Extrastriatal 123I-FP-CIT SPECT impairment in Parkinson’s disease – the PPMI cohort

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Abstract

**Background:** Neuropathological data and nuclear medicine imaging show extensive serotonergic impairment in Parkinson's disease (PD). We aimed at undertaking a case-controlled analysis of $^{123}$I-FP-CIT SPECT images to measure extrastriatal serotonergic transporters (SERT) in PD using the Parkinson’s Progression Markers Initiative (PPMI) cohort.

**Methods:** We included all PD (n=154) and Control subjects (n=62) with available $^{123}$I-FP-CIT SPECT imaging and high-resolution T1-weighted MRI for coregistration (PD: mean age 61.6 years, 62% male, disease duration 26 months, MDS-UPDRS III score 22). $^{123}$I-FP-CIT SPECT images were processed with PETPVE12 using an exploratory voxel-wise analysis including partial-volume effect correction. Linear regressions were performed in the PD group to assess correlations between region of interest $^{123}$I-FP-CIT uptake and clinical motor and non-motor impairment.

**Results:** Compared to Controls, PD exhibited an uptake reduction in bilateral caudate nucleus, putamen, insula, amygdala and right pallidum (family-wise error (FWE)-corrected p<0.05). While lower contralateral putaminal uptake was associated with higher MDS-UPDRS III score (p=0.022), we found a trend association between higher geriatric depression scale and lower pallidum uptake (p=0.09). Higher SCOPA-AUT gastrointestinal subscore was associated with lower uptake in mean putamen and caudate nucleus (p=0.01 to 0.03), whereas urological subscore was inversely correlated with mean caudate nucleus, putamen, and pallidum uptake (p=0.002 to 0.03). No significant association was found for Montreal Cognitive Assessment (all p>0.45).

**Conclusions:** In addition to the well-established striatal deficit, this study provides evidence of a major extrastriatal $^{123}$I-FP-CIT impairment, and therefore of an altered serotonergic transmission in early PD.

**Background**

$^{123}$I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane ($^{123}$I-FP-CIT) is the most widely used single photon emission computed tomography (SPECT) ligand to assess the integrity of presynaptic nigrostriatal pathways [1]. Thus far, little attention has been paid to extrastriatal binding...
of $^{123}$I-FP-CIT which mainly (70%) derives from serotonergic transporters (SERT) density [2]. Serotonin (5-hydroxy-tryptamine, 5-HT) regulates many higher brain functions including cognition, mood and motor behaviour – all being impaired in degenerative parkinsonisms. 5-HT is synthesized in the raphe nuclei of the brainstem which project rostrally to the cortex, thalamus and basal ganglia and caudally to the spinal cord [3]. Evidence from post-mortem and in vivo $^{11}$C-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)benzonitrile ($^{11}$C-DASB) positron emission tomography (PET) imaging has demonstrated serotonergic cell loss in degenerative forms of parkinsonism, especially in Parkinson’s disease (PD) and Progressive Supranuclear Palsy (PSP) [4–6]. $^{123}$I-FP-CIT SERT concentration has been shown to be higher in females and to decline with age [7], and reduced uptake has been observed for PD in frontal areas, thalamus, amygdala and insula [8, 9], confirming $^{11}$C-DASB PET findings.

Using the Parkinson’s Progression Markers Initiative (PPMI) database [10], we here propose a case-controlled extrastriatal $^{123}$I-FP-CIT assessment of early PD subjects. In addition, we performed correlation analyses of striatal and extrastriatal significant regions of interest (ROI) uptake with clinical motor and non-motor scales, i.e. Movement Disorders Society (MDS)-Unified Parkinson’s Disease Rating Scale (UPDRS) part III at baseline and at 1-year follow-up [11], Geriatric Depression Scale (GDS) [12], Montreal Cognitive Assessment (MoCA) [13], and AUTonomic SCale for Outcome in PAarkinon’s disease (SCOPA-AUT) [14].

**Methods**

**Participants**

As of 4th February 2019, 423 PD and 196 Controls (CTL) were enrolled in the PPMI study. For the present work, we included all subjects who had both $^{123}$I-FP-CIT SPECT imaging and high-resolution 3T T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) MRI performed within 3 months. In addition, inclusion was limited to individuals aged over 40 years to ensure that only sporadic rather than genetic cases were taken into consideration. We also collected clinical data from the PPMI database, i.e. total scores of the MDS-UPDRS III scale (off-state, ≥ 6 h after dopaminergic treatment
discontinuation) at baseline (within three months of scans) and at 1-year follow-up. Baseline non-motor impairment was assessed using measures of cognition (MoCA), depression (GDS) and dysautonomia with SCOPA-AUT scale, including gastrointestinal (SCOPA-GI, 7 items) and urinary (SCOPA-URO, 6 items) subscores.

MRI imaging

All patients were scanned in a 3T Siemens Magnetom TRIO Tim MRI scanner (Siemens Medical Solutions, Erlangen, Germany) using a 32-channel head coil. MPRAGE structural T1-weighted images were acquired with the following parameters: TR = 2300 ms, TE = 3 ms, flip angle = 9°, 256 × 256 × 240 mm matrix and voxel size = 1 mm3 (isotropic).

SPECT Imaging acquisition, reconstruction and preprocessing

Reconstructed and attenuation-corrected 123I-FP-CIT SPECT imaging data was downloaded from the PPMI website. Images were acquired on a Siemens or General Electric SPECT tomographs, 3–4 h after 123I-FP-CIT injection. The imaging protocol for the PPMI scans is documented in http://www.ppmi-info.org/wp-content/uploads/2013/02/PPMI-Protocol-AM5-Final-27Nov2012v6-2.pdf.

Preprocessing of SPECT brain images was performed using Statistical Parametric Mapping (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK, https://www.fil.ion.ucl.ac.uk/spm/), running in MATLAB R2018b Version 9.5.0 (MathWorks Inc., Sherborn, MA, USA). SPECT images were coregistered to each patient’s own MPRAGE structural MRI, partial-volume-effect-corrected with the PETPVE12 toolbox running on SPM [15] after segmenting the MRI into grey matter, white matter and CSF tissue compartments using tissue probability maps. Resulting SPECT images were then intensity normalised using the occipital lobe as a reference region and warped into Montreal Neurological Institute (MNI) standard space. We performed a two-sample t-test (PD vs CTL group), with age, gender, antidepressant medication and medical center as covariates. T-maps contrasts were obtained by comparing groups with family-wise error (FWE)-corrected p < 0.05, limiting the results to the expected cluster voxel size according to SPM.

ROI-based analyses
Uptake extraction of the significant striatal and extrastriatal ROIs found in the voxel-wise analysis was performed with PETPVE12 [15] for correlation with clinical scales. After SPECT/MRI coregistration and MRI segmentation described above, we proceeded to ROI uptake extraction using geometric transfer matrix (GTM), including partial volume effect (PVE) correction. SPECT images were smoothed using an 8 mm full width at half-maximum (FWHM) Gaussian kernel. The Desikan-Killiany was used for ROI uptake extraction [16]. Semiquantitative values were obtained using the occipital lobe as the reference (REF) for DAT-rich ROIs (caudate nucleus, putamen and pallidum) or cerebellar grey matter for SERT-rich regions (amygdala and insula) [17] using the specific/non-specific binding ratio (SBR) as

\[
SBR = \frac{\text{Uptake}_{ROI} - \text{Uptake}_{REF}}{\text{Uptake}_{REF}}.
\]

Statistical Analysis
Statistical analyses were performed with Stata Version 14.2 software (College Station, TX).
Continuous variables were assessed for normality with plotted histograms and Shapiro-Wilk test. We used t-test or Mann-Whitney U test (MWU) for continuous variables with a normal and non-normal distribution, respectively. \(\chi^2\) test was performed for categorical variables.
Correlation analyses were performed for PD using univariate linear regressions between clinical motor/non-motor scales and ROIs with significantly reduced uptake in PD. When assessing a correlation with a motor scale (MDS-UPDRS III), we used age, gender, antidepressant medication and center as covariates and striatal ROIs uptake on the contralateral to clinically more affected side. For non-motor scales (GDS, MoCA, SCOPA-GI and SCOPA-URO), MDS-UPDRS III score was added as an additional covariate to adjust for motor severity and we used as the independent variable the mean (average of left and right) ROI uptake.

Results
Patients demographics
According to our inclusion criteria (subjects aged \(\geq 40\) years, available SPECT and MPRAGE MRI performed within 3 months interval), 158 early PD and 63 CTL from 12 different medical centres were eligible for the present work. During the image preprocessing, 4 PD and 1 CTL subjects were excluded because of technical issues related to SPECT/MRI coregistration. Eventually, 154 PD and 62 CTL were
included for group comparisons. Demographics and inclusion flowchart are available in Table 1 and Figure 1.

Voxel-based $^{123}$I-FP-CIT SPECT analyses

Compared to the CTL group, PD subjects showed decreased uptake in a first cluster (total 1109 voxels (vx), peak level T-score 16.3) including right insula, putamen, amygdala and pallidum. The second cluster (total 1195 vx, peak level T-score 14.4) included left insula, putamen and caudate nucleus and amygdala (all FWE-corrected p<0.05) A third smaller cluster (140 vx, peak level T-score 7.4) included right caudate nucleus (Figure 2).

Correlation analysis of clinical scales and ROIs $^{123}$I-FP-CIT uptake

Higher MDS-UPDRS III was associated with lower $^{123}$I-FP-CIT uptake in the contralateral putamen (p=0.022, coefficient = -9.2, 95% confidence interval (CI) -17 to -1.4). No significant correlation was found between ROIs uptake and MoCA (all p>0.45). We found a trend association between higher GDS and lower mean $^{123}$I-FP-CIT pallidal uptake (p=0.08, coefficient -0.65, 95% CI -1.39 to 0.09). Higher SCOPA-GI correlated with lower mean putamen (p=0.01, coefficient -2.2, 95% CI -3.9 to -0.5) and caudate nucleus uptake (p=0.034, coefficient -1.48, 95% CI -2.9 to -0.1). Finally, higher SCOPA_URO subscore was associated with lower mean uptake in the caudate nucleus (p=0.002, coefficient -2.7, 95% CI -4.3 to -1.0), putamen (p=0.013, coefficient -2.7, 95% CI -4.6 to -0.6) and pallidum (p=0.025, coefficient -1.4, 95% CI -2.7 to -0.2).

Discussion

In the present work, we showed that in addition to a well-known decreased $^{123}$I-FP-CIT uptake involving the striatum, early PD subjects exhibit a significant uptake reduction in extrastriatal regions including the pallidum, amygdala and insula.

$^{123}$I-FP-CIT impairment in pallidum was recently observed by Lee et al. [18]. $^{11}$C-PE2I and $^{11}$C-DASB PET studies showed that while the lateral part of the pallidum (globus pallidum externus) has a similar proportion of serotonergic and dopaminergic terminals, the medial part (globus pallidus internus) is mainly a serotonergic nucleus [17]. In addition, our PD subjects exhibited an impaired extrastriatal...
uptake in the insula and amygdala. These findings confirm recent data by Pilotto et al. showing decreased $^{123}$I-FP-CIT uptake in insula, thalamus and cingulate in both PD and dementia with Lewy bodies [9]. Moreover, they confirm previous neuropathological evidence and in vivo $^{11}$C-DASB-PET and $^{123}$I-FP-CIT SPECT studies showing an altered serotonergic uptake for PD in the insula [6, 8], providing additional value for $^{123}$I-FP-CIT SPECT, a major diagnostic imaging tool in daily clinical practice. A reduced $^{123}$I-FP-CIT uptake in the amygdala was observed. These findings are in line with post-mortem studies using chromatography and enzyme-linked immunosorbent assay showing that PD subjects had reduced dopamine and noradrenaline levels in the amygdala [19].

Our correlation analysis confirmed that motor impairment as measured by MDS-UPDRS III total score was associated with decreased putaminal $^{123}$I-FP-CIT uptake [20]. It might seem surprising that MDS-UPDRS III was not more strongly correlated with striatal ROIs $^{123}$I-FP-CIT uptake. However, a recent psychometric assessment of MDS-UPDRS part II and III scales in PD subjects enrolled into the PPMI cohort showed an important floor effect, which can explain the moderate association for our cohort [21].

Clinical correlates of an extensive serotonergic deficit may include apathy, emotional disturbances, depression, cognitive deficits, and dysautonomic manifestations in PD, all of which being potentially present early in the disease course or even in its prodromal phase [22]. While a trend association was found between GDS and pallidal $^{123}$I-FP-CIT uptake, we did not find a significant correlation between SERT-rich regional uptake and cognitive impairment as measured with MOCA. One reason might be that other monoaminergic pathways are involved in the pathophysiology of cognitive impairment [23] and that larger samples would be necessary to tackle such complex processes. In addition, our PD cohort mainly consisted of early subjects with relatively preserved cognition (mean MoCA 27.4), so admittedly, a significant correlation between SERT binding and depression/cognitive scales could have been observed in cohorts with a broader range of impairment [24].

Finally, a significant association was found between SCOPA-GI subscore and caudate/putamen uptake.
This confirms previous observations from Hinkle et al. [25], who described an association between SCOPA-GI score (especially constipation items) and both regions. Additionally, we observed that the SCOPA-URO subscore was also negatively correlated with striatal uptake. This is in line with previous findings from Kim et al. [26] who recently found a correlation between putamen uptake and SCOPA-URO subscore also including the PPMI cohort. For both studies from Hinkle and Kim, SPECT/MRI coregistration was not performed. While our findings are of interest, they should be interpreted with an important caveat in mind. In fact, while bowel motility in late-life has been associated with postmortem neuron density in the substantia nigra [27], a causal relationship between presynaptic striatal dopamine uptake and gastrointestinal impairment in early PD would be hasty. Indeed, one hypothesis would be that dysautonomia would appear concurrently to striatal dopaminergic degeneration and not necessarily be driven by it.

The present study has several major strengths: first, it is based on a large cohort of well-characterized PD and CTL subjects who underwent extensive clinical motor and non-motor evaluation. In addition, we included subjects whose SPECT was acquired within three months of a high-resolution anatomical MRI in order to proceed to MRI/SPECT coregistration and to provide PVE-corrected results. Although our included subjects represent about half of the total PD subjects in the PPMI cohort, given the stringent inclusion criteria we applied for analyses purposes, we believe this provides a major insight into the pathophysiology of monoaminergic degeneration in PD. The present work also presents some limitations. As this is the case in similar clinical studies, diagnoses are not based on neuropathology, so we cannot exclude diagnostic misattribution, especially since some PD cases were enrolled at a very early stage (10 subjects with < 6-month disease duration). In addition, SPECT acquisition was performed 3–4 h after $^{123}$I-FP CIT injection, which is the ideal timeframe for DAT evaluation, whereas the recommended time window for extrastriatal SERT is 2–3 h [2]. Nonetheless, due to a slow $^{123}$I-FP-CIT washout, we expect SERT binding to be relatively stable at 3–4 h [28].

Conclusion

We presented evidence of a widespread $^{123}$I-FP-CIT extrastriatal impairment in early PD, spanning the
amygdala and insular region, which is in keeping with neuropathological and $^{11}$C-DASB PET imaging. As dopamine SPECT imaging is used daily to confirm nigrostriatal degeneration, these results bring novel evidence for a potential role in helping to discriminate PD from non-degenerative conditions by assessing extrastriatal uptake. Further studies are warranted to assess whether atypical parkinsonian syndromes harbour similar extrastriatal $^{123}$I-FP-CIT impairment, therefore confirming complex monoamine transmission abnormalities in degenerative parkinsonisms.

Declarations

**ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

The relevant local institutional review boards approved the PPMI protocol and written informed consent was obtained from all participants prior to inclusion. Details are fully available on the PPMI website (http://www.ppmi-info.org/wp-content/uploads/2018/02/PPMI-AM-13-Protocol.pdf)

**CONSENT FOR PUBLICATION**

Not applicable

**AVAILABILITY OF DATA AND MATERIAL**

Anonymised imaging data analyses performed by the authors are available to researchers upon reasonable request.

**COMPETING INTERESTS**

N.N. is part of the editorial board for BMC Neurology. P.R.B and V.G. declare that they have no conflict of interests.

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**AUTHORS’ CONTRIBUTIONS**

1. N.: data collection and analysis; writing of the first draft of manuscript. V.G.: data interpretation; revision of the first draft of manuscript. P.R.B.: data interpretation; revision of the first draft of manuscript. All authors have read and approved the manuscript

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**Abbreviations**

$^{123}$I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane ($^{123}$I-FP-CIT); Single photon emission computed tomography (SPECT); Serotonin transporter (SERT);

$^{11}$C-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)benzonitrile ($^{11}$C-DASB); Positron emission tomography (PET); Parkinson’s disease (PD); Progressive supranuclear palsy (PSP); region of interest (ROI); Movement Disorders Society (MDS); Unified Parkinson’s disease rating scale (UPDRS); Geriatric Depression Scale (GDS); Montreal Cognitive Assessment (MoCA); Autonomic scale for outcome in Parkinson’s disease (SCOPA-AUT); Parkinson’s Progression Markers initiative (PPMI); Controls (CTL); Magnetization prepared rapid gradient echo (MPRAGE); Statistical parametric mapping (SPM); family-wise error (FWE); partial volume effect (PVE); full-width at half maximum (FWHM); reference (REF); striatal binding ratio (SBR); Mann-Whitney U test (MWU); voxels (vx); confidence interval (CI)

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Table

**TABLE 1: Demographics for the PD and CTL groups**

|                      | PD (n=154)   | CTL (n=62)   | p-value |
|----------------------|--------------|--------------|---------|
| Age (years)          | 61.6 ± 8.9   | 61.5 ± 10    | 0.87 §  |
|                      | (40-82)      | (40-81)      |         |
| Male distribution    | 61.7% (98/154) | 61.5% (41/62) | 0.73 #  |
| Disease duration     | 25.5 ± 17.8  | NA           | -       |
| (months)             | (2-77)       |              |         |
| MDS-UPDRS III at     | 22.3 ± 9.7   | NA           | -       |
| baseline             | (5-46)       |              |         |
| Hoehn-Yahr scale     | 1.5 ± 0.5    | 28.2 ± 1.2   | 0.19 §  |
|                      | (1-2)        | (26-30)      |         |
| MOCA                 | 27.4 ± 2.2   | 28.2 ± 1.2   | 0.19 §  |
|                      | (20-30)      | (26-30)      |         |
| GDS                  | 5.3 ± 1.4    | 5.1 ± 1.2    | 0.39 §  |
|                      | (1-11)       | (3-10)       |         |

Baseline demographics of PD and CTL subjects included in the study. Statistical tests: Chi-square #, Mann-Whitney U test §. NA = not applicable

Figures
inclusion process of the study
Voxel-wise 123I-FP-CIT SPECT group comparisons between CTL and PD subjects, showing reduced uptake in bilateral putamen, caudate nucleus, insula, amygdala and right pallidum (FWE-corrected p<0.05). Color bar represents T-score. R = right. Numbers are Z-axis coordinates in MNI space.