RESEARCH ARTICLE

Monoaminergic Networks of Cognitive and Behavioral Symptoms in Early Parkinson's Disease

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ABSTRACT: Background: Parkinson's disease (PD) is associated with several behavioral and cognitive symptoms, the neurobiological background of which is not yet fully understood.

Objectives: The aim was to investigate the association between monoamine function and four specific nonmotor symptoms in early PD using the Parkinson's Progression Markers Initiative data.

Methods: [^{123}I]FP-CIT SPECT imaging data of healthy controls ($n = 166$) and patients with PD at baseline ($n = 349$), 2-year ($n = 240$), and 4-year follow-up ($n = 140$) were included. Depression, anxiety, rapid eye movement (REM) sleep behavior disorder (RBD) and cognition were evaluated using validated questionnaires. The associations between symptoms and subcortical monoamine transporter binding were analyzed voxel by voxel. Whole brain networks of symptom-specific monoaminergic abnormalities were characterized using a functional connectome ($n = 1000$) and normative neurotransmitter receptor maps.

Results: Cross-sectionally, depression was associated with reduced ventral striatum (VS) binding at 2- and 4-year and dorsal raphe (DRN) at 4-year follow-up ($P_{FWE} < 0.05$); trait anxiety was associated with reduced DRN binding at 4-year follow-up ($P_{FWE} < 0.05$). Longitudinally, lower baseline binding in these regions at baseline predicted more severe future depression and anxiety ($P_{FWE} < 0.05$). RBD was most strongly linked to reduced VS binding at 2- and 4-year follow-up (nonsignificant after correction, $P_{FWE} < 0.1$). Each of the symptom-specific clusters was connected to distinct brain networks, corresponding to specific monoamine receptors: serotonin ($5HT_{1F}$, $5HT_{2A}$, $5HT_{5A}$) and histamine (H_3) for depression; histamine (H_1), serotonin ($5HT_{1E}$, $5HT_{1F}$, $5HT_{2A}$, $5HT_{3B}$), and adrenergic (α_{1D}) for anxiety; and adrenergic (β_2) and serotonin ($5HT_{1F}$, $5HT_{2C}$, $5HT_{5A}$) receptors for RBD.

Conclusions: The findings provide novel information about the monoaminergic networks underlying depression, anxiety, and RBD in PD. © 2026 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: [123I]FP-CIT; anxiety; depression; Parkinson's disease; rapid-eye-movement (REM) sleep behavior disorder; single-photon emission computed tomography (SPECT)

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Parkinson's disease (PD) is characterized by motor parkinsonism but commonly associated with cognitive and behavioral nonmotor symptoms, including depression, anxiety, rapid eye movement (REM) sleep behavior disorder (RBD), and dementia. Depression affects approximately 30%–35%[1] of patients with PD, apathy 35%–60%,[1,2] anxiety 30%–60%,[1,2] RBD up to 50%,[3] and dementia up to 50%[2] during the course of the disease. These symptoms can have profound negative effects on quality of life, even exceeding that of motor symptoms,[4,5] highlighting the need for better understanding of their underlying mechanisms and for efficacious treatments.

Some cognitive and behavioral symptoms respond to dopaminergic medications,[1] the mainstay treatment of motor symptoms.[2] For example, dopamine agonists pramipexole and ropinirole reduce depression in PD,[1] suggesting at least partial dopaminergic mechanism behind parkinsonian depression. Drugs targeting other monoamine systems, including serotonin (using selective serotonin reuptake inhibitors [SSRIs] or serotonin agonists) and norepinephrine (using serotonin and norepinephrine reuptake inhibitors [SNRIs]), are effective in non-PD depression[6] and anxiety,[7] with more limited data in PD.[1] Other symptoms, including RBD and cognitive impairment, may not respond to monoaminergic medications based on limited therapeutic trial data.[1,3]

Molecular brain imaging studies have demonstrated progressive abnormalities across the monoaminergic systems in PD,[8-14] and have shown that cognitive and behavioral symptoms become more common with disease progression and more severe loss of striatal dopamine function.[9,10,13,14] In terms of other monoamine systems, depression and anxiety have also been associated with serotonergic[9,10,15-17] and noradrenergic[8,13] abnormalities, but these studies have usually focused on individual symptoms and neurotransmitters with non-uniform findings.

The most widely used brain molecular imaging tracer used in the context of PD is [^{123}I]FP-CIT, which is used clinically to verify striatal presynaptic dopamine deficit.[18] However, [^{123}I]FP-CIT also has affinity for both serotonin and norepinephrine transporters (SERT and NET, respectively),[19-22] and seems to have a reasonable test–retest reliability in extrastriatal regions, such as the midbrain.[23] Thus, [^{123}I]FP-CIT uptake in brain regions with relatively high concentrations of other monoamines compared to dopamine transporter could be considered to primarily reflect serotonin or norepinephrine transporter function.[24] Examples of such brain regions include the raphe nuclei and locus coeruleus (LC) that are the main serotonergic and noradrenergic nuclei in the brain, respectively.[25,26] Thus, [^{123}I]FP-CIT SPECT has been used to interrogate multiple monoamine systems with a single scan.[21,22,24] Utilizing this feature has been limited by relatively low signal outside the basal ganglia, preventing accurate anatomical registration using available computational algorithms.

Here, we investigated the associations of four specific nonmotor symptoms (depression, anxiety, RBD, cognitive impairment) with monoaminergic function in early PD in the Parkinson Progression Markers Initiative (PPMI), the largest prospective PD neuroimaging cohort available.[27] We hypothesized that these symptoms are associated with regionally specific monoaminergic abnormalities, localizing to distinct functional networks. Using a novel image preprocessing pipeline, we performed accurate registration and voxelwise analyses of subcortical [^{123}I]FP-CIT binding.[28] We then computed symptom-specific functional networks using a normative functional connectome[29] and characterized their receptor-level molecular underpinnings based on spatial distributions, using cross-modal correlation analyses with normative neurotransmitter maps.[30,31]

Subjects/Materials and Methods

Study Sample

Data used in the preparation of this article were obtained on April 12, 2019, from the PPMI database (http://www.ppmi-info.org/access-data-specimens/download-data), RRID:SCR_006431. The PPMI study protocol was registered in 2010 (ClinicalTrials.gov identifier: NCT01141023). The study was approved by the institutional review board at each research site, with all participants providing written informed consent. For up-to-date information on the study, visit http://www.ppmi-info.org. The study sample from the PPMI cohort baseline in 2010–2013 comprised clinical features, anatomical magnetic resonance imaging (MRI), and [^{123}I]FP-CIT SPECT imaging of healthy controls ($n = 166$) and patients with idiopathic Parkinson's disease at three timepoints: baseline ($n = 349$), 2-year ($n = 268$), and 4-year follow-up ($n = 162$).

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

Clinical Data

Age, duration of motor symptoms, motor symptom severity, and medications at each timepoint were obtained for each subject, as available. Monoaminergically active antidepressant and/or anxiolytic medications were considered to include selective serotonin reuptake inhibitor (SSRI), serotonin and norepinephrine reuptake inhibitor (SNRI), noradrenaline-dopamine reuptake inhibitor

(NDRI), noradrenergic and specific serotonergic antidepressant (NASSA), serotonin-modulating, tricyclic antidepressant (TCA), and tetracyclic antidepressant (TeCA) medications. Medications for the treatment of cognitive impairment included acetylcholinesterase inhibitors (AChEIs) and memantine.

At each timepoint, depression was evaluated with the 15-item Geriatric Depression Scale[32] (GDS-15; cutoff for probable depression in PD ≥5 points[33]), anxiety with the State–Trait Anxiety Inventory[34] (STAI) consisting of STAI-S and STAI-T (state and trait anxiety) subinventories (cutoff ≥39 points for each subinventory[34,35]), RBD with the REM sleep behavior disorder screening questionnaire (RBDSQ; cutoff ≥5 points[36]), and cognition with the Montreal Cognitive Assessment[37] (MoCA; cutoff ≤25 points[33]).

Comparisons between the timepoints were conducted using linear mixed models and partially overlapping samples *Z*-tests using *R 4.1.2*, as appropriate.

Cross-Sectional Voxelwise Analyses of the SPECT Data

Image preprocessing was conducted as described previously (see Supporting Information for details).[28] All voxelwise analyses of the SPECT data were performed using the general linear model implemented in Statistical Parametric Mapping (SPM) 12. An analysis mask, including striatum, thalamus, midbrain, and brainstem, was created (Harvard-Oxford Subcortical Atlas with 4 mm dilation) to restrict the analyses to regions with high monoaminergic activity and [^{123}I]FP-CIT binding. Each nonmotor symptom was assessed separately due to some notable intercorrelations between the symptoms (Table S2).

In the cross-sectional analyses at each timepoint, the associations between voxelwise specific binding ratio (SBR) and each nonmotor symptom score were investigated using a general linear model with age, sex, and Movement Disorders Society Unified Parkinson's Disease Rating Scale, Part III (MDS-UPDRS-III) total score as covariates. 2- and 4-year follow-up data analyses were conducted similarly but also controlling for medication state (on/off) during clinical examination (medication state × MDS-UPDRS-III total score interaction). To control for possible confounding effects of dopaminergic medications, the main analyses were repeated by adding levodopa-equivalent daily dose (LEDD) as an additional covariate. In addition, as RBDSQ is a screening tool and not validated for assessment of RBD severity, the findings were confirmed using RBDSQ as a dichotomous variable (cutoff ≥5 indicating RBD). Cluster-level family-wise error-corrected $P_{FWE} < 0.05$ at height threshold of uncorrected $P < 0.001$ was considered significant.

Longitudinal Voxelwise Analyses of the SPECT Data

In the longitudinal analyses, we investigated the association between baseline voxelwise SBR and neuropsychiatric symptoms at 2- and 4-year follow-ups, using the same covariates as in the cross-sectional analyses. Cluster-level family-wise error-corrected $P_{FWE} < 0.05$ at height threshold of uncorrected $P < 0.01$ was considered significant. A slightly lower height threshold was selected for the longitudinal analyses compared to the cross-sectional main analyses because of the expected weaker association with long interval between scanning and behavioral measurement.

ROI Analyses of the SPECT Data

In addition to the voxelwise analyses, region of interest (ROI) analyses were used to confirm and investigate the magnitudes of the main findings. Anatomical ROIs were obtained from the AAL3 atlas.[38] The ROIs were selected based on the voxelwise findings and included bilateral putamen, caudate, nucleus accumbens (NAcc), LC, thalamus, and raphe nuclei. The association between ROI SBRs and symptoms was investigated using multivariable linear regression models with *R 4.1.2* using an identical set of covariates as in the voxelwise analyses.

Functional Network Connectivity of Symptom-Associated Clusters

To investigate the functional brain networks associated with SBR findings, the identified clusters for each symptom were used as seeds for voxelwise whole-brain resting-state functional connectivity fMRI (rs-fMRI) analyses, using data from 1000 healthy volunteers.[29] In addition to the cognitive and behavioral symptoms' clusters, this analysis was also conducted with the cluster set associated with motor parkinsonism (bradykinesia and rigidity), as identified previously.[28] Detailed description of the rs-fMRI analysis has been reported previously.[39] The resulting Pearson's *r* maps were converted to *z*-maps using Fisher-*z*-transformation, and final connectivity maps for each symptom were investigated using one-sample *t* tests.

To evaluate the distinct functional connectivity profiles of neuropsychiatric symptoms, symptom-specific networks were formed with the model described in detail in the Supporting Information Methods. To assess the specificity of the symptom connectivity maps, these maps were also compared to the bradykinesia–rigidity–associated network, using voxelwise linear models (paired setting). Significance was tested using permutation-based test with 10,000 permutations, implemented in *FSL Randomise*. Voxelwise $P_{FWE} < 0.05$ was considered significant.

To investigate potential causal relevance, the motor parkinsonism and depression maps were compared to maps derived from brain lesions causing parkinsonism[40] and depression.[41] These maps represent the connectivity computed from lesions causing these symptoms, contrasted to those of that did not cause the symptoms. Similarity of the maps was computed using atlas-based nonparametric spatial correlation, using *JuSpace 1.5*[30] running on MATLAB R2021b, with the default Neuromorphometrics atlas. To test if the maps are more similar than what would be expected by chance, the resulting spatial correlation coefficient was compared to a null distribution created by randomly permuting the map ROI values 10,000 times. The analyses were adjusted for spatial autocorrelation effect.

Neurotransmitter Receptor Contributions to the Functional Networks

To characterize the neurotransmitter contributions of the monoaminergic networks, spatial correlations of unadjusted networks were computed with spatial, microarray-based reference gene expression profiles, based on the gene microarray probe data provided by the Allen Human Brain Atlas (AHBA, https://human.brain-map.org),[42] using *JuSpace 1.5*[30] (10,000 permutations, adjusted for spatial autocorrelation effect). These neurotransmitter receptor gene expression maps included all the serotonin, adrenergic, dopamine, and histamine receptors available in the reference data. The gene expression maps were formed using Abagen library (version 0.1.4 + 15.gdc4a007),[42-45] running on *Python*[46] 3.11.13, based on the gene microarray probe data provided by the AHBA (https://human.brain-map.org)[42] (more details in Supporting Information Methods). These tests were corrected for multiple comparisons separately for each functional network using Bonferroni correction.

Results

Demographic and Clinical Data

Patients included at each timepoint did not differ in terms of sex, delay between symptom onset and diagnosis, or education (Table 1). Of the PD patients, 14.0% had probable depression (GDS-15 ≥ 5), 22.0%–28.0% clinically relevant anxiety symptoms, 26.6% probable REM sleep behavior disorder (RBDSQ ≥5), and 20.3% probable, at least mild cognitive impairment (MoCA ≤25) (Table S3). During follow-up, depression and anxiety remained at the baseline level, but RBD and

TABLE 1 *Demographic and clinical data*

	Baseline	2-year follow-up	4-year follow-up
	n = 349	n = 268	n = 162
Age (y)	62.1 [54.6, 69.0]	64.3 [56.9, 71.0]⋆	66.5 [59.1, 72.9]†‡
Sex (male/female [male %])	224 / 125 [64.2%]	170 / 98 [63.4%]	108 / 54 [66.7%]
Age at symptom onset (y)	60.1 [52.6, 67.1]	60.0 [53.0, 67.8]	60.5 [53.4, 67.1]
Time from symptom onset to diagnosis (y)	0.9 [0.5, 1.9]	0.9 [0.5, 1.9]	0.9 [0.4, 1.7]
Disease duration (y)	1.5 [0.9, 2.6]	3.6 [3.0, 4.5]⋆	5.6 [5.0, 6.5]†‡
Education years	16 [14, 18]	16 [14, 18]	16 [14, 18]
MDS-UPDRS-III total score	20 [14, 26]	26 [19, 35]⋆	29 [22, 36]†‡
LEDD	0 [0, 0]	303 [150, 560]⋆	590 [325, 850]†‡
Hoehn & Yahr Stage			
0	–	1 [0.4%]	–
1	154 [44.1%]	56 [23.2%]	22 [15.6%]
2	193 [55.3%]	171 [71.0%]	109 [77.3%]
3	2 [0.6%]	10 [4.1%]	9 [6.4%]
4	–	3 [1.2%]	1 [0.7%]
5	–	–	–
Not reported	–	27	21

Note: Differences in scalar variables were evaluated with linear mixed models, in categorical variables with partially overlapping samples *Z*-test. For numeric variables, median with 25th and 75th percentiles [in brackets] are reported. Patients with missing values were excluded from the corresponding analyses. For Hoehn & Yahr stage, no statistical comparison between timepoints was performed. Significant ($P < 0.05$) difference between baseline and 2-year follow-up⋆, baseline and 4-year follow-up†, 2-year and 4-year follow-up‡.

Abbreviations: MDS-UPDRS-III, Movement Disorders Society Unified Parkinson's Disease Rating Scale, Part III; LEDD, levodopa-equivalent daily dose.

cognitive impairment increased slightly (Table S3). At baseline, 10.3% used monoaminergically active antidepressant or anxiolytic medications. Use of these medications increased during follow-up to 16.4% at 2-year follow-up and 19.1% at 4-year follow-up. Medications for treatment of cognitive impairment were only used by 3.1% of patients by the 4-year follow-up.

Cross-Sectional Analyses

At baseline, no significant associations were observed between [^{123}I]FP-CIT binding and neuropsychiatric symptoms. At 2-year follow-up, GDS-15 score was negatively associated with binding in the right ventral striatum (VS), and at 4-year follow-up, in the left VS, caudate, and midbrain, including dorsal raphe nucleus (DRN) (Fig. 1A). STAI Trait score was negatively associated with midbrain binding, including dorsal and median raphe nuclei and LC at 4-year follow-up (Fig. 1B), whereas STAI State score showed no significant associations at any timepoint. Excluding patients on antidepressive/anxiolytic monoaminergic medications did not alter GDS-15 and STAI Trait findings at 4-year follow-up (Fig. S2). RBDSQ score showed the

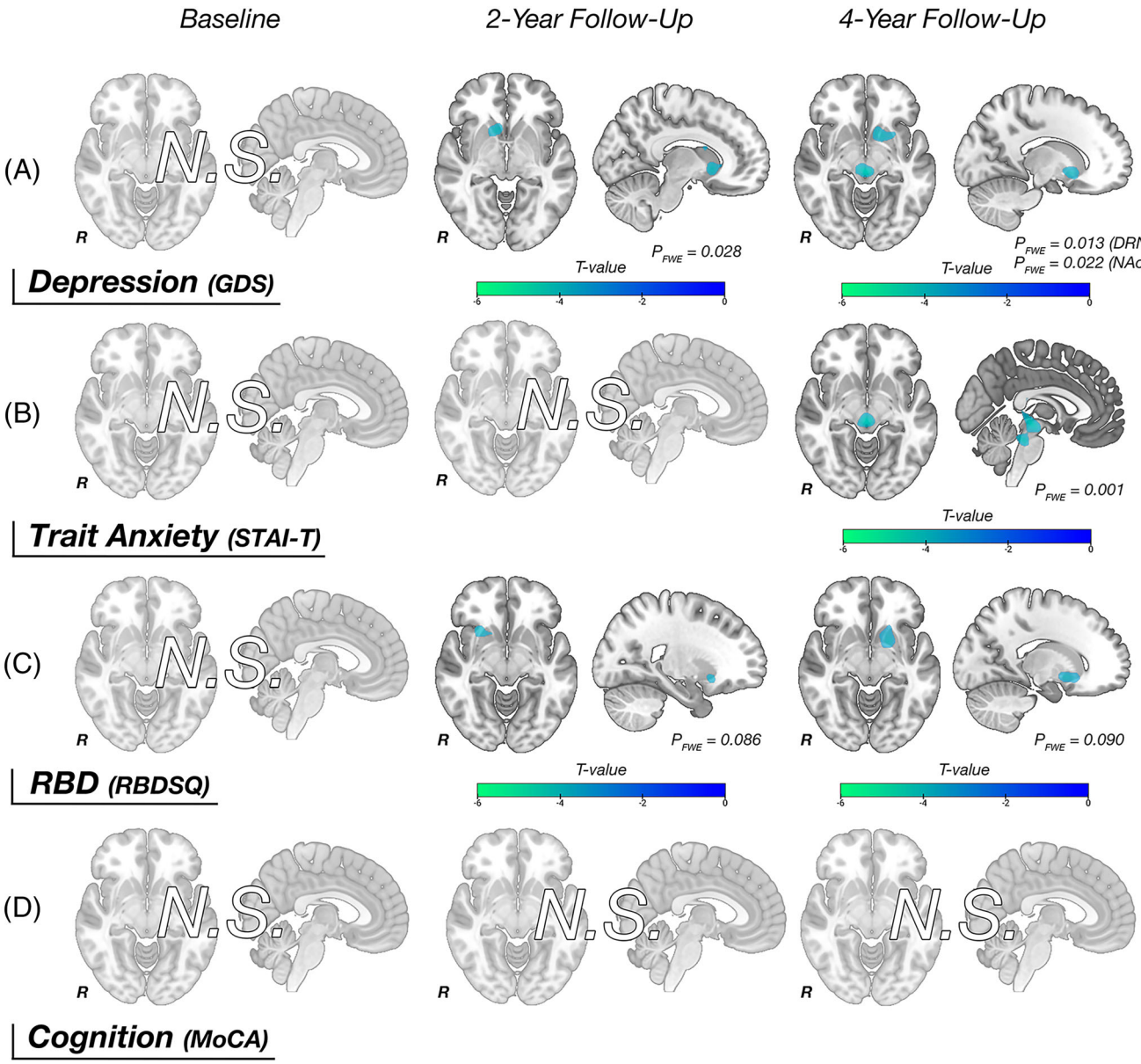

FIG. 1. Association between cognitive and behavioral symptoms and [^{123}I]FP-CIT binding. The association of (**A**) depression, (**B**) trait anxiety, (**C**) rapid eye movement (REM) sleep behavior disorder symptoms, and (**D**) cognition with [^{123}I]FP-CIT binding at baseline, 2-year follow-up, and 4-year follow-up. Multivariable linear regression with age, sex, regression, medication state, and MDS-UPDRS-III total score (medication state × MDS-UPDRS-III total score interaction) as covariates. R, right; DRN, dorsal raphe nucleus; NAcc, nucleus accumbens; MDS-UPDRS-III, Movement Disorders Society Unified Parkinson's Disease Rating Scale, Part III (motor); P_{FWE}, family-wise error-corrected *P* value; N.S., nonsignificant. [Color figure can be viewed at wileyonlinelibrary.com]

strongest association with reduced binding in the right VS at 2-year follow-up and in the left VS and putamen at 4-year follow-up, but these findings did not reach significance (Fig. 1C). MoCA score showed no significant associations at any timepoint (Fig. 1D). The significance of the results did not change when adding LEDD as an additional covariate (Fig. S3). The results did not change when using RBDSQ as a dichotomous variable (Fig. S4). No significant associations were found in healthy controls with any of the studied symptoms.

Linear regression analyses using anatomical ROI data (Fig. S5A) confirmed the findings in the monoaminergic nuclei implicated by the voxelwise findings. In agreement with the voxelwise analyses, GDS-15 score showed strengthening associations with decreased binding in the VS, caudate, and raphe nuclei; STAI Trait in the raphe nuclei and LC; and RBDSQ in the VS and putamen (Fig. S5B; Table S4). MoCA score showed no consistent association in any of the ROIs (Table S4).

Longitudinal Analyses

Lower baseline SBRs in the VS, caudate, raphe nuclei, and thalamus were associated with higher GDS-15 score at 2-year follow-up (Fig. S6A). Similarly, in the left caudate and anterior putamen, lower SBR was most strongly associated with GDS-15 score at 4-year follow-up but did not reach significance (Fig. S6A). Lower baseline SBRs in the DRN, thalamus, and VS were associated with higher STAI Trait at both 2- and 4-year follow-ups (Fig. S6B). There were no significant associations of baseline SBR with RBDSQ or MoCA.

In ROI analyses, lower baseline SBR in the raphe nuclei was associated with higher GDS-15 score at 2- and 4-year and with STAI Trait and State at 2-year follow-up visits (Table S5). Lower baseline SBRs in the striatal ROIs were associated with higher GDS-15 and STAI State at follow-up and lower baseline SBR in the thalamus with higher GDS-15 score at 2-year follow-up visit (Table S5). Baseline SBRs were not associated with RBDSQ or MoCA scores (Table S5). The progression of monoamine transporter binding deficits in key monoaminergic areas among patients developing notable depression and anxiety at 4-year follow-up is illustrated in Figure 2.

Functional Brain Networks of Symptom-Specific [^{123}I]FP-CIT Binding Abnormalities

To characterize whole-brain networks linked to monoaminergic abnormalities, clusters from the 4-year cross-sectional analyses were used as seeds for connectomic analyses. The motor parkinsonism cluster was strongly connected to motor cortical, striatal, thalamic, midbrain, and cerebellar regions (Fig. 3A). Depression clusters

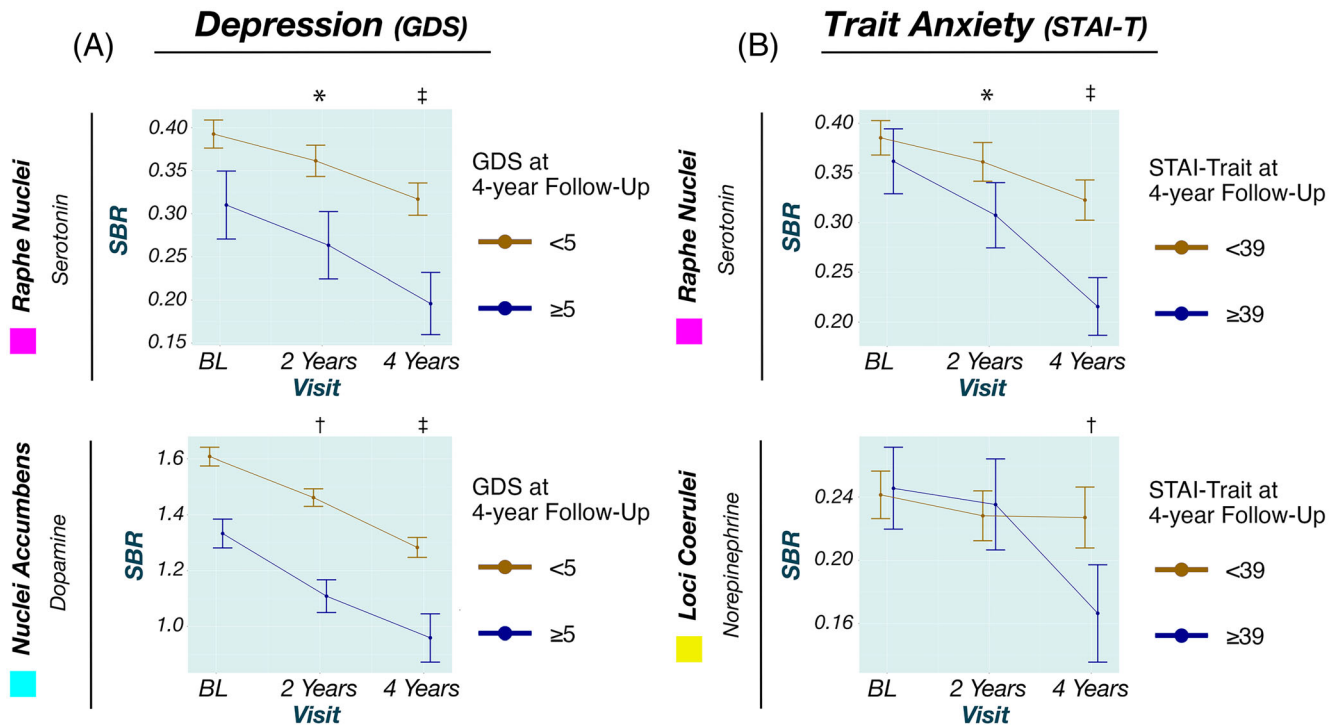

FIG. 2. Progression of monoamine transporter binding deficits in the regions of interest. Progression of monoamine transporter binding deficits in the monoaminergic key regions in patients who did and did not develop depression (**A**) and anxiety (**B**) symptoms above the selected cutoffs by the 4-year follow-up. Dots indicate groupwise average values, whiskers values of ±1 standard error. SBR, specific binding ratio; GDS, 15-item Geriatric Depression Scale; STAI-T, State Trait Anxiety Inventory, Trait Anxiety Score; BL, baseline. Difference between the groups, *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$. [Color figure can be viewed at wileyonlinelibrary.com]

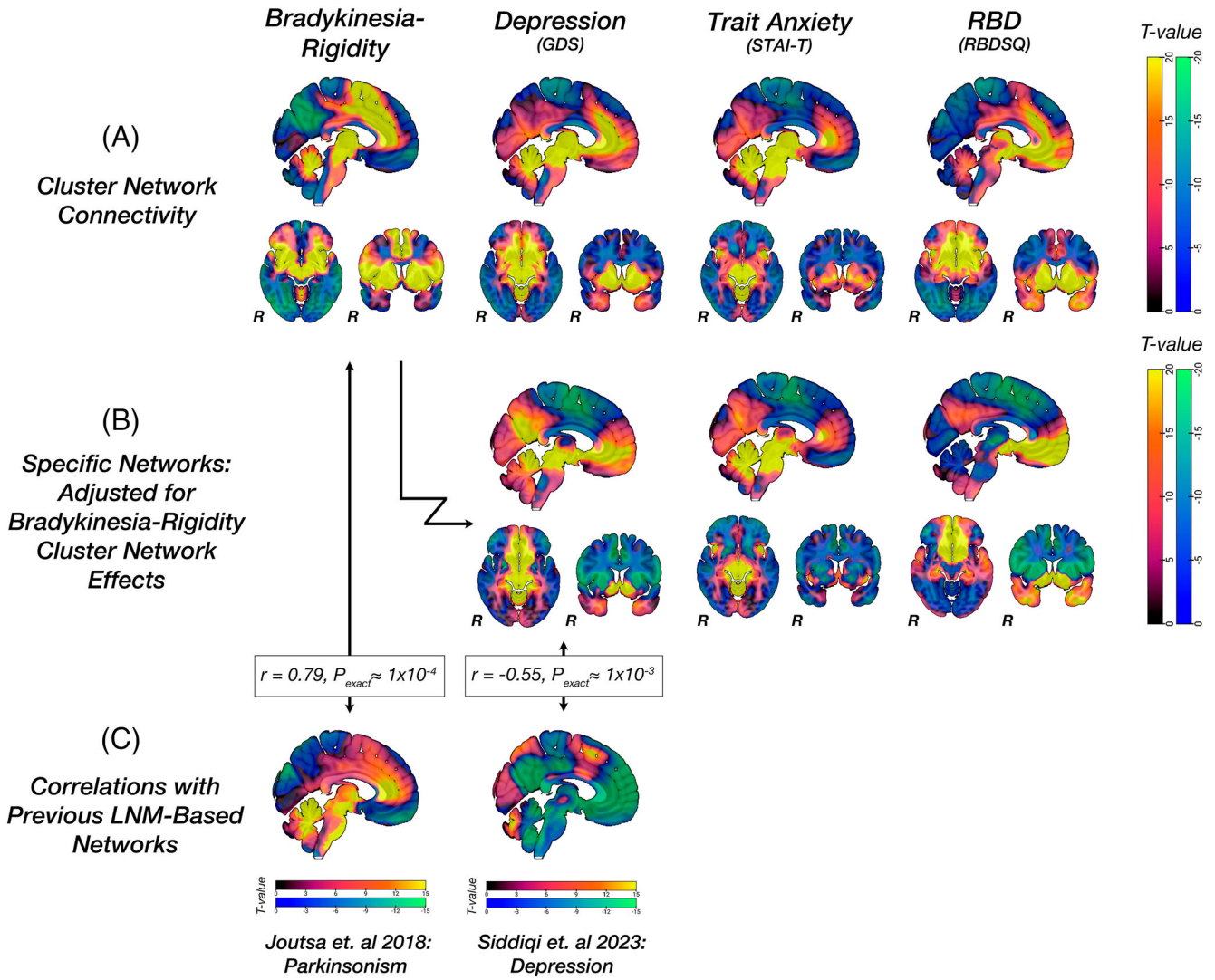

FIG. 3. The whole-brain networks corresponding to the monoaminergic deficits associated with the neuropsychiatric symptoms. (**A**) The networks of the monoaminergic deficits associated with bradykinesia–rigidity, depression, trait anxiety, and rapid eye movement (REM) sleep behavior disorder. (**B**) The specific networks of the monoaminergic deficits associated with depression, trait anxiety, and REM sleep behavior disorder, adjusted for bradykinesia–rigidity. (**C**) Spatial correlations between the bradykinesia–rigidity and specific depression network with the corresponding networks identified based on causal lesions.[40,41] GDS, 15-item Geriatric Depression Scale; STAI-T, State Trait Anxiety Inventory; Trait Anxiety Score; RBD, REM sleep behavior disorder; RBDSQ, RBD Screening Questionnaire; R, right; LNM, lesion network mapping. [Color figure can be viewed at wileyonlinelibrary.com]

connected primarily to the anterior cingulate, dorsomedial frontal, precuneal, and temporal; trait anxiety cluster to the insular, anterior cingulate, and precuneal; and the RBDSQ cluster to anterior cingulate, medial frontal, and temporal cortices (Fig. 3A). Nonmotor networks differed significantly from the motor network ($P_{FWE} < 0.05$; Fig. S7). Adjusting for motor parkinsonism did not alter the nonmotor network patterns (Fig. 3B). The motor parkinsonism and depression networks showed significant spatial similarity to lesion-derived networks, although the sign of spatial correlation differed between the symptoms ($P < 0.01$, Fig. 3C).

Receptor-Level Molecular Correspondence of the Symptom-Specific Networks

Spatial correlation analyses with normative neurotransmitter distributions were used to characterize the molecular-level underpinnings of the identified networks. The depression network most prominently involved serotonin ($5HT_{1F}$, $5HT_{2A}$, $5HT_{5A}$) receptors and histamine autoreceptors (H_3); anxiety network histamine (H_1), serotonin ($5HT_{1E}$, $5HT_{1F}$, $5HT_{2A}$, $5HT_{3B}$) and adrenergic (α_{1D}) receptors; and RBD network adrenergic (β_2) and serotonin ($5HT_{1F}$, $5HT_{2C}$, $5HT_{5A}$) receptors (Fig. 4; Table S6).

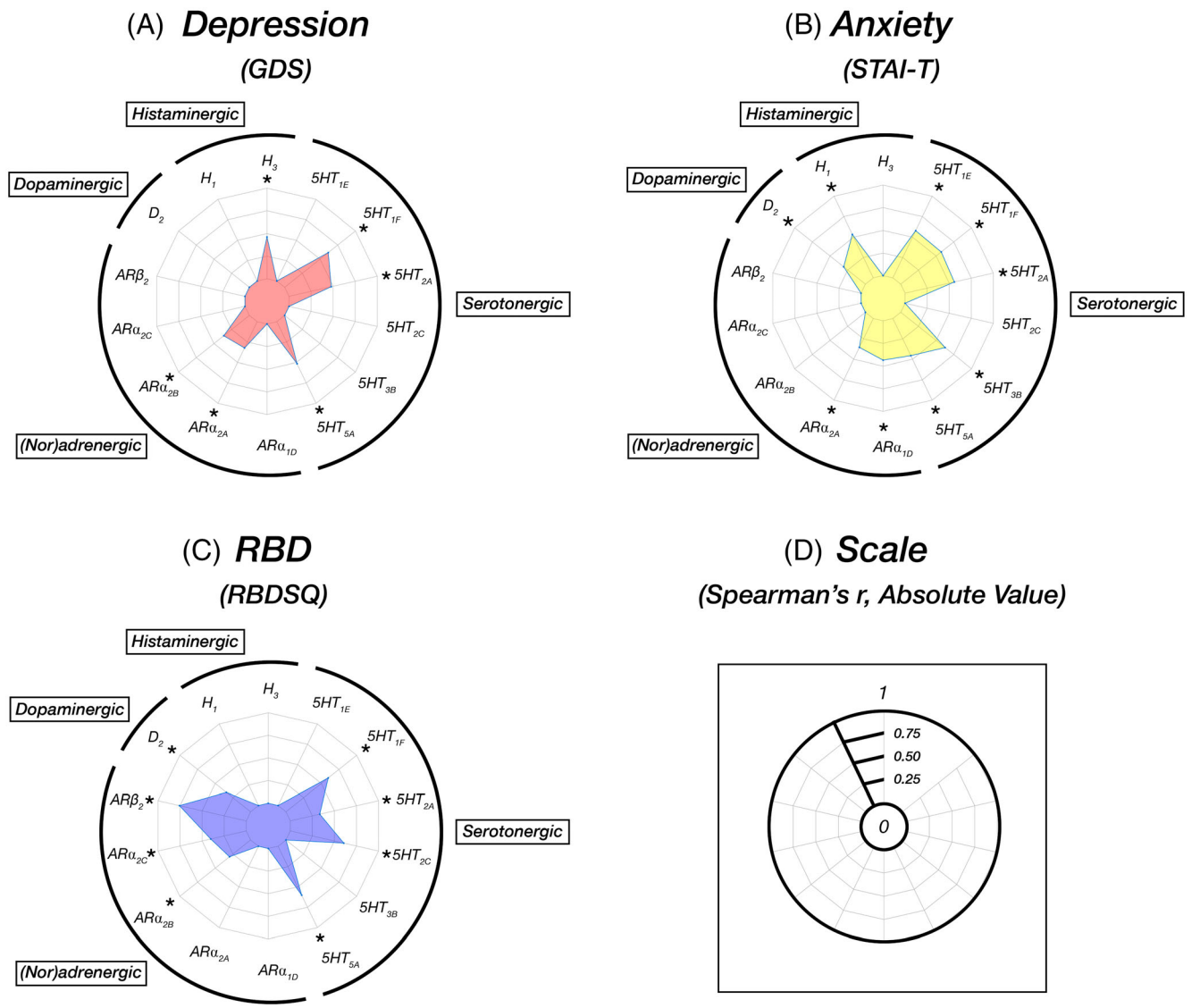

FIG. 4. The spatial correlation strength of the symptom networks with monoaminergic neurotransmitter receptor maps. The spatial correlation strength of (**A**) depression, (**B**) trait anxiety, and (**C**) REM sleep behavior disorder networks with microarray-based neurotransmitter receptor maps. Spatial correlation analyses are based on the Neuromorphometrics atlas. The values presented in the maps are absolute values of Spearman's *r* correlation coefficients (positive or negative correlation strength). The scale is presented in the panel **D**. Only correlations of the neurotransmitter receptor maps with a significant correlation after the nested Bonferroni corrections (10,000 permutations, $P_{\text{Bonferroni,nested}} < 0.05$), with at least one of the networks presented. GDS, Geriatric Depression Scale; STAI-T, State–Trait Anxiety Inventory, Trait–subinventory; RBDSQ, REM sleep behavior disorder questionnaire; 5HT, 5-hydroxy-tryptamine receptor, subtype subscripted; AR α/β, adrenergic receptor α/β, subtype subscripted; D2, dopamine receptor 2; H1/2/3/4, histamine receptor 1/2/3/4. *$P_{\text{Bonferroni,nested}} < 0.05$. [Color figure can be viewed at wileyonlinelibrary.com]

Discussion

The aim of our study was to investigate associations between brain monoaminergic function and four specific nonmotor symptoms in Parkinson's disease. Our cross-sectional and longitudinal results demonstrate anatomically distinct monoaminergic abnormalities associated with depression, anxiety, and RBD, but not with cognitive impairment, reflecting distinct functional brain networks and monoamine neurotransmitter receptor combinations. The findings might help future efforts on therapeutic trials for nonmotor symptoms in Parkinson's disease, and the introduced new approach used in this study, molecular network mapping, could be versatile across brain disorders.

Our study is among the first to simultaneously investigate multiple cognitive and behavioral symptoms and monoaminergic systems. The novel preprocessing algorithm allowed analyses beyond predefined ROIs, covering subcortical brain regions with specific [^{123}I]FP-CIT binding. Of the studied nonmotor symptoms, depression and anxiety showed the strongest associations with [^{123}I]FP-CIT binding, highlighting lower binding in the raphe nuclei, the main serotonergic nuclei in the brain.[47]

These associations emerged during the follow-up, likely reflecting increased power to detect these associations, as variance in binding and symptom severity in later disease stages increase. Our findings showing an association between depression and SERT are in agreement with prior studies using PET ligands, which are specific for SERT, in de novo PD.[9,16,17,48] However, the direction of the association and brain regions implicated are variable across studies, with some studies showing depression to be linked with decreased SERT binding,[9,16] as in the present study, and some studies increased SERT binding.[17,48] These associations are most consistently reported in the subcortical regions, including the raphe nucleus, but may also include some cortical regions, where midbrain serotonergic fibers project.[9,17,48] Thus, although the direction of the association between parkinsonian depression and SERT is still uncertain and it could be influenced by the disease stage, it seems clear that depression is associated with altered serotonin function in PD. Of note, the association between SERT binding and synaptic serotonin levels is uncertain as SERT binding could reflect the number of serotonergic neurons or compensatory changes in SERT expression. Our findings further link depression and anxiety with brain networks that are most strongly associated with serotonin receptor subtypes $5HT_{1F}$ and $5HT_{2A}$, aligning with preliminary evidence of the antidepressive effects of SSRIs and pimavanserin, a serotonin $5HT_{2A}$ inverse agonist, in patients with and without PD.[49-52]

In addition to the raphe nuclei, depression was associated with [^{123}I]FP-CIT binding in the VS, including the NAcc, the key mesolimbic dopaminergic projection site involved in reward functions,[53,54] supporting relevance for mesolimbic dopamine function in parkinsonian depression. These findings are consistent with the therapeutic efficacy of dopamine agonists in parkinsonian depression and the lower nigral dopaminergic neuron density in depressed PD patients.[1,55,56] The findings that suggest the involvement of both serotonin and mesolimbic dopamine systems in parkinsonian depression align with the findings by Maillet et al.[9] However, it should be noted that prior evidence linking striatal DAT to depression in PD is mixed, likely caused by heterogeneous study designs and populations.[57-61]

In contrast, anxiety was directly linked to [^{123}I]FP-CIT binding in the LC, the main noradrenergic nucleus, aligning with reports of a noradrenergic PD subtype with greater anxiety.[62] Although Braak's hypothesis posits early LC involvement,[63] the association between anxiety and [^{123}I]FP-CIT binding in the LC was only evident after 4 years without a rise in anxiety prevalence, possibly reflecting limited sensitivity to early changes in these small brainstem nuclei. The network analyses further demonstrated adrenergic α-receptor involvement in anxiety (and also depression and RBD with differing adrenergic receptor subtype profiles). This finding is supported by the efficacy of SNRIs in the treatment of anxiety and depression[7,56,64,65] and possible detrimental effects of SNRI medications on RBD and REM sleep without atonia.[56,66]

Interestingly, both depression and anxiety networks were spatially aligned with the distribution of histamine receptors; depression with histamine H_3 autoreceptors, and anxiety with histamine H_1 receptors. The association between H_1 and anxiety is supported by the known anxiolytic effects of H_1 antagonist hydroxyzine.[67] H_3 is targeted by pitolisant, which is used to treat narcolepsy and is currently studied for treatment of excessive daytime sleepiness in PD.[68]

In contrast to the other studied nonmotor symptoms, no associations between cognitive impairment and [^{123}I]FP-CIT binding in any of the studied brain regions were found. This supports previous observations that cognitive dysfunction in PD is more closely related to cholinergic than monoaminergic network dysfunction.[69] However, the PPMI cohort had a relatively low number of patients with cognitive impairment even at 4-year follow-up, which may have reduced our power to detect associations between cognition and monoamine function.[2,70]

The connectivity analyses showed that distinct monoaminergic brain regions associated with depression, anxiety, and RBD also represent distinct functional brain networks. Importantly, the motor parkinsonism and depression networks had similar spatial topography with networks derived from brain lesions causing parkinsonism and depression, respectively, suggesting that the identified networks may be causally linked with these symptoms. The motor parkinsonism network derived from monoaminergic clusters and causal lesions had similar positive and negative peaks. However, the monoaminergic depression network had the opposite connectivity compared to the depression network derived from causal brain lesions. The reasons for this are not clear, but it is possible that the effects of reduced monoamine transporter function are opposite to those of brain lesions of the network (eg, excitation by loss of inhibition rather than disruption).[71]

Limitations

There are some limitations to consider when interpreting the results of the present study. First, although [^{123}I]FP-CIT has affinity for SERT and NET, it is primarily validated for striatal dopamine transporters. Our findings reflect a composite of all three monoamines, weighted by the tracer's relative affinities and transporter concentrations in each region. The affinity of [^{123}I]FP-CIT to serotonin and norepinephrine is also weaker than that of dopamine, likely resulting in lower

sensitivity in the analyses. Thus, definite conclusions of brain-wide involvement, beyond the main monoaminergic subcortical nuclei such as the striatum, substantia nigra, LC, and raphe nuclei, of specific monoamines in the studied symptoms cannot be made based on [^{123}I] FP-CIT data alone. Second, although PPMI is the largest PD molecular imaging dataset, limited statistical power may have hindered the detection of weaker binding–symptom associations. Third, as the PPMI cohort included patients in relatively early phases of the disease with low numbers of patients with cognitive impairment, we likely had a limited power for detecting possible associations between cognitive impairment and monoamine function, which may become relevant in the later disease stages. Similarly, we were also not able to investigate nonmotor symptoms that typically are rare in the early stages of the disease, such as hallucinations (prevalence 2.9% at PPMI baseline). Fourth, it is possible that some of the findings linking lower [^{123}I] FP-CIT binding with nonmotor symptoms could reflect overall disease severity. However, we feel that it is unlikely that the findings were driven by disease severity, because the associations were detected cross-sectionally in patients with similar disease duration, and the analyses were adjusted for motor symptom severity and LEDD. Finally, the normative connectome was created from rs-fMRI data from healthy volunteers rather than patients with PD, which would have been optimal. However, previous work has shown that the effects of the disease on broad patterns of connectivity are minimal, unlikely causing any relevant bias in our findings.[72]

Conclusions

In summary, our findings demonstrate that depression, anxiety, and RBD are associated with focal monoaminergic deficits, each embedded within brain networks involving multiple neurotransmitters. The involvement of multiple neurotransmitters in each symptom could be conditional or synergistic and dependent on other factors, such as underlying dopaminergic deficit that characterizes PD, or environmental or neuropsychological factors. Thus, it is possible that for one of these symptoms to emerge, multiple factors are required, and interventions targeting one receptor subtype or even neurotransmitter system solely would not be ideal for treating the symptom. ■

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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

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