binding of HCs at baseline (mean -2SDs=1.76). Three PD subgroups were then categorised as follows: those with no reduced <sup>123</sup>I-FP-CIT binding in either caudate (PD-NC), those with reduced caudate binding in one caudate only (PD-UC) and those with bilaterally reduced caudate binding (PD-BC). Accordingly, we defined significant early caudate dysfunction a caudate <sup>123</sup>I-FP-CIT binding <-2 SDs compared to the controls' mean at the baseline SPECT acquisition.

## **Statistical analysis**

Statistical interrogations were performed using the Statistical Package for the Social Sciences version 21 (SPSS 21). For descriptive analyses means and standard deviations were computed for continuous variables, and the  $\chi^2$  test was used for categorical variables. Data were assessed for a normal distribution using Kolmogorov-Smirnov test. MoCA, GDS and RDBSQ ratings were normally distributed, gait index scores showed a non-normal distribution.

At baseline, between-group differences were investigated using ANOVA followed by a *post hoc* test with Bonferroni correction for normally distributed data. At follow-up, between-group

differences of normally-distributed variables were investigated through ANCOVA followed by a *post hoc* test with Bonferroni correction, holding putamen, age and years of education as covariates where appropriate. Non-normally distributed data were explored through a Kruskal Wallis test followed by Mann-Whitney U tests, and p-values were adjusted through a Bonferroni correction. All multiple comparisons for categorical data at baseline and follow-up were assessed through a  $\chi^2$  omnibus test followed by a standardized residuals analysis; p-values were adjusted through a Bonferroni correction.

## RESULTS

### Baseline

The baseline analysis included 397 PD patients (men/women: 258/139, age: 61.7±9.7 years) and 177 HCs (men/women: 116/61, age: 60.95±11.2 years). In 397 PD patients, normal <sup>123</sup>I-FP-CIT binding in either caudate nuclei (PD-NC) was noted in 51.6% (n=205) of patients, 26.0% (n=103) had reduced tracer binding in one caudate only (PD-UC), and 22.4% (n=89) had reduced tracer binding in both caudate nuclei (PD-BC) (**Figure 1A**). No significant differences were found in the left/right distribution of the most affected caudate across the three PD subgroups. At baseline all patients with a unilateral or bilateral caudate DAT reduction also had either a unilateral or bilateral putaminal reduction. More details about caudate and putamen involvement in individual patients are reported in **Supplementary Tables 1 and 2**. Mean putamen specific binding ratio was significantly different across the three groups (F=90.003, p<0.001), with PD-BC significantly lower than the other two groups, and PD-UC significantly lower than PD-NC. However, the caudate/putamen ratio, which provides an index of the posterior-to-anterior dopaminergic loss gradient, was not significantly different across the three groups. Age across the three PD subgroups and HCs was significantly different (F=3.657, p<0.05), with the PD-BC group being older (64.46±8.13 years) than HCs (60.95±11.20 years) and the other two PD subgroups (PD-NC: 60.98±10.16 years; PD-UC 60.63±9.76 years). In order to assess if there was a significant age-related decline in caudate

DAT availability in our control cohort, we compared mean caudate SBRs in three subgroups of controls classified according to their age (50-59, 60-69,  $\geq 70$ ). No significant differences were found in mean caudate DAT binding across these groups ( $F = 2.305$ ,  $p\text{-value} = 0.103$ ). In regard to gender, we did not find any difference in the distribution of males and females across the three groups PD-NC, PD-UC, PD-BC ( $\chi^2 = 0.221$ ,  $p\text{-value}=0.895$ ). We also did not find any significant difference between males and females in right, left and mean caudate DAT binding. The three PD subgroups did not differ significantly either in terms of disease duration or in motor symptoms as assessed through MDS-UPDRS III and H&Y scale scores (**Table 1**).

**Table 1.** Baseline Cohort Demographics and Characteristics

	<b>Healthy controls</b> (N=177)	<b>PD-NC</b> (N=205)	<b>PD-UC</b> (N=103)	<b>PD-BC</b> (N=89)
	<i>Mean ± SD</i>	<i>Mean ± SD</i>	<i>Mean ± SD</i>	<i>Mean ± SD</i>
<b>Age, years</b>	60.95 ± 11.20	60.63 ± 9.76	60.98 ± 10.16	64.46 ± 8.13 <sup>1</sup>
<b>Male/Female</b>	116/61	131/74	68/35	59/30
<b>Years of Education</b>	16.11 ± 2.93	15.75 ± 2.92	15.20 ± 3.15	15.42 ± 2.97
<b>Duration of symptoms, years</b>		1.53 ± 2.40	1.55 ± 1.63	1.30 ± 1.50
<b>Duration since diagnosis, years</b>		0.14 ± 0.40	0.20 ± 0.53	0.20 ± 0.45
<b>Stage of Disease (H&amp;Y)</b>		1.46 ± 0.50	1.56 ± 0.50	1.56 ± 0.50
<b>Total MDS-UPDRS Part III (motor)</b>		19.47 ± 9.16	21.11 ± (8.69)	21.38 ± 8.89
<b>MOCA exam</b>	28.23 ± 1.10	27.40 ± 2.19 <sup>1</sup>	27.07 ± 2.63 <sup>1</sup>	27.30 ± 2.31 <sup>1</sup>
<b>GDS score</b>	1.30 ± 2.14	2.16 ± 2.45 <sup>1</sup>	2.50 ± 2.43 <sup>1</sup>	2.61 ± 2.61 <sup>1</sup>
<b>GDS ≥ 5</b>	11 (6.2%)	23 (11.2%) <sup>1</sup>	17 (16.5%) <sup>1</sup>	16 (18.0%) <sup>1</sup>
<b>RBDSQ</b>	2.97 ± 2.4	4.35 ± 2.86 <sup>1</sup>	4.29 ± 2.50 <sup>1</sup>	2.97 ± 2.38 <sup>1</sup>
<b>Gait Index</b>	-	0.32 ± 0.80	0.32 ± 0.57	0.40 ± 0.69

*PD-NC = No reduced <sup>123</sup>I-FP-CIT binding in either caudate, PD-UC = Reduced <sup>123</sup>I-FP-CIT binding in one caudate only, PD-BC= bilaterally reduced caudate binding, MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale, H&Y = Hoehn & Yahr scale.*

*Significant difference compared to healthy controls (<sup>1</sup>p<0.05).*

We then compared scores and frequencies of cognitive impairment, depression, RBD and gait problems between PD patients and HCs, and between PD subgroups. All the three PD subgroups had a significantly lower mean MoCA score compared to HCs (PD-NC: 27.40±2.19; PD-UC: 27.07±2.63; PD-BC: 27.30±2.31; HC: 28.38±1.23; F=12.171, p<0.001). Across PD subgroups there were no differences in MoCA scores. For HCs, all scores were within the range for normal cognition (cut-off <26) as outlined in the PPMI protocol.

In terms of clinically significant depressive features as rated by a GDS score  $\geq 5$ , the frequency of these was higher in all PD subgroups (PD-NC: 11.2%; PD-UC: 16.5%; PD-BC: 18.0%) compared to HC (6.2%) ( $\chi^2=10.919$ , p<0.05). There were no significant differences in the frequency of depressive symptoms or in GDS scores between PD subgroups.

A significant difference in mean RBDSQ score was seen between PD subgroups and HC group (PD-NC: 4.35±2.86; PD-UC: 4.29±2.50; PD-BC: 5.02±3.18; HC: 2.97±2.38; F=14.152 p<0.001).

There was no significant difference between PD subgroups in terms of RBD score.

There was no difference in self-reported gait impairment as measured by the gait index between the PD subgroups at baseline (H=3.924, p=0.141).

No significant correlations were found between mean caudate  $^{123}\text{I}$ -FP-CIT binding and cognitive, mood, RBD and gait impairment ratings at baseline.

## **Follow-Up**

Complete four-year clinical assessments were available for 323 PD patients and SPECT imaging for 267. Follow-up clinical data were available for 151 HCs. Given the smaller PD sample at follow-up, we compared the variables of gender, age, MoCA scores, GDS scores, RBDSQ scores and caudate SBRs between patients with and without available data at follow-up in order to check whether the follow-up cohort was representative of the baseline one. We did not find significant differences in these variables (**Supplementary table 3**).

We then compared ratings and frequencies of cognitive impairment, depressive features, RBD and gait problems at the four-year follow-up among the three PD subgroups as classified at baseline according to their caudate SBRs. Since age and mean putamen SBR at baseline were significantly different across the three groups we adjusted the comparisons of continuous scores for these variables. Finally, we analysed the occurrence of caudate dysfunction at follow-up and the conversion to atypical parkinsonism.

### Cognitive impairment

At four-year follow-up, MoCA scores were significantly different across PD subgroups: the PD-BC group had significantly lower MoCA scores compared to the PD-NC group ( $25.05 \pm 4.32$  vs  $26.93 \pm 3.06$ ,  $p < 0.001$ ) and to the PD-UC group ( $25.05 \pm 4.32$  vs  $27.16 \pm 3.21$ ,  $p < 0.001$ ) (**Figure 2A**).

After adjusting for age, years of education and baseline mean putamen SBR, these differences retained statistical significance. We further analysed the relative contributions of baseline caudate and putamen to MoCA scores by carrying out a univariate analysis holding baseline caudate and putamen SBRs as covariates: only caudate SBR was significantly associated with MoCA scores ( $B = 1.522$ ,  $p < 0.01$ ; putamen:  $B = -0.747$ ,  $p = 0.483$ ).

Furthermore, cognitive impairment as determined by the investigator based on the clinical interview, the presence of significant functional impairment, and review of neuropsychological testing, was much more common in the whole cohort of PD patients compared to HCs (21.8% vs 5%,  $p < 0.001$ ). Across the three PD subgroups, the PD-BC patients were significantly more likely to develop cognitive impairment (42.3%,  $\chi^2 = 23.04$ ,  $p < 0.001$ ) compared to PD-UC patients (16.7%) and PD-NC (15.1%).

### Mood disorders

At four-year follow-up, the PD-BC group showed significantly higher GDS scores compared to PD-NC after adjusting for age and mean putamen SBR ( $3.40 \pm 3.01$  vs  $2.25 \pm 2.63$ ,  $p < 0.05$ ); no significant differences were observed between PD-BC and PD-UC groups and between PD-NC and PD-UC groups (**Figure 2B**). Again, we conducted a GLM univariate analysis in order to test whether baseline caudate and putamen SBRs were associated with GDS scores: only caudate binding was significantly associated with GDS scores ( $B = -0.999$ ,  $p < 0.05$ ; putamen:  $B = 0.532$ ,  $p = 0.544$ ).

In terms of clinically significant depression, the PD-BC group had a higher frequency compared to the PD-NC group (29.6% vs 10.8%,  $\chi^2 = 12.67$ ,  $p < 0.001$ ) but the frequency in the PD-UC group (21.2%) did not differ significantly from that of the other two groups.

## RBD

At follow-up, there was no significant difference in RBD scores between PD subgroups.

## Gait impairment

The PD-BC group showed more severe gait impairment compared to the PD-NC group (mean rank 135.31 vs 112.02,  $U = 4735$ ,  $p < 0.001$ ) and to the PD-UC group (mean rank 86.57 vs 72.75,  $U = 2516$ ,  $p < 0.05$ ). No significant differences were found between PD-NC and PD-UC (**Figure 2C**).

## Progression of Caudate involvement and conversion to atypical parkinsonism

Of 267 patients with SPECT imaging available at four-year follow-up, at baseline 134 were classified as PD-NC (50.2%), 74 as PD-UC (27.7%) and 59 PD-BC (22.1%). After four years, 64.3% of the baseline PD-NC group progressed to have either unilateral or bilateral caudate involvement; of the baseline PD-UC group, 78.4% progressed to a bilateral involvement. Overall, at follow-up, 83.9% of the population showed significantly reduced caudate dopamine transporter availability (unilateral 22.5%, bilateral 61.4%), while 16.1% still had a bilateral caudate SBR within -2 SDs of the controls' mean (**Table 2** and **Figure 1B**).

**Table 2.** Degree of caudate involvement in 267 patients with an available DATscan at four-year follow-up and relationship to original PD Subgroups.

<b>Baseline PD Subgroups</b> (n=267)	<b>No Caudate involvement at 4 years</b> (n, %)	<b>Unilateral caudate involvement at 4 years</b> (n, %)	<b>Bilateral Caudate involvement at 4 years</b> (n, %)	<b>Total number of patients</b>
<b>PD-NC Group</b> (n, %)	43 (32.1%)	44 (32.8%)	47 (31.5%)	134
<b>PD-UC Group</b> (n, %)	-	16 (21.6%)	58 (78.4%)	74
<b>PD-BC Group</b> (n, %)	-	-	59 (100%)	59
<b>Total</b> (n, %)	43 (16.1%)	60 (22.5%)	164 (61.4%)	267

*PD-NC = No reduced <sup>123</sup>I-FP-CIT binding in either caudate, PD-UC = Reduced <sup>123</sup>I-FP-CIT binding in one caudate only, PD-BC = bilaterally reduced caudate binding. Percentages and total number of patients are relative to each row.*

The percentage of decline in caudate <sup>123</sup>I-FP-CIT binding from baseline to follow-up was similar in the three groups (PD-NC=-24.5±13.0%, PD-UC=-23.8±16.4%, PD-BC=-25.1±17.2%; F=1.38, p=0.253). In the whole PD cohort the rates of decline in the four nuclei analysed were: right putamen (mean % ± SD) 28.36±25.94%; left putamen: 28.28±27.67%; right caudate: 24.64±17.84%; left caudate: 25.09±19.09%.

Of the eight patients whose diagnosis changed to an atypical parkinsonism, at baseline six presented with bilaterally reduced caudate (three with MSA, three with DLB), while two had a bilaterally normal caudate SBR (one with MSA, one with CBD; their follow-up SPECT scans were not available). Baseline caudate mean SBR of these eight patients were significantly lower than the remaining patients (U=722.5, p<0.01); however, individual values overlapped with idiopathic PD patients (data not shown).

## DISCUSSION

In this longitudinal study, we analysed the occurrence of significant early caudate dopaminergic dysfunction, as defined by  $^{123}\text{I}$ -FP-CIT SBR below -2 SDs compared to the controls' mean, in the large PPMI cohort of recently diagnosed PD patients. Furthermore, we studied the association between this early caudate dopamine transporter loss and the presence or subsequent development of cognitive impairment, depressive features, RBD and gait problems. Unlike previous studies, we provided a clinically viable method to define patients at risk of developing such symptoms. In fact, software for semiquantitative analysis of DAT-SPECT to estimate DAT availability in striatal subregions (i.e. putamen and caudate) are now commercially available and already adopted in many Nuclear Medicine Units. The assessment of the occurrence of early caudate dysfunction as described in this paper can therefore be easily performed in clinical settings and could serve as a risk marker for worse disease progression.

In this study, we have used two standard deviations below the mean of the control population as the threshold to discriminate between normal or abnormal DAT availability of the caudate. DAT availability declines with age and our control population is slightly younger than the PD-BC group. Therefore, in order to assess if there was a significant age-related decline in caudate DAT availability in our control cohort, we compared mean caudate SBRs in three subgroups of controls classified according to their age (50-59, 60-69,  $\geq 70$ ). No significant differences were found in mean caudate DAT binding across these groups, suggesting that age-related decline of caudate binding in our cohort is minimal.

Previous neuroimaging and pathophysiologic studies on striatal dopamine loss have shown uneven patterns of dopamine depletion in the basal ganglia.<sup>14-16</sup> This has led to the concept of a posterior-to-anterior gradient in early PD, with an asymmetric reduced striatal binding in the posterior putamen and relative preservation in the head of caudate. In this study we observed baseline unilateral or bilateral caudate dopaminergic dysfunction, reflected by a reduced  $^{123}\text{I}$ -FP-CIT binding

<-2 SDs compared to controls, in nearly half (48.4%) of this early, untreated PD cohort. This finding indicates that early caudate dopaminergic dysfunction is not uncommon in PD patients at the onset of parkinsonian symptoms, as opposed to what was previously thought. Patients with unilateral and bilateral caudate involvement had a significantly reduced putamen <sup>123</sup>I-FP-CIT binding compared to patients with no caudate dysfunction; however, the caudate/putamen ratio was not significantly different across PD subgroups, suggesting that the posterior-to-anterior gradient of dopaminergic loss is substantially preserved in all patients with PD.

At follow-up, the majority of patients (61.4%) showed significantly reduced DAT availability in both caudate nuclei, and 22.5% had significant reduction in one caudate only. Only 16.1% of patients retained normal caudate <sup>123</sup>I-FP-CIT uptake bilaterally. These findings are in keeping with previous studies that have demonstrated similar caudate and putaminal involvement in patients with longer disease duration.<sup>17,18</sup>

Our results did not show a significant difference between the three PD subgroups, defined by the level of caudate dysfunction, on baseline assessments of cognition, mood or gait but only found a difference between PD subgroups with these measures at the four-year follow-up. It is likely that baseline caudate dopaminergic deficits are not severe enough to cause marked impairment in either cognition, mood or gait but later predispose to such impairments, possibly in combination with other neurotransmitter systems dysfunction. Indeed, we interestingly found that this early, absolute significant reduction of caudate signal on <sup>123</sup>I-FP-CIT SPECT compared to controls at the time of clinical diagnosis is associated with worse outcomes in regard to cognitive impairment, affective symptoms and gait problems at the four-year follow-up.

Several SPECT studies using dopaminergic tracers have proposed a role for caudate dysfunction in cognitive impairment associated with PD.<sup>3,4,24,25</sup> Furthermore, three studies have reported early caudate dopaminergic dysfunction as a predictor for future cognitive impairment.<sup>5-7</sup> Our analysis showed that PD patients with baseline bilateral caudate DAT binding reductions, but not unilateral reductions, are at greater risk of developing cognitive impairment and having lower MoCA scores

regardless of their putamen DAT availability, age and years of education. Therefore, in comparison with the previously mentioned studies, we propose a practical approach that could be used in the clinical practice at time of diagnosis to determine which patients are at increased risk of developing cognitive problems in a near future.

Depression is highly prevalent in PD with rates as high as 40%.<sup>26</sup> The aetiology of depression has been attributed to deficits, with varying degrees, in the dopaminergic, serotonergic, cholinergic and noradrenergic pathways.<sup>27</sup> Several neuroimaging studies have shown an association between reduced DAT availability in the striatum and depressive symptoms.<sup>28-30</sup> One study demonstrated a negative association between right caudate nucleus <sup>123</sup>I-FP-CIT binding and the severity of depressive symptoms.<sup>8</sup> Our study suggests that early bilateral caudate dopaminergic dysfunction is associated with an increased frequency of clinically significant depression and to worse depressive symptoms, regardless of age and mean putamen SBR. Therefore, our results concur with other studies and provide further evidence that depressive symptoms in PD patients may be associated with dopaminergic denervation of the caudate. Again, we provided a clinical neuroimaging marker to determine which patients are at increased risk of developing worse depressive symptoms.

Our study also indicated that early bilateral caudate involvement may predispose to future development of self-reported gait impairment. A previous PET study has demonstrated substantial caudate nucleus dopaminergic denervation in PD patients with gait difficulty which was predominantly associated with the right caudate.<sup>31</sup>

We did not identify significant differences in RBDSQ scores across the three groups of patients at baseline or at the four-year follow-up. Although one study found lower DAT availability in the caudate nucleus of PD patients with RBD compared to those without RBD,<sup>9</sup> it is plausible that a more extensive network involving other neurotransmitter systems, i.e. the cholinergic pathways,<sup>32</sup> are responsible for these symptoms. Furthermore, while the RBD screening questionnaire is a valid and widely used tool to assess RBD symptoms, only polysomnography, which was not performed in the PPMI study, could have provided a complete evaluation of RBD manifestations.

Eight patients initially diagnosed with idiopathic PD had their diagnosis switched to an atypical parkinsonism (MSA or CBD) or to DLB at the four-year follow-up. These eight patients showed caudate mean SBR significantly lower than idiopathic PD patients; however individual values overlapped between the two groups. This is in line with previous studies that have demonstrated that in atypical parkinsonisms <sup>123</sup>I-FP-CIT SPECT generally shows lower striatum uptake and different uptake patterns but is unable to accurately distinguish those syndromes from idiopathic PD.<sup>33,34</sup>

A number of limitations should be addressed. The smaller sample size of 323 patients with clinical assessments and 267 with SPECT scan at follow-up; however, these are still relatively considerable numbers. In order to test whether the baseline and follow-up cohorts were similar, we verified that age, gender, MoCA scores, GDS scores, RBDSQ scores and caudate SBR at baseline were not significantly different between patients included and excluded from the follow-up analysis (**Supplementary table 1**). The clinical follow-up analysis only included the imaging variables of caudate and putamen DAT availability; the symptoms analysed might presumably be caused by extensive networks involving more than one neurotransmitter system; therefore, future multitracer studies may be necessary to confirm and further examine our results. Where appropriate, i.e. for cognitive impairment and depressive symptoms scales scores, we corrected the analysis for the known variables of putamen specific binding ratio, age and years of education. The gait index variable was not normally distributed; therefore, we were unable to carry out a corrected GLM as for the other scales ratings.

## **CONCLUSION**

In this study we have demonstrated a high frequency of early caudate dopaminergic dysfunction in recently diagnosed PD patients. Furthermore, our findings suggest that caudate quantification of DAT availability shortly after diagnosis may have an important role in identifying patients at risk of

clinical progression to cognitive impairment, depression and gait problems in the near future. In fact, early bilateral  $^{123}\text{I}$ -FP-CIT caudate uptake below -2 SDs of the controls' mean may be a valid indicator of more rapid onset of such symptoms. This approach might allow better prediction of disease course for patients with early PD and could also provide the potential to stratify cases for early targeted disease-modifying therapies.

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### **Contributors**

Study conception and design: JP, RD, NP; Data analysis organization and execution: JP, RD, NP; Writing of the manuscript: JP, RD, LW, MGS, LR, DJB, DB, NP; Critical revision of the manuscript: LR, DJB, DB, NP.

### **Competing interests**

None declared

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### **Ethics approval and patient consent**

All participating PPMI sites received approval from an ethical standards committee prior to study initiation and written informed consent for research was obtained from all participants in the study.

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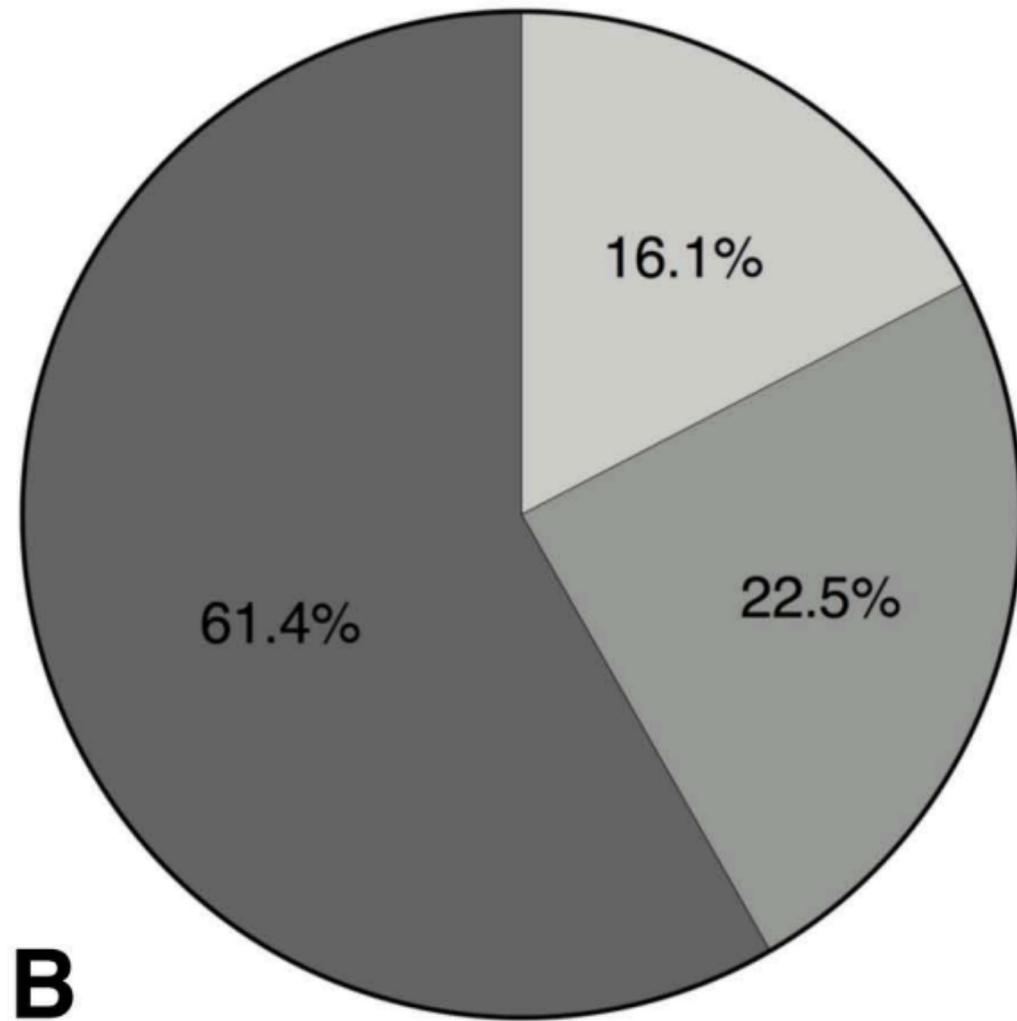
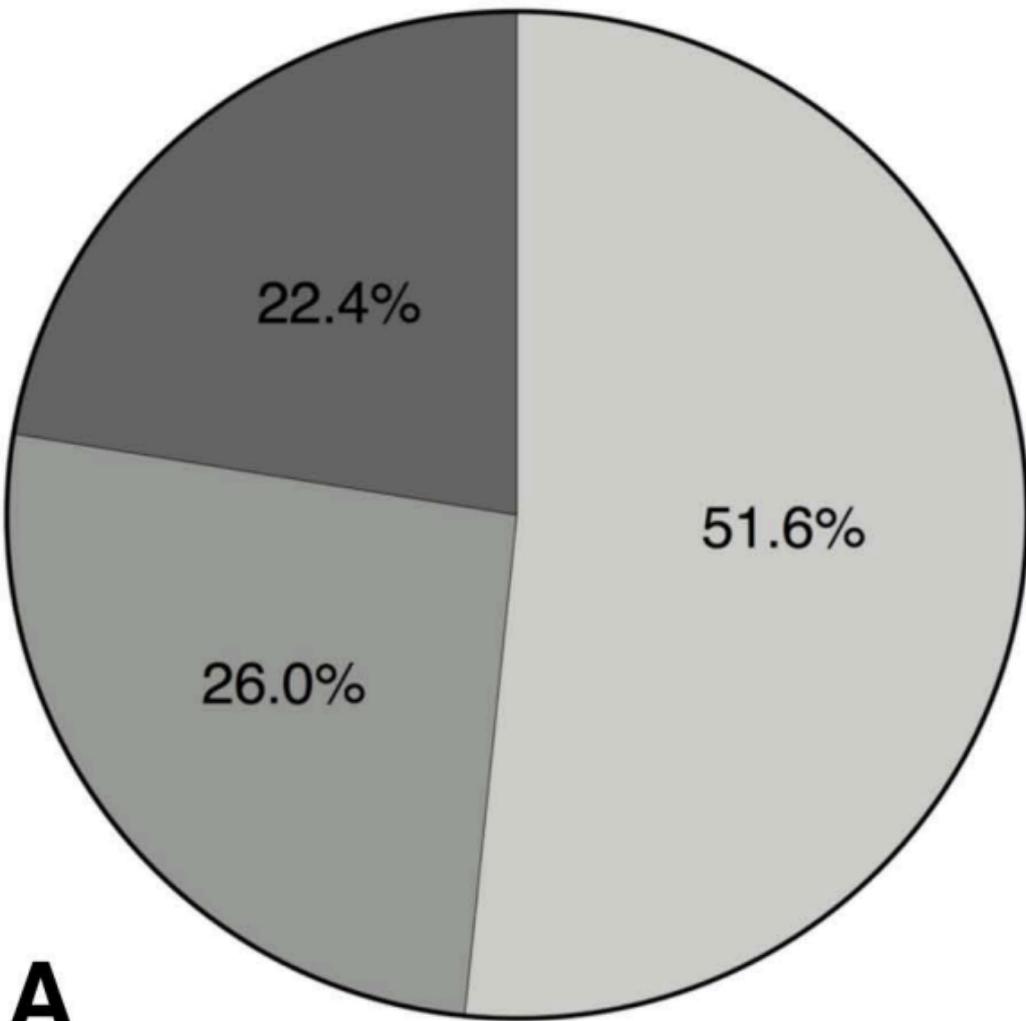
## FIGURES

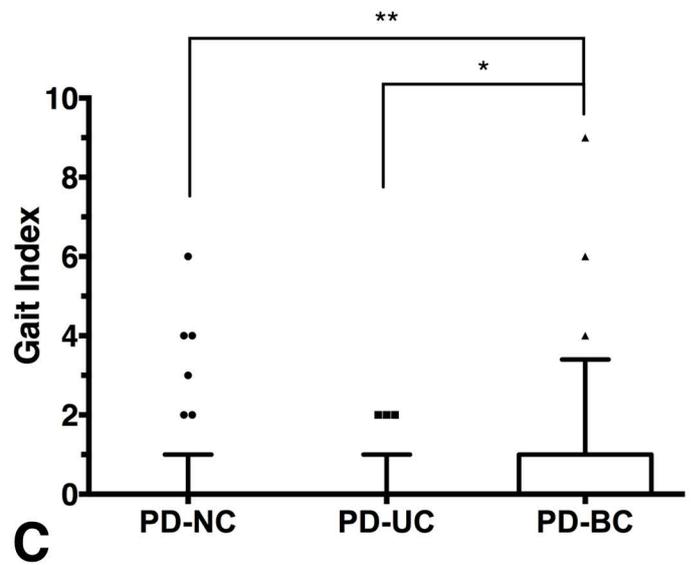
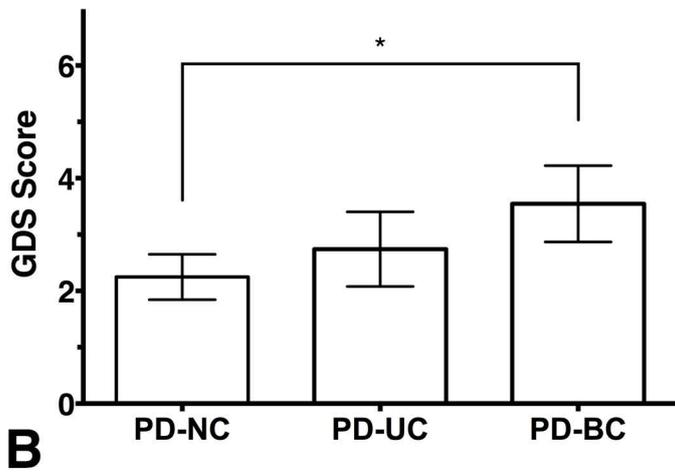
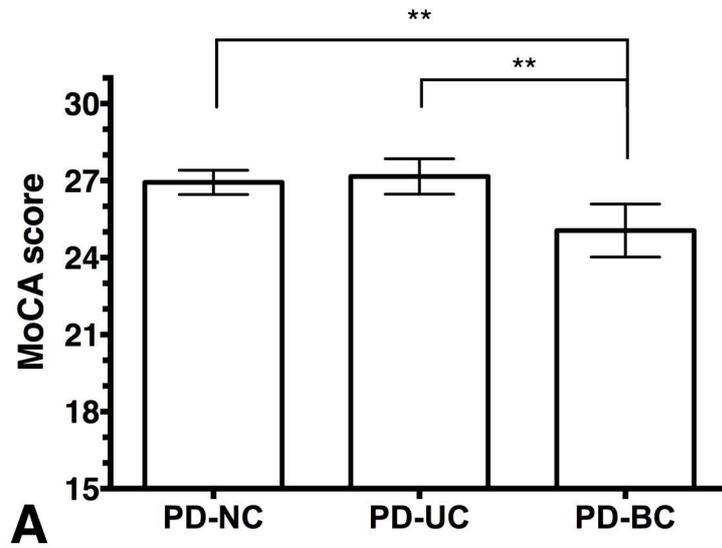
**Figure 1.** Pie chart representing the three groups of patients at baseline (**A**) and follow up (**B**) classified according to their baseline caudate  $^{123}\text{I}$ -FP-CIT SPECT binding compared to healthy controls.

Patients with Parkinson's disease (baseline,  $n = 397$ ; follow-up,  $n = 267$ ) were categorized into three groups based on their baseline caudate specific binding ratios compared to healthy controls: no reduced  $^{123}\text{I}$ -FP-CIT binding in either caudate (PD-NC);  $^{123}\text{I}$ -FP-CIT caudate binding reduced below -2 SDs of the controls' mean in one caudate only (PD-UC);  $^{123}\text{I}$ -FP-CIT caudate binding bilaterally reduced below -2 SDs of controls' mean (PD-BC). The percentage of each subgroup in the PD cohort is displayed on the corresponding pie slice.

**Figure 2.** Boxplots showing differences in outcomes in PD subgroups (n = 323) at the four-year follow up; (A) Montreal Cognitive Assessment score (MoCA), (B) Geriatric Depression Score (GDS) and (C) Gait Index score.

**PD-NC:** Parkinson's disease patients with no reduced caudate  $^{123}\text{I}$ -FP-CIT binding compared to the controls' mean at baseline. **PD-UC:** Parkinson's disease patients with reduced baseline caudate  $^{123}\text{I}$ -FP-CIT binding below -2 SDs of the controls' mean in one caudate only. **PD-BC:** Parkinson's disease patients with reduced baseline caudate  $^{123}\text{I}$ -FP-CIT binding below -2 SDs of the controls' mean in both caudate nuclei. **A:** Bar charts representing mean MoCA scores with 95% CIs at the four-year follow-up. **B:** Bar charts representing mean GDS scores with 95% CIs at the four-year follow-up. **C:** Boxes and whiskers representing distributions of the gait index scores (product of MDS-UPDRS II sub-items 2.12 and 2.13) at the four-year follow-up. Boxes: 25<sup>th</sup> to 75<sup>th</sup> percentiles; whiskers 95<sup>th</sup> percentile. \*p<0.05, \*\*p<0.001.





## SUPPLEMENTARY MATERIAL

### SECTION 1 – PPMI cognitive categorization

The following cognitive tests assessing memory, visuospatial function, processing speed-attention, executive function and semantic fluency were administered to each patient as part of the PPMI study: Hopkins Verbal Learning Test-Revised (HLVT-R), Benton Judgment of Line Orientation (JOLO) 15-item (split-half) version, Symbol-Digit Modalities Test (SDMT), Letter-Number Sequencing (LNS) and semantic fluency tests (animals, vegetables and fruits).

The Cognitive Categorization assessment was used to make a determination of Parkinson Disease Dementia (PDD) and PD with mild cognitive impairment (PD-MCI). Information for this assessment was provided through a combination of responses from the subject or other informant, the Investigator's judgment, and results from the cognitive testing covering the four cognitive domains mentioned above.

The determination of PDD was made on the following factors: (i) History of cognitive decline determined by the investigator based on information from the patient, other informant (spouse, family member or friend) and the investigator's judgment (The investigator reports the presence of cognitive decline [Yes/No] based on clinical evaluation of attention, memory, orientation, executive abilities, praxis and language and the presence of functional impairment compared to premorbid state; this determination is made prior to or independent from review of neuropsychological test scores/results); (ii) Cognitive impairment defined as at least 1 test score (out of 6 scores) from at least 2 domains (out of 4 domains)  $>1.5$  SD below the standardized mean; (iii) Functional limitation as a result of cognitive impairment (IADLs).

The determination of PD-MCI was made based on the following factors: (i) Cognitive complaint by either the patient or informant (spouse, family member or friend); (ii) Cognitive impairment defined as at least 2 test scores (out of 6 scores) from at least 1 domain (out of 4 domains)  $>1.0$  SD below the standardized mean; (iii) No functional impairment as a result of cognitive impairment (IADLs).

### SECTION 2 – PPMI DAT imaging protocol

**Imaging site set up.** All PPMI imaging centres were visited for technical site evaluation and set up which involved performing a SPECT acquisition on an anthropomorphic striatal phantom filled with  $^{123}\text{I}$ oflupane on the same camera with the same parameters and collimators as the subsequent patients imaged in the study. This procedure was used to optimize and standardize the reconstruction and filtration of the SPECT images across the different imaging centers.

**$^{123}\text{I}$ -FP-CIT SPECT procedure.** Before the  $^{123}\text{I}$ -FP-CIT injection, subjects were pre-treated with stable iodine (10 drops of a saturated solution of potassium iodide) to reduce the uptake of  $^{123}\text{I}$ -FP-

CIT by the thyroid. Subjects were injected with 3-5 mCi (111–185 MBq) of  $^{123}\text{I}$ -FP-CIT. Within a 4 hour (+/- 30 minute) window following the injection, subjects underwent SPECT imaging on the camera. Raw SPECT data were acquired into a 128x128 matrix stepping each  $3^\circ$  for a total of 120 (or  $4^\circ$  for a total of 90) projections in a window centred on  $159\pm 10$  KeV with a total scan duration of 30-45 min.

**Processing and analysis.**  $^{123}\text{I}$ -FP-CIT SPECT imaging acquired at each PPMI imaging center were sent to Institute for Neurodegenerative Disorders, New Haven, Connecticut for processing and calculation of SBRs. SPECT raw projection data were imported to a HERMES (Hermes Medical Solutions, Skeppsbron 44, 111 30 Stockholm, Sweden) system for iterative (HOSEM) reconstruction. This was done for all imaging centers to ensure consistency of the reconstructions. Iterative reconstruction was done without any filtering applied. The HOSEM reconstructed files were then transferred to PMOD (PMOD Technologies, Zurich, Switzerland) for subsequent processing. Attenuation correction ellipses were drawn on the images and a Chang 0 attenuation correction was applied utilizing a site specific mu that was empirically derived from phantom data acquired during site initiation for the trial. Once attenuation correction was completed, a standard Gaussian 3D 6.0 mm filter was applied. These files were then normalized to standard Montreal Neurologic Institute (MNI) space so that all scans were in the same anatomical alignment. Next the transaxial slice with the highest striatal uptake was identified and the 8 hottest striatal slices around it were averaged in to generate a single slice image. Regions of interest (ROI) were then placed on the of left and right caudate, the left and right putamen, and the occipital cortex (reference tissue). Count densities for each region were extracted and used to calculate striatal binding ratios (SBRs) for each of the 4 striatal regions. SBR were calculated as (target region/reference region)-1.

## SUPPLEMENTARY TABLES

**Supplementary table 1.** Distribution of caudate and putamen <sup>123</sup>I-FP-CIT binding across PD patients compared to the controls' mean (caudate: mean  $\pm$  SD =  $2.56 \pm 0.60$ ; putamen: mean  $\pm$  SD =  $2.14 \pm 0.55$ ).

	<b>Within -2 SD</b>	<b>Unilateral reduction</b>	<b>Bilateral reduction</b>
<b>Caudate, n</b>	205	103	89
<b>Putamen, n</b>	25*	120	252

Unilateral reduction: one side  $< -2$  SDs of the controls' mean. Bilateral reduction: both sides  $< -2$  SDs of the controls' mean.

**Supplementary table 2.** Reciprocal distribution of caudate and putamen <sup>123</sup>I-FP-CIT binding across PD patients as classified in comparison to the controls' mean (caudate: mean  $\pm$  SD =  $2.56 \pm 0.59$ ; putamen: mean  $\pm$  SD =  $2.14 \pm 0.55$ ).

		<b>Caudate, SDs with respect to HCs' mean</b>		
		Within -2 SD, n	Unilateral reduction, $< -2$ SDs, n	Bilateral reduction, $< -2$ SDs, n
<b>Putamen, SDs with respect to HCs' mean</b>	Within -2 SD, n	25*	0	0
	Unilateral reduction $< -2$ SDs, n	91	28	1
	Bilateral reduction $< -2$ SDs, n	89	75	88

\* All these patients had an abnormal pattern of putaminal uptake on DAT SPECT visual assessment compatible with the presence of nigrostriatal hypofunction. Their mean  $\pm$  SD reduction in the most affected putamen compared to healthy controls [ $((\text{mean putamen in HCs} - \text{most affected putamen PD}) / \text{mean putamen in HCs}) * 100$ ] was  $63.61 \pm 30.64\%$ .

**Supplementary Table 3.** Comparison of baseline clinical variables between patients with and without available data at follow up.

	<b>Available</b> (n = 323)	<b>Not available</b> (n =74)	<b>P-value</b>
<b>Age</b> (years, mean $\pm$ SD)	61.26 $\pm$ 9.88	63.49 $\pm$ 8.87	0.119
<b>Gender</b> (M/F)	173/94	85/45	0.591
<b>MoCA score</b> (mean $\pm$ SD)	27.28 $\pm$ 2.31	27.34 $\pm$ 2.46	0.852
<b>GDS score</b> (mean $\pm$ SD)	2.26 $\pm$ 2.40	2.76 $\pm$ 2.81	0.121
<b>RBDSQ score</b> (mean $\pm$ SD)	4.43 $\pm$ 2.79	4.75 $\pm$ 3.16	0.437
<b>Caudate SBR</b> (mean $\pm$ SD)	1.99 $\pm$ 0.52 (n=267)	2.00 $\pm$ 0.64 (n=130)	0.934

An independent t-test was used in order to assess differences between groups in age, MoCA score, GDS score, RBDSQ score and caudate SBR. A Fisher exact chi-square test was used in order to assess differences in gender between groups.

MoCA: Montreal Cognitive Assessment

GDS: geriatric depression scale

RBDSQ: REM sleep behavior disorder questionnaire

SBR: specific binding ratio