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Striatal Dopamine Transporter and Rest Tremor in Parkinson Disease

A Clinical Validation

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Supplementary Material

Abstract

Background and Objectives

The mechanisms underlying tremor generation in Parkinson disease (PD) remain unclear. Previously, we demonstrated a connection between rest tremor amplitude and higher dopamine transporter (DAT) binding in the ipsilateral striatum among the Parkinson Progression Markers Initiative cohort. Here, we investigated the association of parkinsonian motor symptoms with striatal DAT binding in a sizable and clinically representative sample of patients with parkinsonian signs to validate the previously observed ipsilateral relationship in PD.

Methods

This observational cross-sectional study included right-handed patients referred for [^{123}I]FP-CIT SPECT because of clinically uncertain parkinsonism or tremor at Turku University Hospital and the Helsinki and Uusimaa Hospital District, Finland. Each patient underwent a comprehensive clinical evaluation and follow-up (median 3.0 years [interquartile range (IQR) 2.5]). Associations between striatal tracer binding and symptoms were investigated using voxel-wise linear models, adjusting for age, sex, motor symptom severity, and medication. The primary outcome measure was the association between rest tremor amplitude and striatal DAT binding.

Results

At the end of the follow-up period, of the 414 patients included (median age 68 years [IQR 14], 49.4% female), 148 were evaluated to have PD and 79 other forms of parkinsonism with striatal DAT deficit. In total, 187 patients had normal binding. Among the patients with PD, left and right rest tremor amplitudes were positively associated with ipsilateral striatal DAT binding (β = +0.12 [95% CI +0.05, +0.19] and +0.10 [+0.05, +0.15] specific binding ratio [SBR] per point; $p_{\text{FWE + Bonf.}} < 0.05$, respectively). Left and right bradykinesia (β = −0.16 [−0.22, −0.09] and −0.18 [−0.25, −0.10] SBR per 5 points, $p_{\text{FWE + Bonf.}} < 0.05$, respectively) and rigidity (β = −0.07 [−0.08, −0.04] and −0.08 [−0.11, −0.05] SBR per point, $p_{\text{FWE + Bonf.}} < 0.05$, respectively) mainly showed a negative association with contralateral striatal DAT binding. No consistent associations were observed in non-PD groups.

Discussion

These findings confirm the positive association between rest tremor amplitude and ipsilateral striatal DAT binding in a clinical sample of PD patients. However, the non-PD groups were diagnostically heterogeneous, limiting conclusions about disease specificity.

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Glossary

3D = 3-dimensional; **DAT** = dopamine transporter; **FWE** = family-wise error; **FWHM** = full-width-at-half-maximum; **IQR** = interquartile range; **LEDD** = levodopa-equivalent daily dose; **MDS-UPDRS-III** = Movement Disorders Society Unified Parkinson's Disease Rating Scale, part III; **MNI** = Montreal Neurological Institute; **PD** = Parkinson disease; **PPMI** = Parkinson's Progression Markers Initiative; **ROI** = region of interest; **SBR** = specific binding ratio.

Introduction

Parkinson disease (PD) manifests clinically through the presentation of 3 cardinal motor symptoms: rigidity, bradykinesia, and rest tremor.[1] While rigidity and bradykinesia are well-established to associate with contralateral striatal dopaminergic deficit[2,3] and overall motor severity with progression of dopamine transporter (DAT) deficit in the less affected hemisphere,[4] the connection between dopaminergic function and rest tremor remains unclear.[2,3,5-7] Notably, existing studies have often examined the association between tremor and dopaminergic function in PD by aggregating all tremor subtypes,[2,3,5] whereas rest tremor may warrant separate investigation, owing to its potentially unique pathophysiology among tremor subtypes.[6-8]

Rest tremor in PD is believed to be generated within the cerebello-thalamo-cortical circuit and its expression regulated by the basal ganglia.[9] However, this conventional theory fails to fully explain the observed phenomenon, wherein unilateral deep brain stimulation (DBS) not only has efficacy for contralateral tremor symptoms but also alleviates ipsilateral tremor,[10] implying the involvement of less dominant interhemispheric or crossing pathways.[11-14] Nevertheless, the observed therapeutic response of rest tremor to dopaminergic treatment suggests a potential, partial link with dopaminergic dysfunction.[8,15]

In a previous study, we identified a robust association between rest tremor amplitude and higher ipsilateral DAT binding within the Parkinson's Progression Markers Initiative (PPMI) neuroimaging cohort.[16] This association was observed both at baseline and at 2-year follow-up, including patients with various levels of dexterity, and those expressing rest tremor exclusively. However, it is noteworthy that the PPMI cohort predominantly comprises selected tremor-dominant early PD patients (approximately 70%),[17] and a substantial number may have undergone DAT imaging without typical clinical indications. Consequently, the generalizability of these findings to a broader clinical PD population may be limited, given the distinct characteristics of the PPMI cohort.

Therefore, in this study, our aim was to investigate the potential link between rest tremor amplitude and increased ipsilateral dopaminergic activity in a real-world clinical cohort of patients presenting with parkinsonian symptoms, who underwent DAT imaging as a part of their diagnostic evaluation.

Methods

Study Sample

The main data used in this cross-sectional observational multicenter study consisted of clinical, medication, and [^{123}I]FP-CIT SPECT imaging data of patients who had undergone diagnostic [^{123}I]FP-CIT SPECT imaging in Turku University Hospital and Helsinki and Uusimaa Hospital District during years 2014–2020 to evaluate suspected parkinsonism, in which assessment of potential nigrostriatal involvement was clinically indicated. Inclusion criteria were age 18–100 years and referral for clinical [^{123}I]FP-CIT SPECT imaging at Turku University Hospital or the Helsinki and Uusimaa Hospital District. Recruitment was consecutive, apart from patients who opted not to participate. All clinical data were reviewed in August 2022 by 2 movement disorder specialists, who reassessed the diagnoses according to the Movement Disorders Society clinical criteria for PD,[1] based on symptoms, signs, progression, levodopa response, and imaging findings. Left-handed and ambidextrous patients were excluded to minimize the confounding effects of brain lateralization. All analyses were conducted using baseline data only. Follow-up clinical information and patient records were used exclusively for diagnostic confirmation.

To investigate the similarity of striatal findings between cohorts, previously identified region of interest (ROIs) with statistically significant effects were acquired from the PPMI baseline cohort used in the earlier study,[16] examined off medication, with equivalent preprocessing steps. Data used in the preparation of this article were obtained on April 12, 2019, from the PPMI database,[18] RRID:SCR_006431. For up-to-date information on the study, visit the PPMI website.[19]

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was registered in 2015 (ClinicalTrials.gov identifier: NCT02650843). The study was approved by the Ethics Committees of the Hospital Districts and was conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained from all participants included in the study.

The PPMI study protocol was registered on June 8, 2010 (ClinicalTrials.gov identifier: NCT01141023). The study was approved by the institutional review board at each research site. All participants provided written informed consent.

Measures of the Motor Symptoms

The motor symptom measures used in the analysis were defined as composite scores derived from specific Movement Disorders Society Unified Parkinson's Disease Rating Scale, part III (MDS-UPDRS-III) items, as presented in eTable 1. Sidewise total rest tremor amplitude scores (i.e., the sums of either left or right rest tremor amplitude scores in the upper and lower extremity) were used as the primary measures of rest tremor.

SPECT Imaging

Participants were injected with 185 MBq of the radiopharmaceutical [^{123}I]FP-CIT 3 hours before SPECT imaging. To protect the thyroid from radiation exposure, participants were administered either 250–300 mg of potassium perchlorate or potassium iodide tablets (130 mg) 30–60 minutes before the radiopharmaceutical injection. SPECT imaging acquisition was performed using 1 of 6 SPECT/CT devices. Before the study, all SPECT/CT devices were calibrated using a striatal phantom (RSD, Radiology Support Devices, Inc., Long Beach, CA) following a recommended calibration procedure.[20,21]

ROI Value Acquisition and Image Preprocessing

SPECT images were reconstructed using a 3-dimensional (3D) ordered-subsets expectation maximization reconstruction algorithm (HybridRecon Neurology, version 1.3, Hermes Medical Solutions AB, Stockholm, Sweden), with 16 iterations, 4 subsets, uniform attenuation correction with the attenuation coefficient of 0.146 1/cm, collimator response correction using Gaussian diffusion model, Monte-Carlo-based scatter correction for the ^{123}I isotope and 3D Gaussian postfiltering with a full-width-at-half-maximum (FWHM) of 0.7 cm. The reconstructed images were originally analyzed using the BRASS analysis software (Hermes Medical Solutions AB, Stockholm, Sweden) in the clinical context.

The camera-specific calibration coefficients were implemented into BRASS software. With BRASS software, the specific binding ratios (SBRs) of DAT binding were calculated over 6 striatal ROIs (the right and left anterior putamen, the right and left posterior putamen, and the right and left caudate nucleus), which were automatically segmented. The occipital cortex was used as the reference region, and the SBRs were calculated as:

$$SBR = \frac{ROI - ROI_{occipital}}{ROI_{occipital}} \quad (1)$$

An [^{123}I]FP-CIT scan was classified as abnormal if SBR of at least 1 anatomical ROI was more than 2 SDs below the normative reference mean.[22-24] ROI SBR values were nonnormally distributed (Shapiro-Wilk test p < 0.001 for all ROIs), with marked right-skewness; therefore, natural logarithm-transformed values were used in the regression analyses.

The preprocessing of the imaging data for the voxel-wise analyses involved the registration of [^{123}I]FP-CIT SPECT images to the same standard space ($2 \times 2 \times 2$ mm^3 voxel size) with BRASS software using the built-in template, with consequent registration to Montreal Neurological Institute (MNI) standard space and smoothing with a Gaussian kernel (FWHM 4 mm). Voxel-wise SBR values were defined analogically to the ROI SBR values:

$$SBR_{i,j,k} = \frac{Intensity_{i,j,k} - ROI_{occipital}}{ROI_{occipital}} \quad (2)$$

The voxel-wise SBR values were log-transformed in the same manner as the ROI values, resulting in voxel-wise distributions within the striatum that more closely approximated normality (eFigure 1).

For further analyses, DAT asymmetry indices were calculated for each patient based on the ROI data. DAT asymmetry index was defined as:

$$DAT - AI = \frac{SBR_{mean,R} - SBR_{mean,L}}{SBR_{mean,R} + SBR_{mean,L}}, \quad (3)$$

where $SBR_{mean}(,L/R) = SBR_{Caudate}(L/R) + SBR_{Anterior\ Putamen}(L/R) + SBR_{Posterior\ Putamen}(L/R)$.

PPMI Data: Image Preprocessing

To acquire applicable external ROIs for the validation of the rest tremor amplitude findings in the PPMI data,[16] the PPMI data were reanalyzed without partial volume effect correction, with registration to MNI standard space based on the structural imaging data, and with FWHM 4-mm Gaussian kernel smoothing. SBR values were log-transformed identically to the main analyses of this study. Other steps of the PPMI data preprocessing and analysis workflow have been described earlier.[16]

Voxel-Wise Analyses

The voxel-wise analyses were conducted with Statistical Parametric Mapping 12[25] (Functional Imaging Laboratory, UCL Queen Square Institute of Neurology, London, the United Kingdom) using generalized linear model running on MATLAB R2021b (MathWorks Inc., Natick, MA). The main analyses of the association between striatal [^{123}I]FP-CIT binding and the clinical motor evaluation subscores were conducted adjusting for age, sex, medication state, and levodopa-equivalent daily dose (LEDD) (only for medicated patients; interaction medication state × LEDD). Additional analyses were conducted with MDS-UPDRS-III total score as an additional covariate (interaction medication state × MDS-UPDRS-III). A 3-mm dilated striatal mask from Harvard-Oxford Subcortical Atlas (eFigure 2) was used to restrict all the voxel-wise analyses to the striatum where SBR almost selectively reflects DAT binding, in contrast to other brain regions where SBR is influenced by binding to other monoamine transporters.[26]

Similar analyses were also conducted in 2 non-PD subgroups: (1) patients with normal striatal DAT binding (all ROI Z-scores ≥−2 SD) and (2) patients with abnormal binding (at least 1 ROI Z-score <−2 SD). The imaging outcomes were classified as normal or abnormal according to the primary semiquantitative analysis with BRASS software combined with confirmatory visual evaluation made by a nuclear medicine physician. The classifications were reviewed, and borderline cases were carefully re-evaluated by the investigators who were blinded to the clinical diagnoses, as described previously.[27,28]

Separate voxel-wise analyses for patients with rest tremor (i.e., MDS-UPDRS-III lateralized rest tremor items >0) were not conducted due to the limited sample size (n = 69 for PD with left and n = 69 for PD with right rest tremor), as sample size of 125 would be required to observe the effects with 80% power.

Clusters with cluster-wise familywise error (FWE) corrected p values (p_{FWE}) < 0.05 (with voxel-wise height threshold set to $p < 0.005$) were considered potentially significant. For the main analysis models, p_{FWE} values were further post hoc Bonferroni-corrected across all tested nonsignificant contrasts (positive and negative) and all potentially significant clusters (211 in total), yielding $p_{\mathrm{FWE\ +\ Bonf}}$. To test the robustness of voxel-wise findings against remaining heteroscedasticity, log-transformed cluster mean values were analyzed using multivariable robust regression (with optimal Ψ function).[29,30] Clusters with $p_{\mathrm{FWE\ +\ Bonf.}} < 0.05$ and significant associations in the corresponding robust regression models ($p < 0.05$) were considered significant.

ROI Analyses

First, associations between clinical characteristics and 6 automatically segmented ROI SBR values were evaluated using robust regression, with identical sets of covariates as employed in the voxel-wise analyses. Robust regression was selected to accommodate residual heteroscedasticity and occasional outliers not tolerated by ordinary least squares linear regression.

Second, to further validate these association in relation to the PPMI, significant clusters identified in earlier PPMI analyses were resampled to match the resolution of the present study's data, using nearest neighbor interpolation. Given the unmedicated status of PPMI patients during baseline imaging, SBR values for these areas were extracted exclusively from SPECT imaging data of unmedicated patients with PD in this study and were subsequently used in multivariable robust regression analyses identical to those in the voxel-wise analyses. As the regression models describe a slightly nonlinear (exponential) relationship between raw SBR values and the studied symptoms, the beta coefficients reported (β_{mean}) refer to local slopes at the mean of the symptom severity score in a group of interest.

Statistics

Analyses with the clinical, cluster, and ROI data were performed with R 4.1.2 (R Foundation for Statistical Computing, Austria) running on macOS 10.15 (Apple Inc., Cupertino, CA). The between-group comparisons were conducted using 2-sided Mann-Whitney U tests or Fisher exact tests, as appropriate. Diagnostic measures to assess the validity of robust regression models were tested with Shapiro-Wilk (residual normality), Breusch-Pagan (homoscedasticity), and variance inflation factor (absence of marked multicollinearity) analyses. These tests showed that the key assumptions of the chosen analysis methods were met consistently. The use of motor symptom severity scores as continuous (rather than categorical) variables was supported by likelihood ratio, Akaike information criteria, and Bayes information criteria tests.[31] The statistical significance of in-sample proportions was tested with 2-sided Z test. p Values <0.05 were considered statistically significant.

Data Availability

The data that support the findings of this study are available from the corresponding author on reasonable request, subject to the national and institutional regulations. The data of the PPMI cohort were downloaded from the publicly available PPMI database.[18] For up-to-date information on the study and the data handling protocol, visit the PPMI website.[19] As PPMI manages the use of the original data, the processed data are not publicly available.

Results

Clinical Characteristics

In total, 414 right-handed patients who had undergone [^{123}I]FP-CIT SPECT imaging for clinical diagnostic purposes were included in this study. At the conclusion of the follow-up period, 148 patients received a clinical diagnosis of PD, while 79 individuals were diagnosed with other movement disorders with abnormal [^{123}I]FP-CIT SPECT imaging results, and 187 patients had normal [^{123}I]FP-CIT SPECT imaging results with varying diagnoses. The specific diagnoses of the non-PD groups are presented in eTable 2. Across the entire sample, the median age was 68 years (interquartile range [IQR] 14), with a median follow-up duration of 3.0 years (IQR 2.5). Among all patients, 215 (50.6%) were male and the median motor symptom severity, as evaluated on the MDS-UPDRS-III scale, was 34 points (IQR 22) (Table 1). Limb rest tremor was most frequent in patients diagnosed with PD (n = 101 [68.2%]) (Fisher test, $p = 1.8 \times 10^{-5}$) but was also observed in patients with other movement disorders, both those with abnormal DAT binding (n = 31 [39.2%]), and those with normal imaging (n = 90 [48.1%]).

Patients With PD

In the patients with PD, both left-sided and right-sided total rest tremor amplitude scores were associated with higher ipsilateral striatal [^{123}I]FP-CIT binding (β_{mean} = +0.12 [95% CI +0.05, +0.19] and +0.10 [95% CI +0.05, +0.15] SBR units per 1 point, $p_{\mathrm{FWE\ +\ Bonf.}} < 2.1 \times 10^{-14}$ and $<2.1 \times 10^{-14}$, respectively) (Figure 1A). Left-sided rest tremor amplitude

Table 1 Demographic and Clinical Data

	Patients with PD (n = 148)	Patients with any other diagnosis than PD: Normal SPECT (n = 187)	Patients with any other diagnosis than PD: Abnormal SPECT (n = 79)
Age (y)	67 [59, 72]	67 [57, 74]	69 [63.5, 73]
Sex (male/female [male %])	71/77 [48]	90/97 [48.1]	46/33 [58.2]
MMSE	28 [26, 29]†‡	27 [25, 28.75]	27 [24, 28]
Predominant side of symptom onset (R/L/S)	65/58/21[a]†‡	81/46/56[a]	25/25/28[a]
Predominant side of limb rest tremor (R/L/S/N)	44/37/20/47†‡	49/17/24/97*	13/10/8/48
Disease duration from symptom onset (mo)	18 [11, 36]†	27 [16.5, 72]*	24 [12, 30]
Unmedicated/medicated [medicated %][b]	108/40 [27.0]†	165/22 [11.8]*	60/19 [24.1]
LEDD (medicated)	300 [103.75, 429.8]	265 [150, 300]	300 [175, 375]
MDS-UPDRS-III score	34 [25.75, 46]‡	33 [23, 45]*	40 [31.5, 51.5]
MDS-UPDRS-III score, unmedicated	33.5 [24.2, 43.2]‡	32 [23, 43]*	38.5 [32, 51.2]
MDS-UPDRS-III score, medicated	35 [26, 48.2]	44 [25, 47.8]*	42 [26, 55.5]
MDS-UPDRS-III bradykinesia-rigidity	21 [14, 31]‡	19 [13, 27]*	26 [19.25, 33]
MDS-UPDRS-III bradykinesia-rigidity, unmedicated	19.5 [13, 30]‡	19 [13, 26]*	28 [20.5, 32.5]
MDS-UPDRS-III Bradykinesia-rigidity, medicated	23.5 [17.75, 35]	26 [19, 32]	24 [12.5, 37]
MDS-UPDRS-III total tremor	6.5 [3, 10]‡	6 [3, 9]*	5 [3, 8]
MDS-UPDRS-III total tremor, unmedicated	7 [3, 11]‡	6 [3, 9]*	4 [3, 7.2]
MDS-UPDRS-III total tremor, medicated	4.5 [3, 8]	4.5 [2, 10.5]	7 [2.5, 10.5]
Hoehn & Yahr stage†‡			
0	1 [0.7]	6 [3.2]	1 [1.3]
1	32 [21.6]	16 [8.6]	6 [7.6]
2	82 [55.4]	109 [58.3]	45 [57]
3	25 [16.9]	38 [20.3]	17 [21.5]
4	8 [5.4]	14 [7.5]	5 [6.3]
5	—	4 [2.1]	5 [6.3]
Mean (L&R) caudate *Z*-score	−2.34 [−2.89, −1.67]†	−0.54 [−1.14, 0.48]*	−2.49 [−3.14, −1.64]
Mean (L&R) anterior putamen *Z*-score	−2.84 [−3.60, −2.26]†	−0.46 [−0.95, 0.41]*	−2.73 [−3.58, −1.94]
Mean (L&R) posterior putamen *Z*-score	−3.76 [−4.28, −3.22]†‡	−0.45 [−1.02, 0.32]*	−3.20 [−3.82, −2.38]

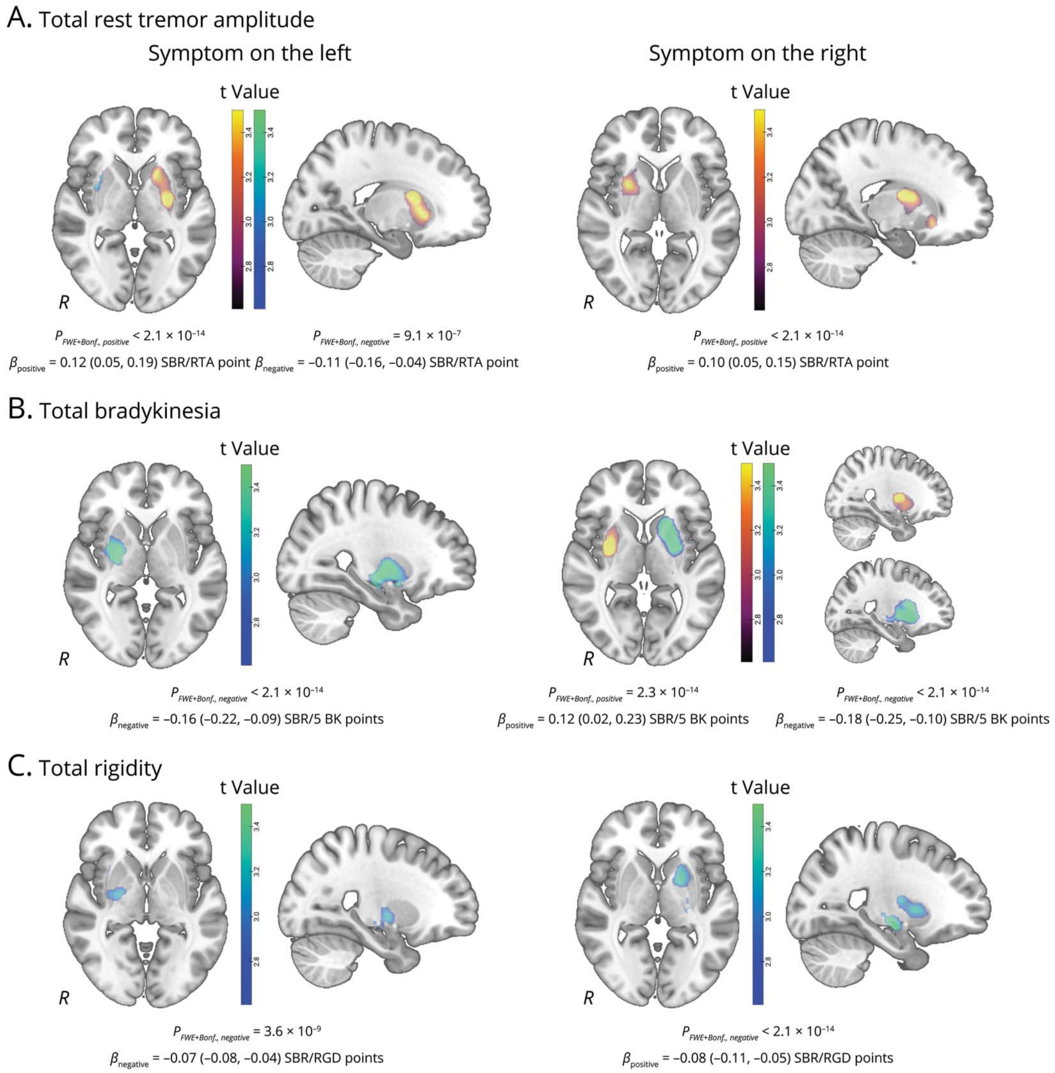
Abbreviations: L = left; LEDD = levodopa-equivalent daily dose; MDS-UPDRS-III = Movement Disorders Society Unified Parkinson's Disease Rating Scale, part III; MMSE = Mini-Mental State Examination; N = none; PD = Parkinson disease; R = right; S = symmetrical.
For the scalar variables, the median with 25th and 75th percentiles [in square brackets] are reported. Percentages of categorical variables are reported [in square brackets]. Differences of scalar variables were evaluated with 2-tailed Mann-Whitney *U* test and categorical variables with Fisher exact test. Statistically significant ($p < 0.05$) difference † between PD group and non-PD normal imaging group; ‡ between PD group and non-PD abnormal imaging group; * between non-PD normal imaging and non-PD abnormal imaging groups.
[a] Data missing.
[b] Terms "medicated" and "unmedicated" refer to patients receiving antiparkinsonian dopaminergic drugs.

additionally showed a limited region of negative association in the contralateral striatum and claustrum ($\beta_{mean} = -0.11$ [95% CI −0.16, −0.04] SBR units per 1 point, $p_{FWE + Bonf.} = 9.1 \times 10^{-7}$). Left-sided and right-sided bradykinesia showed associations with contralateral binding deficits ($\beta_{mean} = -0.16$ [95% CI −0.22, −0.09] and −0.18 [95% CI −0.25, −0.10] SBR units per 5 points, $p_{FWE + Bonf.} < 2.1 \times 10^{-14}$ and $< 2.1 \times 10^{-14}$, respectively) (Figure 1B). Right-sided bradykinesia also showed an association with higher ipsilateral binding ($\beta_{mean} = +0.12$ [95% CI +0.02, +0.23] SBR units per 5 points, $p_{FWE + Bonf.} = 2.3 \times 10^{-14}$). Left-sided and right-sided rigidity had associations with contralateral tracer binding deficit ($\beta_{mean} = -0.07$ [95% CI −0.08, −0.04] and −0.08 [95% CI −0.11, −0.05] SBR units per 1 point, $p_{FWE + Bonf.}$ 3.6×10^{-9} and $< 2.1 \times 10^{-14}$, respectively) (Figure 1C). These results remained consistent when adjusting for overall motor symptom severity, as assessed by the MDS-UPDRS-III total score (eFigure 3, A–C), but negative association with left rest tremor became insignificant (eFigure 3A). The composite bradykinesia-rigidity scores showed similar findings as bradykinesia alone (eFigure 3, D and E). In addition, comparison of the clusters associated with left and right rest tremor amplitude in this study with those identified in the PPMI data set revealed a substantial overlap volumes of 4096 mm^3 and 3504 mm^3, respectively (eFigure 4A).

The key associations between rest tremor amplitude and ipsilateral binding remained significant after additionally adjusting for DAT asymmetry index and MDS-UPDRS-III total score (eFigure 5, A and B). Only including unmedicated PD patients (n = 108), left-sided and right-sided rest tremor amplitude scores were significantly associated with higher [^{123}I]FP-CIT binding in the ipsilateral striatum ($p_{FWE} < 1 \times 10^{-16}$ and $p_{FWE} < 1 \times 10^{-16}$; with MDS-UPDRS-III as an additional covariate, $p_{FWE} < 1 \times 10^{-16}$ and $p_{FWE} < 1 \times 10^{-16}$, respectively) (eFigure 6, A and B).

Furthermore, left-sided and right-sided rest tremor severity index, calculated as the product of amplitude and constancy, had a significant association with ipsilateral DAT binding

Figure 1 Association of the Cardinal Motor Symptoms With [^{123}I]FP-CIT Binding in PD



The association of sidewise (A) total rest tremor amplitude, (B) total bradykinesia, and (C) total rigidity with voxel-wise [^{123}I]FP-CIT SBR in the right-handed patients with PD. The analyses of the association between binding and the clinical motor evaluation subscores were conducted adjusting for age, sex, the medication state, and levodopa-equivalent daily dose (only for medicated patients; interaction with medication state), with log-transformed SBR values. Rest tremor amplitude (A) showed a positive association with ipsilateral binding (left side rest tremor amplitude also a negative association with contralateral binding in a limited region), while bradykinesia showed (B) negative associations with contralateral binding (right side bradykinesia also a positive association with ipsilateral binding) and rigidity (C) showed negative associations with contralateral binding. Cluster-level FWE corrected *p* values, further corrected among all the contrasts and clusters tested ($p_{FWE + Bonf.}$) are shown below each image. $\beta_{mean, cluster}$ = the local strength of association between the cluster region mean SBR and the subscore at the score level nearest to mean symptom severity in the PD group. Negative association is indicated with blue-green color scale, and positive association with red-yellow color scale. BK = bradykinesia; FWE = family-wise error; PD = Parkinson disease; R = right; RGD = rigidity; RTA = rest tremor amplitude; SBR = specific binding ratio.

(β_{mean} = +0.13 [95% CI +0.06, +0.21] and +0.05 [95% CI +0.02, +0.08] SBR units per 4 points, $p_{FWE + Bonf.} = 2.1 \times 10^{-14}$ and 2.1×10^{-14}, respectively, with MDS-UPDRS-III as an additional covariate, $p_{FWE + Bonf.} < 2.1 \times 10^{-14}$ and $p_{FWE + Bonf.} < 2.1 \times 10^{-14}$) (Figure 2, eFigure 7). Left-sided rest tremor severity index was also associated with lower binding in a narrow region in the contralateral striatum (β_{mean} = −0.05 [95% CI −0.10, −0.004], $p_{FWE + Bonf.} = 0.017$) (Figure 2), but this association was not significant when the model was additionally adjusted for MDS-UPDRS-III-score (eFigure 7).

Overall rest tremor severity index was associated with higher binding in the right anterior striatum (β_{mean} = +0.11 [95% CI +0.06, +0.16] SBR per 4 points, $p_{FWE + Bonf.} < 2.1 \times 10^{-14}$; with MDS-UPDRS-III as an additional covariate, $p_{FWE + Bonf.} < 2.1 \times 10^{-14}$) (eFigure 8A). Overall rest tremor constancy was associated with higher binding in the left caudate (β_{mean} = +0.07 [95% CI +0.02, +0.12] SBR per point; $p_{FWE} = 0.006$) and with MDS-UPDRS-III as an additional covariate, with higher binding in the left and right caudates (β_{mean} = +0.10 [95% CI +0.03, +0.18] and β_{mean} = +0.07 [95% CI +0.03, +0.12] SBR per point; $p_{FWE + Bonf.} = 4.0 \times 10^{-4}$ and $p_{FWE + Bonf.} = 0.007$) (eFigure 8B).

Of other tremor measures, left postural tremor of the hand was associated with higher ipsilateral and lower contralateral binding (β_{mean} = +0.18 [95% CI +0.09, +0.30] and −0.19 [95% CI −0.25, −0.12] SBR per point; $p_{FWE + Bonf.} = 1.1 \times 10^{-4}$ and $<2.1 \times 10^{-14}$, respectively; with MDS-UPDRS-III as an additional covariate, $p_{FWE + Bonf.} = 2.0 \times 10^{-6}$ and $p_{FWE + Bonf.} = 7.0 \times 10^{-14}$) (eFigure 9, A and B). Right postural tremor was not significantly associated with binding. Left kinetic tremor and right kinetic tremor of the hands were associated with higher ipsilateral binding in the striatum (β_{mean} = +0.21 [95% CI +0.10, +0.35] and +0.12 [95% CI +0.004, +0.25] SBR per point; $p_{FWE + Bonf.} = 1.3 \times 10^{-11}$ and $<2.1 \times 10^{-14}$, respectively; with MDS-UPDRS-III as an additional covariate, $p_{FWE + Bonf.} < 2.1 \times 10^{-14}$ and $p_{FWE + Bonf.} < 2.1 \times 10^{-14}$) (eFigure 9, C and D). However, these findings did not replicate in the PPMI data, as only postural tremor was consistently associated with higher ipsilateral binding on both sides and only when adjusted with MDS-UPDRS-III total score (eFigure 10).

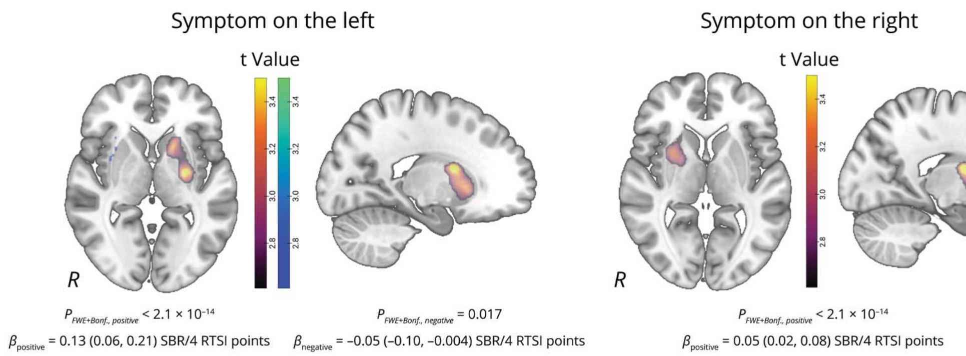
In the ROI analyses, scores of rest tremor amplitude on both sides were significantly associated with higher ipsilateral striatal DAT binding (Table 2), whereas scores of bradykinesia and rigidity on both sides correlated with contralateral striatal binding deficits (Table 2). In the analyses with ROI SBR values extracted from the PPMI analysis cluster areas adjusted for age, sex, and MDS-UPDRS-III total score, significant associations were observed for both left-sided and right-sided rest tremor amplitude scores (β_{mean} = +0.16 [95% CI +0.06, +0.26] and +0.15 [95% CI +0.07, +0.24], respectively; $p < 0.001$ for both).

Excluding patients without rest tremor on the side of interest, the associations of left-sided and right-sided rest tremor amplitude scores with binding in the associated areas were still statistically significant (n = 49, β_{mean} = +0.20 [95% CI +0.03, +0.40], $p = 0.018$, and n = 52, β_{mean} = +0.17 [95% CI +0.02, +0.33], $p = 0.021$, respectively) (Figure 3). The results of left-sided and right-sided rest tremor amplitude also remained significant when also DAT asymmetry index was added as a covariate in the model (β_{mean} = +0.18 [95% CI +0.03, +0.35], $p = 0.011$, and β_{mean} = +0.12 [95% CI +0.02, +0.22], $p = 0.015$, respectively).

Non-PD Patients

Among the patients with abnormal DAT SPECT imaging results and diagnosis other than PD, no significant associations were observed between left-sided or right-sided rest

Figure 2 Association of Rest Tremor Severity Index With [^{123}I]FP-CIT Binding in PD



The association of side-wise rest tremor severity index with voxel-wise [^{123}I]FP-CIT SBR in the right-handed patients with PD. The analyses of the association were conducted adjusting for age, sex, the medication state, and levodopa-equivalent daily dose (only for medicated patients; interaction with medication state), with log-transformed SBR values. Cluster-level FWE corrected p values, further corrected among all the contrasts and clusters tested ($p_{FWE + Bonf.}$), are shown below each image. β = the local strength of association between the cluster region mean SBR and the subscore at the score level nearest to mean symptom severity in the PD group. Negative association is indicated with blue-green color scale and positive association with red-yellow color scale. FWE = family-wise error; PD = Parkinson disease; R = right; SBR = specific binding ratio.

Table 2 Robust Regression Models of Original Region-of-Interest SBR Values and Main Parkinsonian Motor Symptoms in PD Patients

	Left total bradykinesia	Left total rigidity	Left total rest tremor amplitude	Right total bradykinesia	Right total rigidity	Right total rest tremor amplitude
Region-of-interest SBR values from the original imaging evaluation	**β coefficient (SBR/5 points)**	**β coefficient (SBR/point)**	**β coefficient (SBR/point)**	**β coefficient (SBR/5 points)**	**β coefficient (SBR/point)**	**β coefficient (SBR/point)**
Caudate (left)	−0.05 [−0.15, 0.05]	−0.04 [−0.09, 0.02]	0.10 [0.02, 0.20]†	−0.20 [−0.30, −0.09]‡	−0.09 [−0.13, −0.04]‡	0.06 [−0.00, 0.13]
Anterior putamen (left)	−0.04 [−0.15, 0.08]	−0.03 [−0.08, 0.03]	0.08 [0.02, 0.16]†	−0.20 [−0.31, −0.08]†	−0.08 [−0.13, −0.03]†	0.06 [0.01, 0.12]*
Posterior putamen (left)	−0.00 [−0.08, 0.08]	−0.02 [−0.05, 0.01]	0.08 [0.03, 0.13]‡	−0.18 [−0.27, −0.09]‡	−0.08 [−0.10, −0.04]‡	−0.01 [−0.05, 0.03]
Caudate (right)	−0.18 [−0.28, −0.07]†	−0.09 [−0.15, −0.02]*	−0.03 [−0.09, 0.04]	0.00 [−0.09, 0.10]	−0.02 [−0.08, 0.05]	0.14 [0.08, 0.20]‡
Anterior putamen (right)	−0.28 [−0.40, −0.14]‡	−0.09 [−0.14, −0.04]‡	−0.08 [−0.13, −0.01]*	0.04 [−0.08, 0.16]	−0.02 [−0.07, 0.04]	0.15 [0.08, 0.23]‡
Posterior putamen (right)	−0.23 [−0.33, −0.12]‡	−0.09 [−0.11, −0.06]‡	−0.05 [−0.09, −0.00]*	0.02 [−0.05, 0.10]	−0.01 [−0.04, 0.03]	0.11 [0.06, 0.17]‡

Abbreviations: LEDD = levodopa-equivalent daily dose; PD = Parkinson disease; RTA = rest tremor amplitude; SBR = specific binding ratio.
Robust regression models, age, sex, medication state during examination (medicated/unmedicated) and LEDD (if medicated) as additional covariates. Local slope of the association, confidence intervals [in brackets] at the mean symptom score level in the PD group, and their statistical significance in robust regression models of log-transformed original region-of-interest SBR values and main parkinsonian motor symptoms (left and right total bradykinesia, rigidity and rest tremor amplitude) in the PD group, with age, sex, medication state during examination (medicated/unmedicated), and LEDD (if medicated) as additional covariates. Uncorrected **p* < 0.05, †*p* < 0.01, ‡*p* < 0.001.

tremor amplitude, rest tremor consistency, rest tremor severity indices, bradykinesia, or rigidity, and striatal tracer binding in any of the voxel-wise analyses. Left kinetic tremor showed an association with stronger binding in the contralateral anterior striatum ($\beta_{mean} = +0.25$ [95% CI +0.06, +0.48] SBR per 1 point; $p_{FWE + Bonf.} = 0.002$; with MDS-UPDRS-III as an additional covariate, $p_{FWE + Bonf.} = 0.006$) (eFigure 11).

Among the patients with normal DAT SPECT imaging results, right-sided total rest tremor amplitude showed an association with increased binding in the contralateral anterior striatum ($\beta_{mean} = +0.13$ [95% CI +0.04, +0.23] SBR per 1 point; $p_{FWE + Bonf.} = 0.019$; with MDS-UPDRS-III as an additional covariate, $p_{FWE + Bonf.} = 1.5 \times 10^{-6}$) (eFigure 12A). In addition, several rest tremor measures had associations with binding but only when adjusted for MDS-UPDRS-III total score: left-sided rest tremor amplitude was associated with weaker binding in the contralateral posterior striatum ($\beta_{mean} = -0.07$ [95% CI −0.12, −0.01]; $p_{FWE + Bonf.} = 0.049$) (eFigure 12B). Right-sided rest tremor severity index had an association with stronger binding in the left caudate and pallidofugal areas ($\beta_{mean} = +0.15$ [95% CI +0.07, +0.23] SBR per 4 points; $p_{FWE + Bonf.} = 9.6 \times 10^{-6}$) (eFigure 12C). Overall rest tremor severity index was also associated with stronger binding in the left caudate ($\beta_{mean} = +0.15$ [95% CI +0.07, +0.24] SBR per 4 points; $p_{FWE + Bonf.} < 2.1 \times 10^{-14}$) (eFigure 12D).

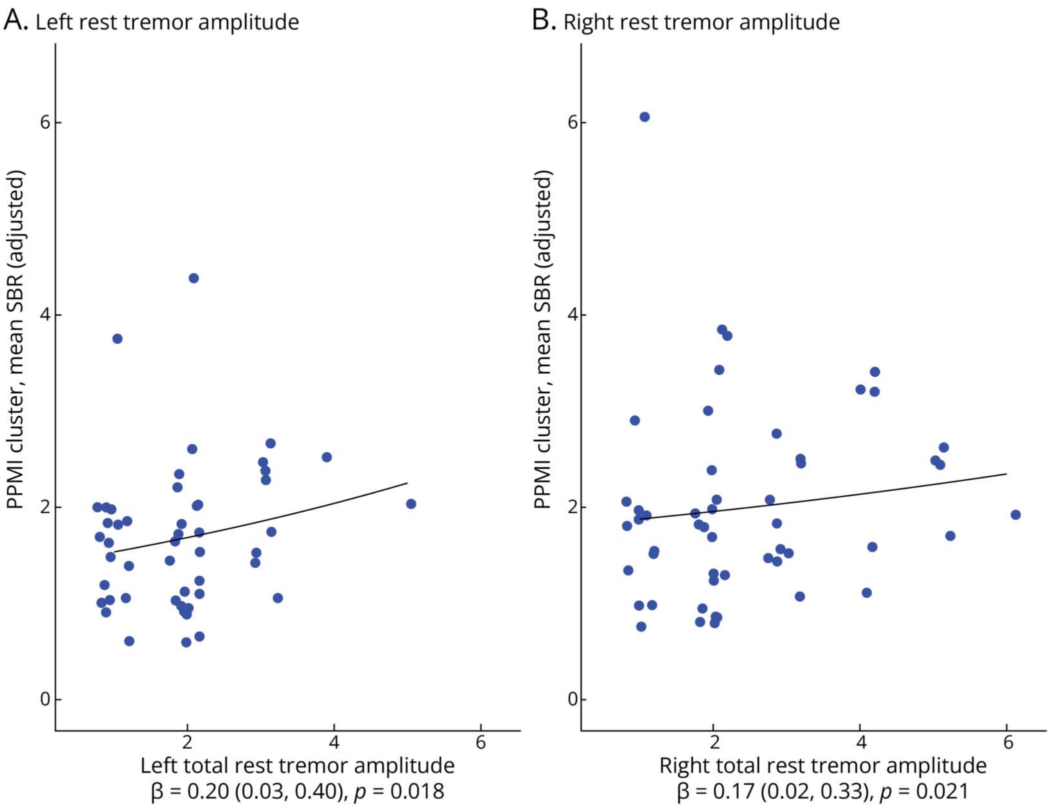
Considering other measures than those of rest tremor, left postural tremor was associated with increased binding in the left striatum and globus pallidum and right striatum ($\beta_{mean} =$ +0.23 [95% CI +0.09, +0.38] and +0.27 [95% CI +0.10, +0.46], $p_{FWE + Bonf.} = 5.6 \times 10^{-5}$ and 0.006), but when adjusted for MDS-UPDRS-III total score, only in the left globus pallidum ($\beta_{mean} = +0.21$ [95% CI +0.07, +0.36], $p_{FWE + Bonf} = 0.006$) (eFigure 12E). In addition, left-sided rigidity was linked to lower binding in the contralateral caudate and pallidum ($\beta_{mean} = -0.10$ [95% CI −0.16, −0.01]; $p_{FWE + Bonf.} = 0.006$), but not if corrected for MDS-UPDRS-III total score (eFigure 12F). Instead, left-sided bradykinesia-rigidity composite score was associated with lower binding in the contralateral anterior striatum ($\beta_{mean} = -0.21$ [95% CI −0.27, −0.14], $p_{FWE} = 1.2 \times 10^{-8}$) and, when adjusted for MDS-UPDRS-III total score, showed a stronger association with lower binding bilaterally in the pallidofugal areas ($\beta_{mean} = -0.22$ [95% CI −0.27, −0.14], $p_{FWE} < 2.1 \times 10^{-14}$) (eFigure 12 G). No significant associations with the examined motor symptoms were observed otherwise.

Discussion

In this study, we validated the association between rest tremor amplitude and higher ipsilateral striatal DAT binding in an independent, clinical sample of patients with PD. This association was not observed in non-PD patients with either normal or abnormal striatal dopaminergic function, demonstrating robustness of the link between rest tremor amplitude and ipsilateral DAT binding in PD.

Previous evidence suggests that the emergence of rest tremor may be associated with preceding changes in integrative brain states affecting both hemispheres, which may fluctuate under

Figure 3 The Association of Rest Tremor Amplitude and [^{123}I]FP-CIT Binding in the PPMI-Derived, Associated Regions in the Unmedicated PD Patients, Excluding Patients With No Rest Tremor on the Side of Interest



The association of sidewise total rest tremor amplitude with mean [^{123}I]FP-CIT SBR in the regions derived from the PPMI, with robust regression models adjusting for age, sex and MDS-UPDRS-III total score. Only unmedicated, right-handed patients with PD were included in these analyses, corresponding to the region-defining analyses, and additionally patients with no rest tremor on the side of interest were excluded (leaving 49 patients with left (A) and 52 patients with right (B) rest tremor). β = the strength of association between the region mean SBR and the subscore at rest tremor amplitude score 1; MDS-UPDRS-III = Movement Disorders Society Unified Parkinson's Disease Rating Scale, part III; PD = Parkinson disease; PPMI = Parkinson's Progression Markers Initiative; SBR = specific binding ratio.

cognitive load.[32] However, earlier studies attempting to unravel the connection between tremor and dopaminergic function in PD have often investigated multiple tremor types together, yielding incongruous results.[2,3,5-7,33] The diverse neurobiological mechanisms underlying different tremor subtypes may explain why the dopaminergic correlates of rest tremor have remained partially unrecognized. Recent independent findings in a separate cohort of 60 PD patients using another presynaptic dopaminergic tracer targeting the vesicular monoamine transporter 2 support the specific association between rest tremor and increased striatal dopamine function.[34] Thus, the positive link between rest tremor and presynaptic ipsilateral dopaminergic function has now been observed in 3 distinct PD patient populations.

The paradox regarding rest tremor and dopaminergic function in PD arises from the fact that while nigrostriatal dopamine depletion may be a prerequisite for developing rest tremor, the expression of tremor appears to occur independently of this degeneration.[9] Instead of the striatum, there are indications that pallidal dopaminergic depletion may play a significant role in rest tremor generation.[7] Our findings further complicate this picture by revealing links between dopaminergic function in the ipsilateral striatum. Notably, pallidal neurons exert distinct and robust effects on the striatum, with over 25% of striatal interneurons receiving direct synaptic input from arkypallidal cells in the pallidum.[35] Thus, it is possible that the previously observed findings related to pallidal dysfunction in tremulous PD patients are associated with the present results, warranting further investigation.

We interpret increased ipsilateral DAT binding not as evidence of an increased number of dopaminergic neurons, but rather as a possible functional activity change, possibly due to compensatory activation. The mechanism underlying the observed association between ipsilateral higher DAT binding and greater rest tremor amplitude in PD remains unclear based on this study alone. However, potential pathways that could contribute to this association include interhemispheric cortical,[11] crossing cortico-striatal[11] and nondecussating dentatorubrothalamic[14] connections, while tremor oscillations themselves may originate within the striato-pallidal and cerebello-thalamo-cortical circuits.[9] Similar connection of bilateral cortical activity with unilaterally manifesting tremor in essential tremor has been recognized recently.[36] Previous observations of ipsilateral tremor alleviation with unilateral DBS also support the involvement of both hemispheres in the emergence of rest tremor,[10] while the beneficial effects of dopaminergic medications on parkinsonian tremor support the involvement of the dopaminergic system.[8,15] Nevertheless, it is vital to note that no functional imaging data beyond DAT SPECT were used in this study.

In the non-PD patients with normal scans, we observed a negative association between [^{123}I]FP-CIT binding and rigidity, particularly in the caudate nucleus. These additional results suggest that even in symptomatic patients with striatal DAT binding in normal range, motor symptoms may be relevantly linked to dopaminergic function, especially in the caudate nucleus, which has a role in de novo motor learning, goal-directed motor behavior,[37] and gait.[38] Further research is warranted to investigate the association between motor symptom severity and dopamine function in individuals with motor symptoms but normal striatal DAT binding.

[^{123}I]FP-CIT SPECT is the most common molecular imaging method used in the differential diagnostics of unclear parkinsonism,[39] with the best diagnostic predictive value achieved in distinguishing individuals with striatal dopaminergic degeneration from those with essential tremor,[40] drug-induced parkinsonism, and vascular parkinsonism.[41,42] However, its diagnostic utility is weaker in atypical parkinsonism syndromes with nigrostriatal defects, such as multiple system atrophy and progressive supranuclear palsy, which may be clinically indistinguishable from PD in the early stages.[43] Although the relationship between motor features and molecular imaging markers could, in principle, inform diagnostic evaluation, such applications would require substantially more evidence across different movement disorders. At present, our findings primarily support a pathophysiologic link between tremor amplitude and dopaminergic function.

This study has certain limitations that should be acknowledged. First, the image registration workflow did not incorporate separate anatomical imaging, and the number of patients with PD was smaller than in our previous study using PPMI data. Because [^{123}I]FP-CIT SPECT has limited anatomical resolution, inherently smooth signal characteristics, and relatively low signal-to-noise ratio, the combination of these technical limitations with the commonly applied smoothing procedure results in some spillover into adjacent white matter areas, which must be considered when interpreting the results. If these limitations had affected the results relevantly, their effect would most likely have been to bias the analysis toward false-negative findings or to produce spatial misalignments. The latter possibility is unlikely, however, given the accurate alignment observed with the PPMI data. Second, the spectrum of diagnoses other than PD was varied, and no definitive conclusions regarding the specific differences between PD and other, separate types of parkinsonism syndromes in terms of the association of molecular imaging and clinical findings, can be drawn based on the data. Third, a selection bias is possible since the patients represent those who were referred for SPECT imaging due to diagnostic difficulties. Thus, although the sample was derived from a clinical population, it may not fully represent the general patient population with parkinsonism. Fourth, in the non-PD groups, rest tremor was less frequent, reducing sensitivity to detect tremor-binding associations. Moreover, referral-based selection and diagnostic heterogeneity in these groups limit conclusions about the specificity of the tremor-DAT association for PD.

Our study provides evidence supporting the association between rest tremor amplitude and greater ipsilateral striatal DAT binding in PD within a clinical sample. Further electrophysiologic, functional MRI, molecular imaging, and connectivity studies are needed to elucidate the mechanisms underlying this finding and to clarify its relevance for the pathophysiology of rest tremor in PD.

Author Contributions

K.J. Niemi: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. E. Jaakkola: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. E.M. Myller: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M.R.E. Eklund: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Nuuttila: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. T. Mertsalmi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. K.-M. Murtomäki: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. R. Levo: major role in the acquisition of data. T. Noponen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. T. Ihalainen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F. Scheperjans: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. Joutsa: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. V. Kaasinen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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