RESEARCH ARTICLE

Rest Tremor in Parkinson's Disease Is Associated with Ipsilateral Striatal Dopamine Transporter Binding

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ABSTRACT: Background: The cardinal motor symptoms of Parkinson's disease (PD) include rigidity, bradykinesia, and rest tremor. Rigidity and bradykinesia correlate with contralateral nigrostriatal degeneration and striatal dopamine deficit, but association between striatal dopamine function and rest tremor has remained unclear.
Objective: The aim of this study was to investigate the possible link between dopamine function and rest tremor using Parkinson's Progression Markers Initiative dataset, the largest prospective neuroimaging cohort of patients with PD.
Methods: Clinical, [^{123}I]N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ([^{123}I]FP-CIT) single photon emission computed tomography (SPECT), and structural magnetic resonance imaging data from 354 early PD patients and 166 healthy controls were included in this study. We employed a novel approach allowing nonlinear registration of individual scans accurately to a standard space and voxelwise analyses of the association between motor symptoms and striatal dopamine transporter (DAT) binding.
Results: Severity of both rigidity and bradykinesia was negatively associated with contralateral striatal DAT binding ($P_{FWE} < 0.05$ [FWE, family-wise error corrected]). However, rest tremor amplitude was positively associated with increased ipsilateral DAT binding ($P_{FWE} < 0.05$). The association between rest tremor and binding remained the same controlling for Hoehn & Yahr stage, Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III score, bradykinesia–rigidity score, or motor phenotype. The association between rest tremor and binding was independent of bradykinesia-rigidity and replicated using 2-year follow-up data ($P_{FWE} < 0.05$).
Conclusion: In agreement with the existing literature, we did not find a consistent association between rest

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Relevant conflicts of interest/financial disclosures: K.J.N. reports research grants from the Finnish Parkinson Foundation, the Finnish Cultural Foundation (Pertteli Aaltonen Fund), Sigrid Juselius Foundation, the Finnish Neurological Society, the University of Turku, the University of Turku Foundation, Turku University Hospital, TYKS Foundation, and Satakunta Wellbeing Services County; conference travel support from the Finnish Parkinson Foundation, the Finnish Neurological Society, the Finnish Society of Nuclear Medicine, the Finnish Cultural Foundation (Pertteli Aaltonen Fund), Turku University Hospital, the University of Turku, and Merck; and minor stock ownership in CareCloud, GlaxoSmithKline, Modulight, Nightingale Health, and Physicians Realty Trust. J.J. reports research grants from the Finnish Medical Foundation, Sigrid Juselius Foundation, the Finnish Foundation for Alcohol Studies, the University of Turku, and Turku University Hospital; conference travel support from Insightec, AbbVie, and Abbott; consulting fees from Summaryx and Adamant Health; and lecturer honoraria from Lundbeck. Other authors have no conflicts of interest to report.

Funding agencies: This research was supported by the Finnish Parkinson Foundation, Turku University Hospital, Satakunta Wellbeing Services County, and Sigrid Juselius Foundation.

Received: 11 March 2024; **Accepted:** 7 August 2024

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29997

tremor and contralateral dopamine defect. However, our results demonstrate a link between rest tremor and increased or less decreased ipsilateral DAT binding. Our findings provide novel information about the association between dopaminergic function and parkinsonian rest tremor.

Key Words: Parkinson's disease; motor symptoms; rest tremor; [^{123}I]FP-CIT SPECT; voxelwise

Parkinson's disease (PD) is characterized by nigrostriatal degeneration,[1,2] and the cardinal motor symptoms include rigidity, bradykinesia, and rest tremor.[3] The most commonly used molecular brain imaging technique in clinical practice is [^{123}I]FP-CIT SPECT, which shows a clear, progressive signal loss in the striatum in PD.[2] Clinically, [^{123}I]FP-CIT is widely used for differential diagnostics between PD and conditions not associated with nigrostriatal degeneration.[2] [^{123}I]FP-CIT has also been considered as a possible proxy for disease progression, which however has been questioned more recently by studies showing lack of correlation between striatal [^{123}I]FP-CIT binding and nigrostriatal cell loss, at least in the more advanced stages of the disease.[4–7]

Of the cardinal motor symptoms, bradykinesia and rigidity show a negative correlation with contralateral striatal presynaptic dopamine function and, accordingly, patients with akinetic-rigid dominant symptoms show more pronounced dopaminergic deficit compared to tremor dominant disease.[8–12] However, most studies have failed to conclusively demonstrate a similar association between presynaptic dopamine function and rest tremor severity, leaving the dopaminergic contribution to rest tremor unclear.[8,9,13–15] This is particularly relevant as trials using dopamine imaging, such as [^{123}I]FP-CIT, as an outcome measure may be confounded by the lack of association with one of the three cardinal motor symptoms of PD, substantially contributing to the main clinical outcome measure, Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor score. The lack of consistent findings between presynaptic dopamine function and tremor is unclear but may be related to lack of true association or to false-negative findings caused by, for example, variability in used tremor metrics, weaker association compared to bradykinesia and rigidity, or spatially more restricted localization, covering only a part of the commonly used anatomical regions of interest (ROIs).

The Parkinson's Progression Markers Initiative (PPMI) is the most comprehensive observational, longitudinal study including [^{123}I]FP-CIT SPECT and structural brain imaging data in patients with PD.[16] The PPMI data provide an excellent opportunity to investigate the clinical correlates of dopaminergic function in early PD. Most studies using the [^{123}I]FP-CIT SPECT data of PPMI have relied on visual or anatomical ROI analyses, or investigated methods for improving diagnostic reliability.[14,16–22] The reasons for the lack of more detailed voxelwise analyses using [^{123}I]FP-CIT imaging data include the low spatial information and relatively poor signal-to-noise ratio in SPECT scans, preventing accurate registration to a standard space and limiting statistical power.

In this study, we utilized the PPMI data to investigate the association between striatal presynaptic dopamine function and cardinal motor symptoms of PD. To achieve this, we first developed an image preprocessing workflow for linear registration of [^{123}I]FP-CIT SPECT images to the T1-weighted magnetic resonance imaging (MRI), which were used to compute the nonlinear registration to the Montreal Neurological Institute (MNI) standard space. Next, we conducted voxelwise analyses to investigate the association between rest tremor and striatal [^{123}I]FP-CIT binding, carefully controlling for other disease-related factors, and replicated these analyses with data from two different time points to shed light on dopaminergic contribution to rest tremor.

Patients and Methods

Study Sample

Data used in the preparation of this article were obtained from the PPMI database (www.ppmi-info.org/access-data-specimens/download-data). For up-to-date information on the study, visit www.ppmi-info.org. The available clinical characteristics and T1-weighted brain MRI and [^{123}I]FP-CIT SPECT scans of 166 healthy controls (HC group) and 360 patients with idiopathic PD (PD group) from the PPMI cohort baseline from 2010 to 2013 were included in the present study (Fig. 1). Patients with SWEDD (scan without evidence of dopaminergic deficit) were excluded, because the number of these patients was relatively small and the underlying pathology in this patient group may differ from the patients with PD. To repeat the analyses at a later disease stage, similar data from a 2-year follow-up time point with a sufficient number of patients were downloaded for the same patients with PD, as available ($n = 275$, right handed $n = 220$). The HC group was not included in the follow-up visits with repeated imaging in the PPMI data collection.

Standard Protocol Approvals, Registrations, and Patient Consents

The PPMI study protocol was registered on June 8, 2010 (ClinicalTrials.gov identifier: NCT01141023). The study was approved by the institutional review

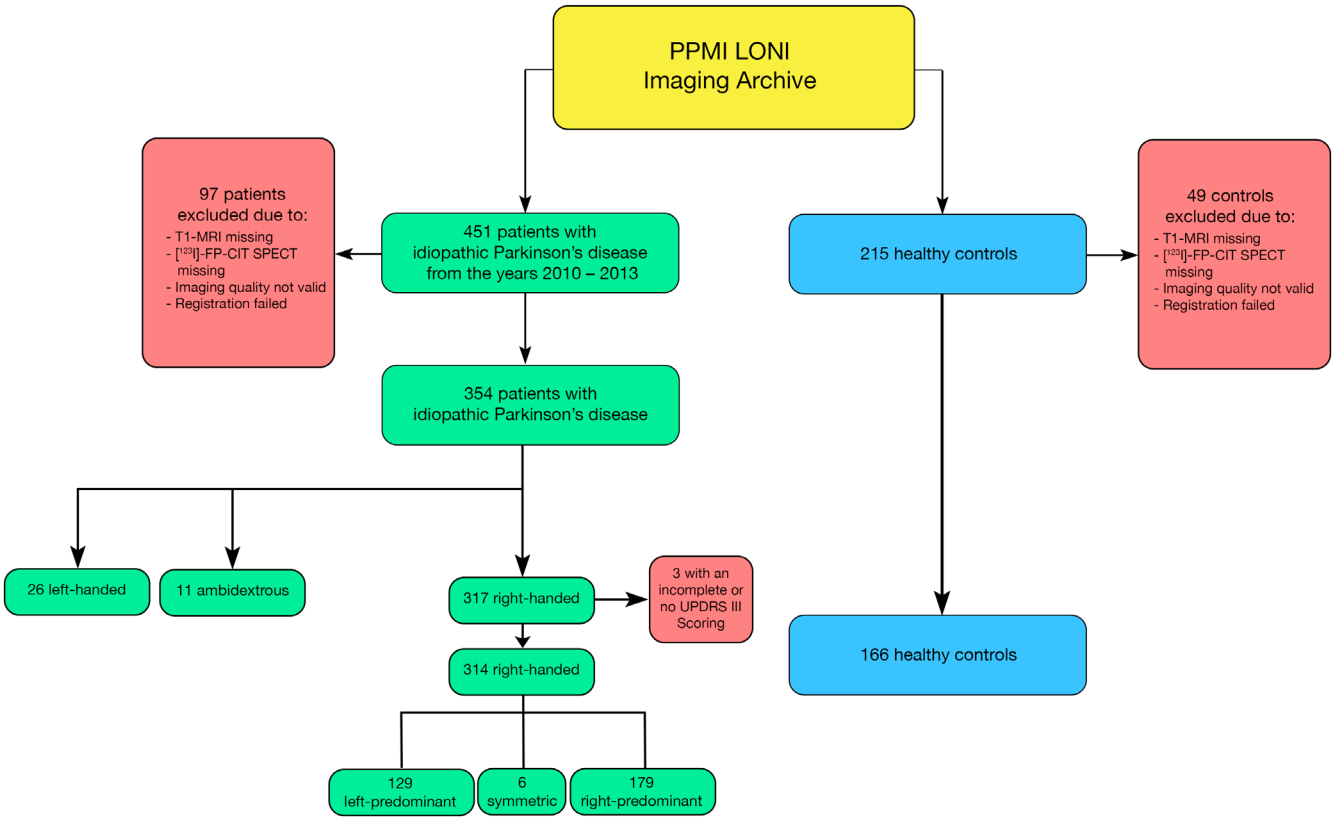

FIG. 1. Study sample selection. The group comparisons were run with all patients with Parkinson's disease (PD) (n = 354) and healthy controls (n = 166). Correlations with cardinal motor symptoms were run with right-handed patients only (n = 314). [Color figure can be viewed at wileyonlinelibrary.com]

board at each research site. All participants provided written informed consent.

Clinical Data

Demographic and clinical data were obtained from the PPMI database, including age, duration of symptoms, and dopaminergic medications in use at baseline and 2-year follow-up. Total MDS-UPDRS-III score and rigidity, bradykinesia, and rest tremor amplitude subscores on each side (total and upper limb) were calculated as sum of the scores of items included, and rest tremor severity indices (SI) as the product of the side-wise rest tremor amplitude scores and consistency, as described in Table S1. Motor phenotypes (tremor dominant, indeterminate, and postural instability and gait disorder) were determined as described earlier.[23] In addition, combined scores of bradykinesia–rigidity were calculated as the sum of the corresponding scores (Table S1).

Image Preprocessing

The preprocessing workflow consisted of (1) linear registration to the individual T1 MRI, (2) partial volume error (PVE) correction, (3) nonlinear transformation to the MNI standard space (voxel size, $1 \times 1 \times 1\ mm^3$) using the warp field computed from nonlinear T1 MRI to MNI registration, and (4) and Gaussian kernel post-smoothing ($\sigma = 2$; full width at half maximum 4.7 mm) applied after spatial normalization. The workflow is described in detail in Figure S1. Finally, the voxelwise specific binding ratios (SBR) for each of the [^{123}I]FP-CIT SPECT images were calculated using the bilateral occipital cortex as the reference region:

$$SBR_{i,j,k} = \frac{I_{i,j,k}}{I_{mean,occipital}} - 1 \qquad (1)$$

The registration results were inspected stepwise visually: (1) linearly registered [^{123}I]FP-CIT SPECT image and T1-weighted MRI in the native space, (2) nonlinearly registered MRI and the MNI template in the MNI space, and (3) the nonlinearly registered individual [^{123}I]FP-CIT SPECT image and MNI template in the MNI space (Supplementary Methods, Figs. S2 and S3). Registration failed in 6 PD patients at baseline and 7 at follow-up.

Voxelwise Analyses of DAT Binding in Parkinson's Disease

All voxelwise analyses were performed with SPM12[24] using the general linear model running on

MATLAB R2021b in Ubuntu Linux 20.04 (Zorin OS-branch). For descriptive purposes, the group comparisons and correlations with symptom severity were conducted across the whole brain to identify all brain regions showing SBR abnormalities in PD. For all subsequent analyses investigating the association between the cardinal motor symptoms and striatal DAT binding, a 3-mm-dilated striatal mask from Harvard-Oxford Subcortical Atlas was used to restrict these 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.[21] Age and sex were added as nuisance covariates to all analyses. Stringent voxel-level family-wise error (FWE) corrected *P* values <0.05 were considered significant to avoid false positives for all voxelwise analyses, correcting for multiple comparisons problem for the search volume used in the analyses (whole brain or striatum).

Specific binding ratio abnormalities in PD were investigated by comparing the PD group to the control group, including all subjects with successfully preprocessed imaging data ($n_{HC} = 166$, $n_{PD} = 354$). Of the 354 PD patients with successfully preprocessed imaging data, 317 were right-handed, 26 left-handed, and 11 ambidextrous. To exclude the effects of handedness and investigate SBR abnormalities based on the predominant side of the symptoms, right-handed left-predominant (LPD_{RH}, n = 129) and right-predominant (RPD_{RH}, n = 179) PD subgroups with complete MDS-UPDRS-III scores (total n = 308) were compared with the HC group, and with each other in the main analyses (9 right-handed patients were excluded from the analyses because of incomplete MDS-UPDRS-III scores [n = 3] or symmetrical symptom onset [n = 6]). The associations between SBR and Hoehn & Yahr (H&Y) grade, MDS-UPDRS-III total score, left-side MDS-UPDRS-III total score, and right-side MDS-UPDRS-III total score were evaluated using separate linear models only in the PD patients.

Associations between Striatal DAT Binding and Cardinal Motor Symptoms

First, the associations between DAT binding and left-side and right-side total extremity rigidity, bradykinesia, and rest tremor amplitude were investigated using separate linear models. These analyses were repeated for upper extremity scores, as the lower limb scores in early PD may be more susceptible to be influenced by non-PD symptoms and signs. The findings were confirmed by adding (1) H&Y grade, (2) H&Y grade and MDS-UPDRS-III total score, (3) H&Y grade and bradykinesia–rigidity total score, (4) H&Y grade and Parkinson phenotype, and (5) Montreal Cognitive Assessment (MoCA) score as covariates. These analyses were repeated with data from the 2-year follow-up visits, with successfully preprocessed imaging data (n = 268, right-handed n = 216).

Second, to ensure that the findings on rest tremor are not driven by patients without rest tremor, multivariate regression analyses were repeated including only right-handed patients with rest tremor (with complete MDS-UPDRS-III scores, regardless of symmetry of symptom onset), separately at baseline and 2-year follow-up (n = 220 and 132, respectively).

Multivariate Analyses of DAT Binding and Cardinal Motor Symptoms

To investigate if the effect of rest tremor was independent of bradykinesia-rigidity on the same side, the rest tremor effect was confirmed by adding bradykinesia-rigidity as a covariate (left and right sides of the body were analyzed separately). To investigate the main clinical symptoms driving the association with striatal SBRs, both left- and right-side rest tremor and bradykinesia rigidity were included in the same model. All these analyses were conducted separately for both baseline and 2-year follow-up data. Finally, this analysis was repeated with each of the PPMI Core Lab ROI SBRs to illustrate the contribution of each cardinal symptom to ROI-level DAT binding and provide reference to previous studies applying only ROI data.

Statistics

Analyses with clinical and ROI data were performed using R, version 4.1.2, running on macOS 10.15. The group comparisons were conducted using two-sided Mann-Whitney *U* test or Fisher's exact test, as appropriate. Correlation analyses were conducted using Spearman's rank-order correlation coefficient. Multivariate linear regression was used to investigate the independence of the effects and factors predominantly associated with striatal SBRs. The contributions of each symptom entity to the total model R^2 were estimated using proportional marginal variance decomposition (PMVD).[25]

Results

Demographic and Clinical Data

There were no significant differences between the HC and the PD groups in age, sex, education, or handedness. As expected, MoCA, H&Y, and MDS-UPDRS-III motor scores were significantly different between the groups (Table 1). The clinical data of the 2-year follow-up visits are presented in Table S2.

In the PD group, 89.5% were right-handed (n = 317), 7.3% (n = 26) were left-handed, and 3.1% were ambidextrous (n = 11). All main analyses involving laterality of the cardinal motor symptoms were

TABLE 1 *Demographic and clinical data*

Characteristics	Groups			PD subgroups		
	HC (n = 166)	PD (n = 354)	*P* value	RPD (n = 196)	LPD (n = 151)	*P* value
Age (y)	61.3 [54.6, 68.4]	62.2 [54.8, 69.0]	0.313	62.8 [57.4, 69.1]	60.7 [52.3, 68.1]	0.031*
Gender (male/female) [male percentage]	105/61 [63.3%]	227/127 [64.1%]	0.845	134/62 [68.4%]	87/64 [57.6%]	0.043*
Handedness (right/left/ambidextrous) [right percentage]	137/20/9 [82.5%]	317/26/11 [89.5%]	0.081	181/10/5 [92.3%]	130/16/5 [72.2%]	0.136
Education years	16 [14, 18]	16 [14, 18]	0.087	16 [14, 18]	16 [14, 18]	0.941
MoCA total score	28 [27, 29]	28 [26, 29]	<0.0001*	28 [26, 29]	28 [26, 29]	0.399
Age at onset (y)	–	60.1 [52.6, 67.3]	–	60.4 [55.0, 67.8]	58.9 [50.3, 66.5]	0.047*
Time from onset to diagnosis (mo)	–	11.0 [5.9, 23.0]	–	11.5 [7.0, 23]	11.0 [5.0, 22.0]	0.443
Disease duration (mo)	–	18.5 [11.1, 29.5]	–	19.0 [10.9, 30.6]	18.3 [11.5, 28.3]	0.618
With total MDS-UPDRS-III information	**(n = 164)**	**(n = 349)**		**(n = 194)**	**(n = 148)**	
Hoehn & Yahr stage						
0	164	0	<0.0001*	0	0	0.042*
1	0	154		96	58	
2	0	193		98	88	
3	0	2		0	2	
4	0	0		0	0	
5	0	0		0	0	
MDS-UPDRS-III total score	0.0 [0.0, 1.0]	18.0 [13.0, 24.0]	<0.0001*	17.0 [12.3, 23.0]	20.0 [14.0, 26.0]	0.021*
Tremor-dominant/Indeterminate/PIGD phenotype [%]						
TD	–	222 [62.7%]	–	126 [64.9%]	93 [62.8%]	0.686
IND	–	49 [13.8%]	–	28 [14.4%]	19 [12.8%]	
PIGD	–	77 [21.8%]	–	40 [20.6%]	36 [24.3%]	
Time difference (y): $time_{MDS\text{-}UPDRS\text{-}III}$ − time[^{123}I]FP-CIT SPECT	0.003 [−0.077, 0.036]	0.014 [−0.019, 0.043]	<0.0001*	0.019 [−0.014, 0.053]	0.020 [−0.030, 0.044]	0.034*

The data for subjects with successfully registered imaging data are presented. For numerical variables, median, lower quartile, and upper quartile are shown.
*$P < 0.05$.
Abbreviations: HC, healthy control; PD, Parkinson's disease; RPD, right predominant; LPD, left predominant; MoCA, Montreal Cognitive Assessment; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; TD, tremor-dominant; IND, indeterminate; PIGD, postural instability and gait difficulty.

investigated in right-handed patients with complete MDS-UPDRS-III motor scores only (n = 314) to avoid potential confounding effects of dexterity. Of these patients, 179 (57.0%) had right-predominant, 129 (41.1%) left-predominant, and 6 (1.9%) symmetrical PD according to the reported laterality of the symptom onset.

At baseline, only 10 (3.2%) of the right-handed patients included in the main analyses used dopaminergic medications, but their MDS-UPDRS-III motor scores were evaluated without medications (either at least 3-hour washout and motor status off or at least 6-hour washout independent of motor status). These main analyses were repeated regardless of dexterity. At the 2-year follow-up,

186 (86.1%) patients used dopaminergic medications. In the main analyses of 2-year follow-up visits, only the patients with MDS-UPDRS-III scores evaluated *off* medications (n = 175) were included to avoid confounding effects of the medications. However, all main analyses using the 2-year follow-up data were also repeated, including all patients with PD regardless of whether they were *on* or *off* medications at clinical examination (n = 216, with medication state as an additional covariate) and, additionally, regardless of dexterity (n = 194 with only patients *off* medication, n = 240 regardless of whether the patients were *on* or *off* medications). More details about the medication state at the 2-year follow-up are presented in Table S3.

Main Effects of Parkinson's Disease and Motor Symptom Severity

As expected based on the selection criteria, patients with PD showed a substantially lower [^{123}I]FP-CIT binding in the striatum compared to controls (Fig. 2A), more prominent contralaterally to the side of predominant motor symptoms (Fig. 2B–D). H&Y stage and total MDS-UPDRS-III motor score were also associated with lower binding in the striatum, with significance only in the right hemisphere (Fig. 2E,F). Left and right MDS-UPDRS-III motor scores were negatively associated with contralateral striatal [^{123}I]FP-CIT binding (Fig. 2G,H).

Voxelwise Association between Striatal [^{123}I] FP-CIT SPECT Binding and Cardinal Motor Symptoms

Voxels associated with each cardinal motor symptom (rigidity, bradykinesia, and rest tremor) on both sides of the body were evaluated separately. Both left- and right-side rigidity (Fig. 3A) and bradykinesia (Fig. 3B) showed a significant negative association with contralateral striatal [^{123}I]FP-CIT binding. However, rest tremor was associated with higher [^{123}I]FP-CIT binding

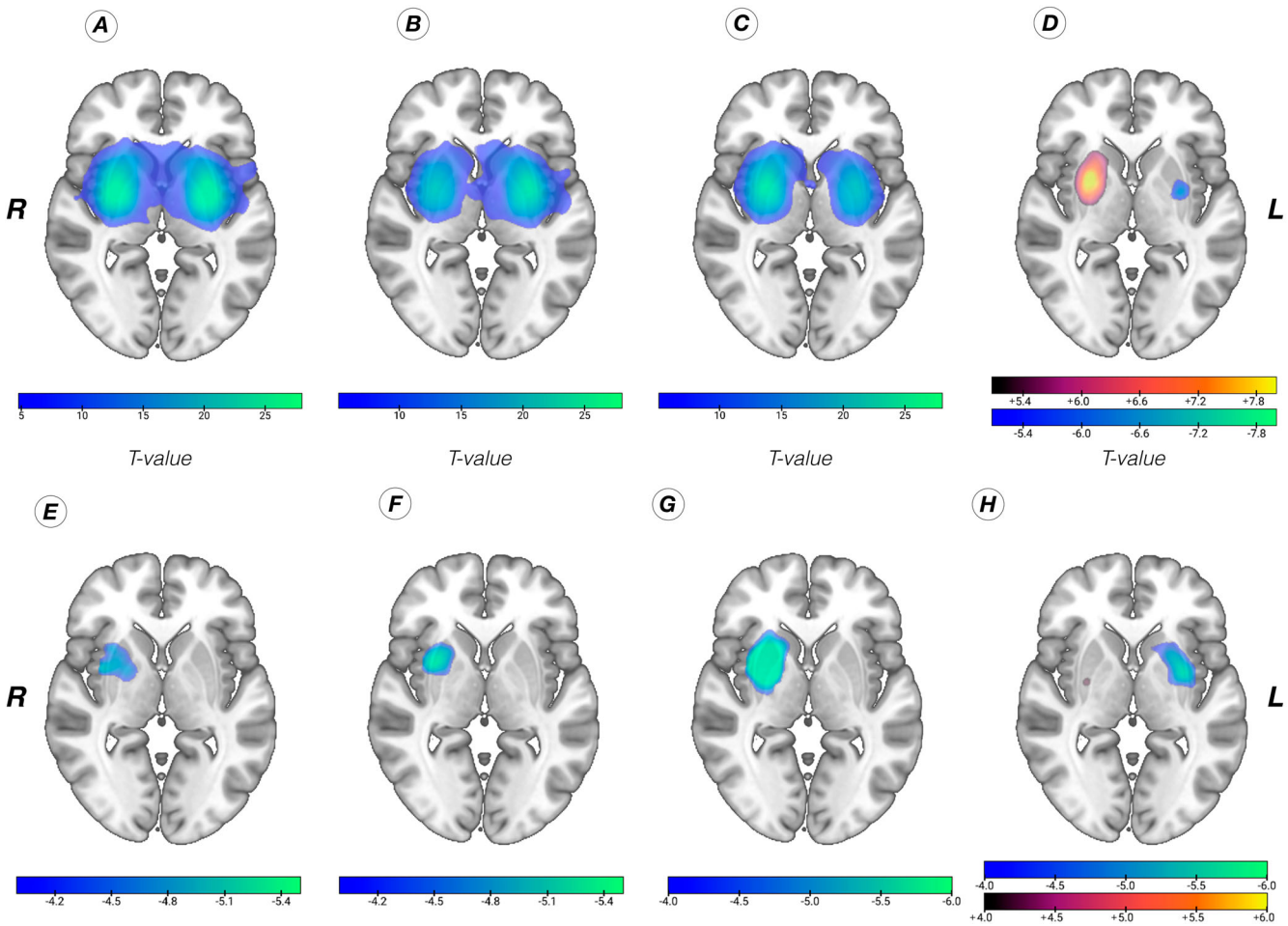

FIG. 2. Group comparisons and correlation with disease severity. Regions showing significant decreased specific binding ratio (SBR) in Parkinson's disease (PD) compared to controls or negative correlation (blue-green scale) and higher SBR or positive correlation (red-yellow). Montreal Neurological Institute (MNI) space plane coordinates $z = 0$ for all panels. Only voxels with voxel-level family-wise error (FWE)–corrected $P < 0.05$ are shown. (**A**) PD_{ALL} < HC (healthy control). (**B**) RPD_{RH} < HC. (**C**) LPD_{RH} < HC. (**D**) RPD_{RH} > LPD_{RH}. (**E**) Hoehn & Yahr grade. (**F**) MDS-UPDRS-III (Movement Disorder Society Unified Parkinson's Disease Rating Scale, part III) total score. (**G**) Left-side MDS-UPDRS-III total score. (**H**) Right-side MDS-UPDRS-III total score. L, left; R, right. [Color figure can be viewed at wileyonlinelibrary.com]

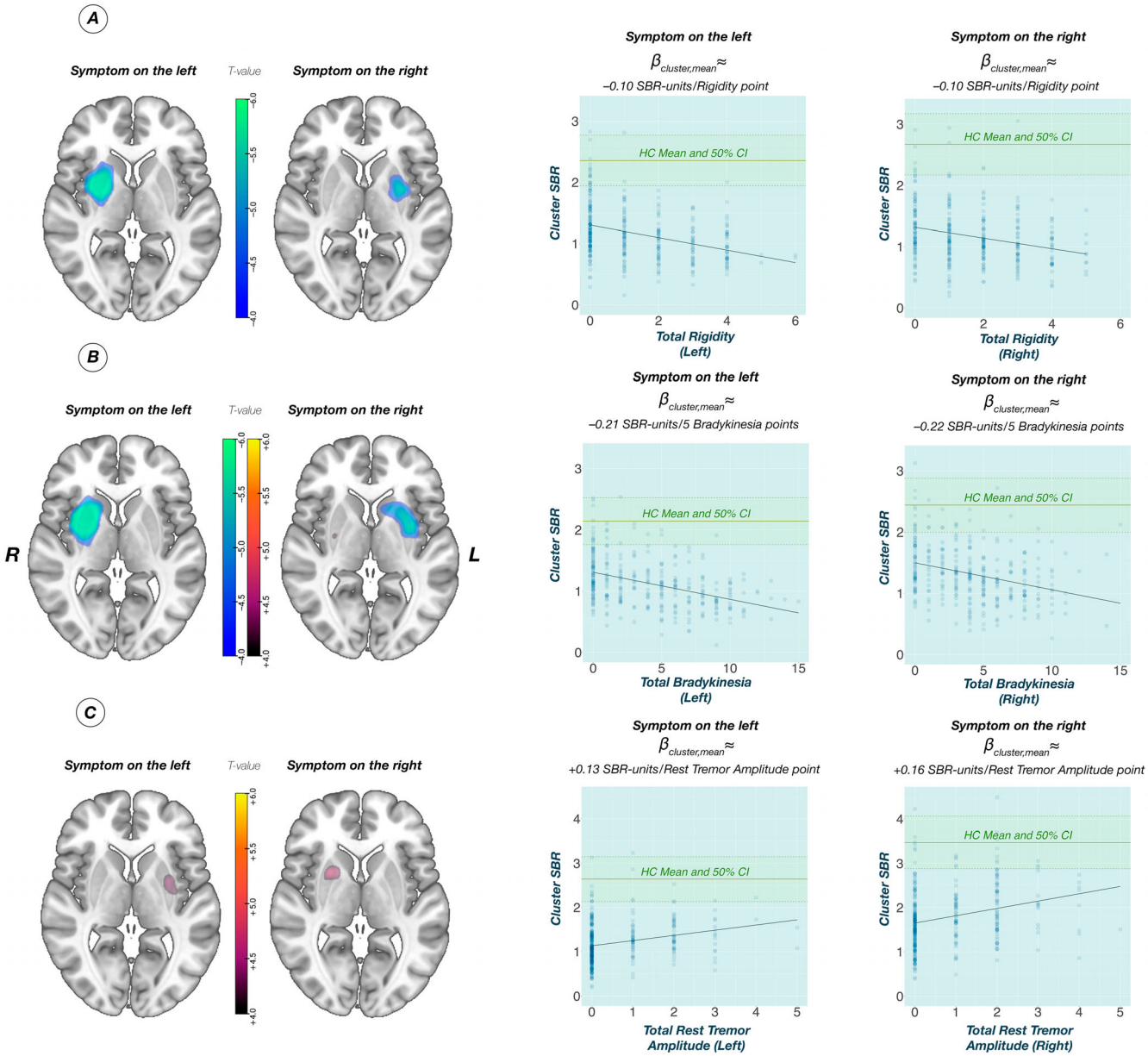

FIG. 3. Association with cardinal motor symptom severity. Rigidity and bradykinesia were associated with lower contralateral, but rest tremor with higher ipsilateral specific binding ratios (SBRs); volumes of the significant clusters were 1667 mm^3 (0.70% of the Harvard-Oxford Subcortical Atlas caudate ROI [regions of interest], 8.32% of the putamen) and 1249 mm^3 (0.70% of the caudate, 6.19% of the putamen) for the total left and right rest tremor, respectively. The analyses were performed in the right-handed PD group, with multivariate linear regression, age, and sex as covariates. On the right side of the figure, the corresponding scatterplots of the association between MDS-UPDRS-III (Movement Disorder Society Unified Parkinson's Disease Rating Scale, part III) subscores and cluster mean intensity are shown. Note that the scatterplots are used to illustrate only the strength of the association, and *P*-values are not calculated because the cluster analyses are circulatory. Only voxels with voxel-level family-wise error (FWE)–corrected $P < 0.05$ are shown. (**A**) Total extremity rigidity. (**B**) Total extremity bradykinesia. (**C**) Total extremity rest tremor amplitude. L, left; R, right. [Color figure can be viewed at wileyonlinelibrary.com]

in the ipsilateral striatum (Fig. 3C; Table S3). The findings were similar when upper-limb symptoms were analyzed (Fig. S4; Table S4) and when disease severity, phenotype, or cognitive function was controlled (Figs. S5 and S6; Table S5).

To ensure that the association was not driven by patients without rest tremor, the main analyses were repeated including only patients with any rest tremor (n = 220) or upper-extremity rest tremor (n = 203) with practically identical results (Fig. S7; Table S6).

We investigated the association between unilateral rest tremor controlling for bradykinesia and rigidity on the same side. As bradykinesia and rigidity were strongly intercorrelated (Spearman's $r = 0.70$ and $r = 0.60$ on the left and right sides, respectively), the combined bradykinesia–rigidity score was used.

Again, rest tremor was associated with increased ipsilateral but not with contralateral binding (Figs. S8 and S9; Table S7).

Replication of Ipsilateral Rest Tremor Finding at 2-Year Follow-Up

The voxelwise analyses for the left- and right-side total rest tremor were replicated at the 2-year follow-up visit, similarly as with the baseline data. Both left-sided rest tremor and right-sided rest tremor were significantly associated with higher ipsilateral but not with contralateral [^{123}I]FP-CIT binding (Fig. S10).

Including ambidextrous and left-handed patients in the analyses did not change the main results at baseline or 2-year follow-up (Figs. S11 and S12). Including patients examined while on medication at the 2-year follow-up did not change the main results (Fig. S13).

Associations of Other Rest Tremor Measures with Striatal [^{123}I]FP-CIT Binding

Both left- and right-side rest tremor SI were associated with increased ipsilateral [^{123}I]FP-CIT binding at baseline and 2-year follow-up, similar to the rest tremor amplitude (Fig. S14). Rest tremor consistency alone was not associated with binding at neither baseline nor 2-year follow-up.

Symptoms Most Strongly Associated with Striatal [^{123}I]FP-CIT Binding

To investigate the relative contribution of rest tremor and bradykinesia-rigidity to [^{123}I]FP-CIT binding, we included both left- and right-sided rest tremor amplitude and bradykinesia-rigidity into the same model, with age and sex as nuisance covariates. In the voxelwise analyses, contralateral bradykinesia-rigidity was the main factor associated with [^{123}I]FP-CIT binding at baseline. At the 2-year follow-up, both left rest tremor and left bradykinesia-rigidity were the main factors associated with striatal [^{123}I]FP-CIT SPECT binding (increased ipsilateral and decreased contralateral, respectively) (Fig. 4).

Replicating this analysis with the four striatal PPMI Core Lab ROI SBR values, rest tremor was independently associated with higher ipsilateral striatal [^{123}I]FP-CIT binding in the analyses at both time points, but not with contralateral [^{123}I]FP-CIT binding in any of the analyses. Bradykinesia-rigidity was associated with decreased contralateral [^{123}I]FP-CIT binding across the analyses and two time points. The contribution of rest tremor amplitude to the total model R^2 was higher in the 2-year follow-up compared to baseline (Fig. 4; Table S8).

Discussion

The aim of this study was to investigate the connection between striatal DAT binding and the three cardinal motor symptoms of PD using voxelwise analysis of the PPMI dataset. We confirmed the well-known negative correlation of striatal DAT binding to contralateral rigidity and bradykinesia. However, we found an association between rest tremor and increased or better-preserved ipsilateral striatal DAT binding, largely ignored in the previous literature. This finding may shed new light into the role of the striatal dopamine function in parkinsonian rest tremor and is relevant for the use of [^{123}I]FP-CIT imaging as a biomarker in PD.

Previous studies have shown that, compared to the akinetic-rigid subtype, tremor-dominant patients have more preserved dopamine function.[10–12,14,26] This finding may reflect general differences between subtypes, as tremor-dominant phenotype might have less-aggressive disease course compared to other subtypes.[27] In addition, studies focused on the association between tremor severity and presynaptic striatal dopamine function are heterogeneous, investigating many different types of tremor in patients with PD, and the results have remained inconclusive.[8,9,13–15,28] This includes the largest such study (382 PD patients from the PPMI dataset at baseline), showing no correlation between pallidal or putamen ROI [^{123}I]FP-CIT binding and rest tremor in the more affected side of the body.[14] Lack of a clear association between striatal dopamine function and rest tremor has led to the study of striatal postsynaptic dopamine function,[10] extra-striatal regions (e.g., the globus pallidus),[14,15,21] and other neurotransmitter systems (e.g., the serotonin and norepinephrine systems).[21,29,30] Despite the lack of clear association with striatal dopamine function and rest tremor, tremor in PD may respond to levodopa (L-dopa), indicating that dopamine plays a significant role in rest tremor.[31,32]

The advantages of the present study are that it includes a large homogenous dataset and focuses on rest tremor severity rather than composite tremor scores or differences between the motor phenotypes. Although it is known that PD patients with tremor-dominant phenotype have relatively preserved striatal dopaminergic function overall,[10–12] our results show that the ipsilateral rest tremor amplitude also correlates with striatal DAT binding independent of the motor phenotype. The vast majority of previous [^{123}I]FP-CIT SPECT studies have used a classical ROI-based methodology[22] that relies on a priori–defined anatomical structures, which may not correspond well with the functional organization of the striatum and therefore miss the effects localized to only a part of a structure or between structures.[33] In this study, we addressed this limitation by developing a new registration workflow, which facilitated accurate transformation of the individual scans to the MNI space with PVE correction, allowing voxelwise analyses of [^{123}I]FP-CIT binding that may be more sensitive to detect

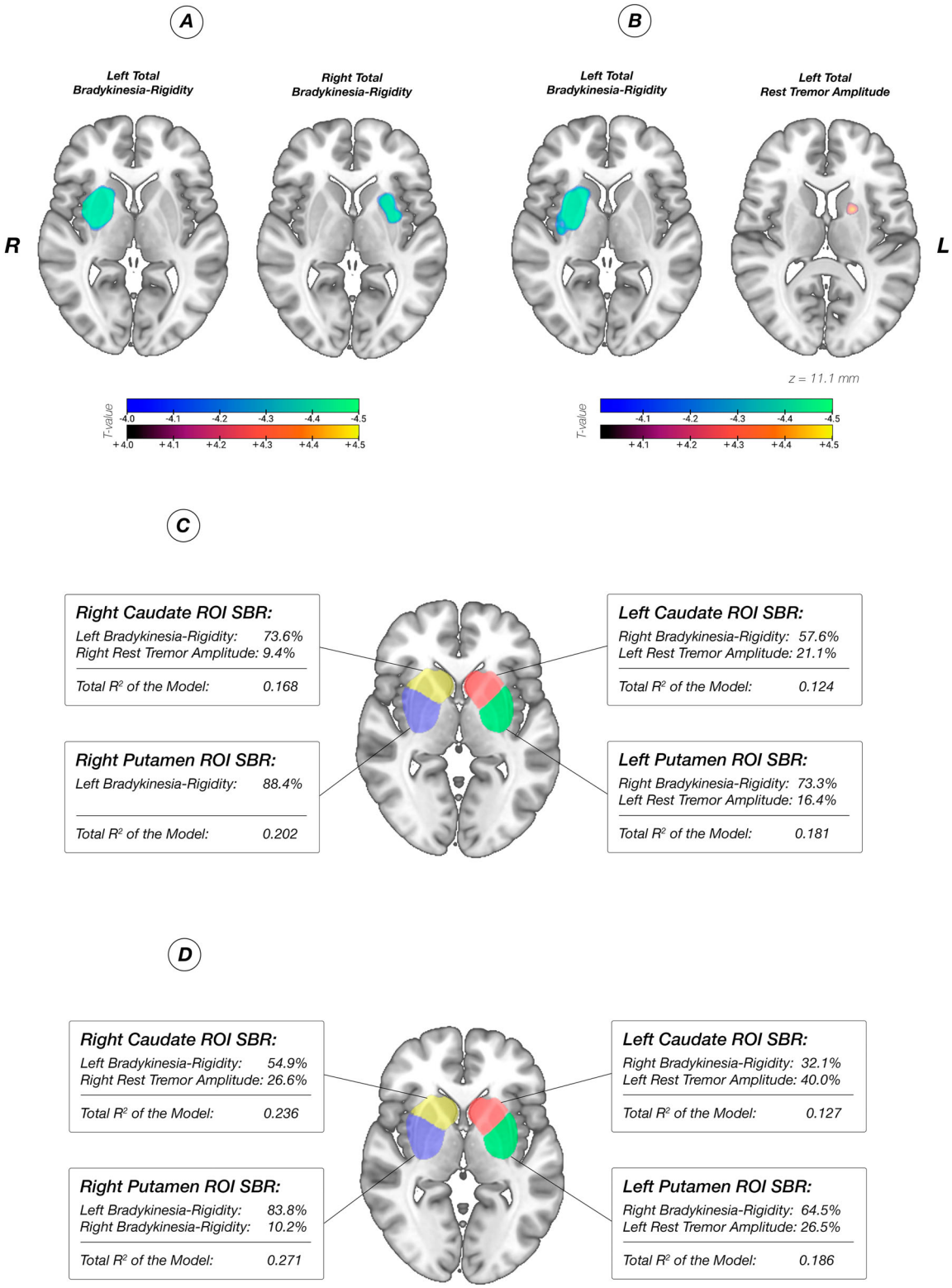

FIG. 4. Cardinal motor symptoms driving [^{123}I]FP-CIT binding at baseline and 2-year follow-up. (**A**, **B**) Motor symptoms with the strongest association with specific binding ratios (SBR) in the voxelwise multivariate model including left and right bradykinesia-rigidity and rest tremor with age and sex as covariates. Only voxels with voxel-level family-wise error (FWE)–corrected $P < 0.05$ are shown. (**C**, **D**) Results of the corresponding multivariate regression models using Parkinson's Progression Markers Initiative (PPMI) Core Lab ROI SBR values. Proportion of the decomposed R^2 values of the total model R^2 is shown. (**A**) Baseline. (**B**) Two-year follow-up. (**C**) Baseline: PPMI Core Lab SBR ROI R^2 proportions in a multisymptom model. (**D**) Two-year follow-up: PPMI Core Lab SBR ROI R^2 proportions in multisymptom model. L, left. R, right. ROI, region of interest. [Color figure can be viewed at wileyonlinelibrary.com]

the effects localized in specific parts of or in the boundaries of anatomical ROIs. Interestingly, the exact location of the striatal clusters significantly associated with ipsilateral tremor also differed between the left and right sides, a finding that may be related to the hemispheric anatomical asymmetry[34,35] or differences in functional organization between the hemispheres.[34–37]

The association between rest tremor and higher DAT in the ipsilateral striatum could be considered counterintuitive. The ipsilateral localization of rest tremor may explain why this issue has gone unrecognized previously, as most motor tracts decussate and motor function is primarily controlled by the contralateral hemisphere. However, there are also interhemispheric cortical, decussating corticostriatal,[38] decussating pallidothalamic and -tegmental[39] and nigrostriatal[40] connections, and nondecussating dentatorubrothalamic tracts[41] that may contribute to tremor. The relevance of the ipsilateral connections is supported by ipsilateral symptom alleviation in PD patients with unilateral deep brain stimulation (DBS),[42] although the ipsilateral effects of DBS and therapeutic lesions are less pronounced than with contralateral treatment.[42–46] The ipsilateral benefits have also been more often reported for bradykinesia and rigidity rather than tremor,[43–46] but there are data suggesting that the ipsilateral effects are similarly relevant for tremor too.[42] Moreover, the role of nondecussating dentatorubrothalamic tracts in patients with essential tremor undergoing MR-guided focused ultrasound treatment has also been acknowledged.[47] Thus, rest tremor seems to be controlled both ipsi- and contralaterally, but the clinical relevance of the ipsilateral tracts in PD rest tremor needs further research.

The biological interpretation of the association between rest tremor and increased striatal [^{123}I]FP-CIT binding is not straightforward. Although in clinical use [^{123}I]FP-CIT binding is considered as a marker of the number of surviving nigrostriatal neurons, [^{123}I]FP-CIT binding actually does not correlate with the number of nigral neurons[6] or putaminal fibers[5] in neuropathological examinations. There are also known functional or compensatory changes in striatal DAT concentration, for example, associated with neurodegeneration[2] and medications.[48] Taking into account the effects of L-dopa on rest tremor,[31] our finding may more likely reflect DAT upregulation rather than a greater number of dopaminergic neurons. However, as this study focused only on PD, the association between rest tremor and striatal dopamine function in other conditions, such as SWEDD, should be investigated separately.

Limitations

First, the cardinal motor symptoms are intercorrelated, which makes parceling out the association with individual symptoms challenging. Thus, we were forced to combine rigidity and bradykinesia variables and therefore were not able to fully evaluate their independent associations with binding. Second, ipsilateral rest tremor was not the main driving factor in the multivariate models in the early phase of the disease (baseline). However, this does not negate the existence of the link between ipsilateral DAT and rest tremor but suggests that the effect of rest tremor is weaker than that of bradykinesia-rigidity. Furthermore, the effects of rest tremor became stronger along with disease progression. Third, as head motion was not tracked, influence of the head movement on the findings cannot be excluded. However, there was no visible movement artifact in the scans, and excessive movement in patients with rest tremor would be reflected in lower, not higher, striatal SBRs, biasing us against the current finding of higher SBR associated with tremor severity. Fourth, the PPMI study design did not allow for investigating differences between treatment-resistant and treatment-responsive rest tremor.[32]

Conclusions

Our study provides novel evidence of a link between rest tremor in PD and ipsilateral striatal [^{123}I]FP-CIT binding, showing that more severe rest tremor is associated with higher ipsilateral binding. This finding may open new avenues into studying the neural mechanisms underlying rest tremor and may be relevant for the previous observations in unilateral functional neurosurgery. Further research is needed to test these findings beyond early PD, determine the molecular-level changes underlying the observation, and find how to leverage this toward improved treatments for rest tremor.

Acknowledgments: Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/access-data-specimens/download-data). For up-to-date information on the study, visit www.ppmi-info.org. PPMI—a public–private partnership—is funded by The Michael J. Fox Foundation for Parkinson's Research and funding partners, including Allergan, Amathus Therapeutics, Aligning Science Across Parkinson's (ASAP), Biogen, Bristol Myers Squibb, Celgene Corporation, Denali Therapeutics Eli Lilly and Company, GE Healthcare, GlaxoSmithKline, Janssen Pharmaceuticals, Lundbeck, Merck & Co. Inc., F. Hoffmann-La Roche Ltd and its affiliated company Servier, Takeda Pharmaceutical Company UCB, Verily Life Sciences, and Voyager Therapeutics Inc.

Data Availability Statement

All data used in this study were downloaded from the publicly available PPMI database (www.ppmi-info.org/access-data-specimens/download-data). For up-to-date information on the study and the data handling protocol, visit www.ppmi-info.org. As PPMI manages the use of the original data, the processed data are not publicly available.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Full financial disclosures of all authors for the previous 12 months

K.J.N reports research grants from the Finnish Parkinson Foundation, the Finnish Cultural Foundation (Pertteli Aaltonen Fund), Sigrid Juselius Foundation, the Finnish Neurological Society, the University of Turku, the University of Turku Foundation, Turku University Hospital, TYKS Foundation, and conference travel support from the Finnish Parkinson Foundation, the Finnish Neurological Society, the Finnish Society of Nuclear Medicine, the Finnish Cultural Foundation (Pertteli Aaltonen Fund), Turku University Hospital, the University of Turku, and Merck; and minor stock ownership in CareCloud, GlaxoSmithKline, Modulight, Nightingale Health, and Physicians Realty Trust. J.J. reports research grants from the Finnish Medical Foundation, Sigrid Juselius Foundation, the Finnish Foundation for Alcohol Studies, the University of Turku, and Turku University Hospital; conference travel support from Insightec, AbbVie, and Abbott; consulting fees from Summaryx and Adamant Health; and lecturer honoraria from Lundbeck and Novartis.