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ORIGINAL ARTICLE

Nonmotor and Dopamine Transporter Change in REM Sleep Behavior Disorder by Olfactory Impairment

Jee-Young Lee,[1,2] Eun Jin Yoon,[3,4] Yu Kyeong Kim,[3,5] Chae Won Shin,[6] Hyunwoo Nam,[1,2] Jae Min Jeong,[4,5] Han-Joon Kim,[5,6] Beomseok Jeon[2,7]

[1]Department of Neurology, Seoul National University–Seoul Metropolitan Government Boramae Medical Center, Seoul, Korea
[2]Department of Neurology, Seoul National University College of Medicine, Seoul, Korea
[3]Department of Nuclear Medicine, Seoul National University–Seoul Metropolitan Government Boramae Medical Center, Seoul, Korea
[4]Institute of Radiation Medicine, Seoul National University Medical Research Center, Seoul National University, Seoul, Korea
[5]Department of Nuclear Medicine, Seoul National University College of Medicine, Seoul, Korea
[6]Department of Neurology, Kyung Hee University Medical Center, Seoul, Korea
[7]Department of Neurology and Movement Disorders Center, Seoul National University Hospital, Seoul, Korea

ABSTRACT

Objective It is unclear whether the decline in dopamine transporters (DAT) differs among idiopathic rapid eye movement sleep behavior disorder (iRBD) patients with different levels of olfactory impairment. This study aimed to characterize DAT changes in relation to nonmotor features in iRBD patients by olfactory loss.

Methods This prospective cohort study consisted of three age-matched groups: 30 polysomnography-confirmed iRBD patients, 30 drug-naïve Parkinson's disease patients, and 19 healthy controls without olfactory impairment. The iRBD group was divided into two groups based on olfactory testing results. Participants were evaluated for reported prodromal markers and then underwent ^{18}F-FP-CIT positron emission tomography and 3T MRI. Tracer uptakes were analyzed in the caudate, anterior and posterior putamen, substantia nigra, and raphe nuclei.

Results Olfactory impairment was defined in 38.5% of iRBD patients. Mild parkinsonian signs and cognitive functions were not different between the two iRBD subgroups; however, additional prodromal features, constipation, and urinary and sexual dysfunctions were found in iRBD patients with olfactory impairment but not in those without. Tracer uptake showed significant group differences in all brain regions, except the raphe nuclei. The iRBD patients with olfactory impairment had uptake reductions in the anterior and posterior putamen, caudate, and substantia nigra ($p < 0.016$ in all, adjusted for age), which ranged from 0.6 to 0.8 of age-normative values. In contrast, those without olfactory impairment had insignificant changes in all regions ranging above 0.8.

Conclusion There was a clear distinction in DAT loss and nonmotor profiles by olfactory status in iRBD.

Key Words Idiopathic REM sleep behavior disorder; Olfaction; Parkinson's disease; Dopamine transporters; Positron emission tomography.

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Corresponding author: Jee-Young Lee, MD, PhD
Department of Neurology, Seoul National University–Seoul Metropolitan Government Boramae Medical Center, 20 Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Korea / **Tel:** +82-2-870-2476 / **Fax:** +82-2-831-2826 / **E-mail:** wieber04@snu.ac.kr
Corresponding author: Yu Kyeong Kim, MD, PhD
Department of Nuclear Medicine, Seoul National University–Seoul Metropolitan Government Boramae Medical Center, 20 Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Korea / **Tel:** +82-2-870-2591 / **Fax:** +82-2-870-3863 / **E-mail:** yk3181@snu.ac.kr

Prodromal Parkinson's disease (PD) is defined in individuals exhibiting symptoms or signs of the disease but not meeting the diagnostic criteria for clinical PD. Such individuals may have already developed some degree of neurodegeneration, but it is generally unknown when and how neurodegeneration starts and progresses in prodromal PD. Many prodromal markers of PD have been identified, but among them, polysomnography-confirmed idiopathic rapid eye movement sleep behavior disorder (iRBD) carries the highest likelihood of developing PD based on previous cohort study results.[1,2] Olfactory dysfunction is another important prodromal sign linked to early disease transition in large cohort studies.[3-8]

With regards to monitoring neurodegeneration in prodromal PD, it has been reported that iRBD patients have a faster rate of decline in putaminal dopamine transporter (DAT) binding than that in normal aging.[9] However, it is unclear when the putaminal DAT starts to decline at an increased rate because some iRBD patients have stable disease conditions for more than 20 years, whereas others develop neurodegenerative disease within 5 years. Because the olfactory bulb is suggested to be an initial pathological site in PD and Lewy body diseases as well as in the staging of incidental Lewy body diseases, a Parkinson Associated Risk Syndrome study[5] showed that selecting hyposmic individuals enriches the potential prodromal PD population, and combining hyposmia with male sex and constipation further increases the probability of a DAT deficit. However, it is still unknown whether DAT declines differ among iRBD patients with different levels of olfactory impairment or differences in other prodromal markers. Those previous DAT imaging studies used single photon emission computed tomography (SPECT).[5,9] SPECT is inferior to positron emission tomography (PET) regarding the resolution for quantitative assessment of DAT expression that may reveal early compensatory change[10,11] and for investigating DAT inside the substantia nigra.[12-14]

This study primarily investigated DAT changes in the caudate nucleus, putamen, and substantia nigra in iRBD patients by analyzing *N*-(3-^{18}F-fluoropropyl)-2-carbomethoxy-3-(4-iodophenyl) nortropane (^{18}F-FP-CIT) PET data in the baseline. A secondary aim was to reveal whether neurodegeneration differs by olfactory status in iRBD patients. We constructed a prospective cohort with a 4-year follow-up plan consisting of three age-matched groups: 1) healthy controls without reported prodromal features as defined below; 2) iRBD patients without and with hyposmia; and 3) newly diagnosed drug-naïve PD patients with prolonged symptoms of probable RBD. Then, we prospectively evaluated our cohort for reported prodromal markers and undertook correlative analysis of measurements obtained by ^{18}F-FP-CIT PET.

MATERIALS & METHODS

Study participants

This study was approved by the Institutional Review Board of Boramae Medical Center (16-2013-101). All participants gave informed consent prior to participation in the study in accordance with the Declaration of Helsinki.

A cohort was consecutively constructed between September 2013 and August 2015. The iRBD group consisted of patients aged 60 to 80 years old. The diagnosis of RBD was made according to the International Classification of Sleep Disorders, 2nd edition, criteria by a sleep disorders specialist (H.W.N.) and confirmed by video polysomnography. The drug-naïve PD patients were consecutively recruited among those who were newly diagnosed during the study period in accordance with the UK PD brain bank criteria. All PD patients had a prolonged history of probable RBD with an RBD screening questionnaire score ≥ 5.[15,16] The healthy control group was recruited during the study period from those who visited the same hospitals for health check-ups. The PD and control groups were recruited to be matched for the ages of the iRBD group.

Exclusion criteria for all three groups included white matter changes greater than grade I small vessel disease, space-occupying lesions, structural lesions revealed on conventional brain MRI, history of nasal or sinus diseases, history of depression or other psychiatric illness, presence of other neurological diseases, presence of dementia or symptoms of cognitive fluctuation and visual hallucination suggesting dementia with Lewy bodies (DLB). For this, all subjects underwent a validated neuropsychological test battery (Seoul Neuropsychological Screening Battery; Human Brain Research & Consulting, Seoul, Korea)[17] during the screening period. We also excluded patients taking antipsychotics or antidepressants that affect the dopamine and serotonin systems due to the possibility of alterations in tracer uptake.

Clinical evaluations

Demographic data, information on RBD symptom duration, and age at disease onset were recorded. Olfactory function was evaluated by using the brief smell identification test (B-SIT)[18,19] and the buthanol threshold test (BTT).[20,21] We defined olfactory impairment in our patients only if individuals consistently showed abnormal BTT (< 6) and more than a mild degree of impairment in B-SIT (scores < 6). Parkinsonian nonmotor and motor symptoms were assessed by using the Movement Disorders Society Task Force-revised Unified PD Rating Scale (MDS-UPDRS; evaluations performed by a certified movement specialist J.Y.L.) and the Non-Motor Symptoms Scale (NMSS).[22] Mild parkinsonian motor symptoms were categorized into four do-

mains based on the MDS-UPDRS part III: 1) rigidity (item 3.3), 2) limb and body bradykinesia (items 3.4–3.8 and 3.14), 3) axial symptoms (items 3.1, 3.2, and 3.9–3.13), and 4) rest tremor (items 3.17 and 3.18). General cognitive status was determined by using the Korean version of the Mini-Mental Status Examination and Geriatric Depression Scale-15, and cognitive functions were further evaluated using the digit span backward test, Korean color Word Stroop Test, Trail Making Test (TMT) A and B, Controlled Oral Word Association Test, Seoul Verbal Learning Test (SVLT), Rey Complex Figure Test (RCFT) copy, and Korean version of the Boston Naming Test.

Image acquisition

Before scanning, all subjects were confirmed to be in a drug-naïve state both for dopaminergic and serotonergic drugs. Each participant underwent PET (Philips Gemini TF-64 PET/CT scanner, Philips Healthcare, Best, the Netherlands). After a bolus injection of 185 MBq of ^{18}F-FP-CIT, subjects waited for 2 hours and then underwent 10 minute-emission scans. After routine corrections for physical effects, images were reconstructed by applying a 3D row-action maximum-likelihood algorithm for 90 slices, each 2 mm thick, in a 128 × 128 matrix with corrections for attenuation and scatter.[23] Each participant also underwent 3T brain MRI (Philips Achieva, Philips Healthcare). The acquisition parameters for the volumetric T1 images were as follows: repetition time/echo time = 9.9/4.6, flip angle of 8.0°, 1 mm slice thickness, image matrix of 224 × 224 × 180, and voxel size of 0.98 × 0.98 × 1 mm^3.

Analysis of 18F-FP-CIT uptakes

In addition to basal ganglia structures, we included raphe nuclei as a reference for serotonin transporter uptake by considering that FP-CIT has cross-affinity to serotonin transporters. Anatomical boundaries for the bilateral caudate, putamen, and cerebellum (as a reference) were obtained automatically on T1-weighted MR images by using the segmentation tool FIRST integrated in FSL version 5.0.2 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/first). The putamen for each hemisphere was divided into anterior and posterior halves along its longitudinal axis.[24] For the substantia nigra and the dorsal and median raphe nuclei, circular-shaped, fixed-size regions of interest were set manually on PET-overlaid MR images by using ITK-SNAP software (version 3.6.0-RC1; www.itksnap.org) (Figure 1). For raphe nuclei, we used the inferior colliculus as a landmark following the protocol reported previously.[25,26] After identifying the anatomical locations, we placed the regions of interest on 1 mm-thickness transverse slices centered on the maximal PET signals. The volume of interest was 46.3 mm^3 for the subthalamic nucleus, 169.8 mm^3 for the substantia nigra, and 127.3 mm^3 for each raphe nucleus. The specific uptake of ^{18}F-FP-CIT in the target volume of inter-

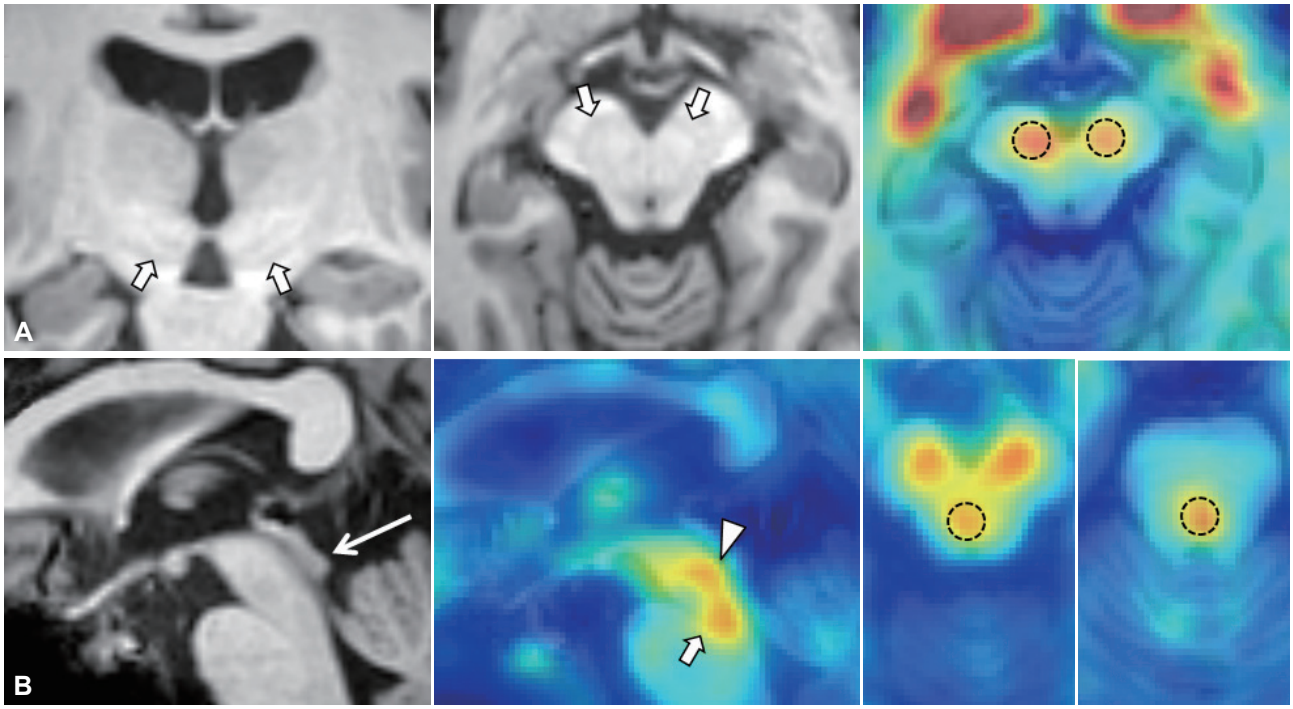


Figure 1. Defining regions of interest for the substantia nigra and raphe nuclei. Circular-shaped regions of interest with a fixed size were set manually on ^{18}F-FP-CIT PET images overlaid onto MR images on transverse slices (1 mm thickness) centered on the maximal PET signal in each region. (A) The substantia nigra (arrows) on four transverse slices with a radius of 4 voxels (169.8 mm^3), and (B) the dorsal (arrow head) and median (arrow) raphe nuclei on three transverse slices with a radius of 4 voxels (127.3 mm^3). A long arrow indicates the inferior colliculus.

est was calculated as follows: specific uptake of ^{18}F-FP-CIT = [(average count in target/average count in cerebellum) - 1].

Statistical analysis

Initial analysis included comparisons of clinical variables and tracer uptakes in each region among the PD, iRBD, and control groups. Subsequent analysis compared the two subgroups of iRBD patients with the control subjects. In the analysis of ^{18}F-FP-CIT uptake according to the iRBD subgroups, we used linear regression analysis with age as a cofactor after confirming the fulfilment of the normality assumption in our FP-CIT data distribution. For other analyses, we used ANOVA, nonparametric Kruskal-Wallis, and Mann-Whitney U tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. In the post hoc analysis of intergroup comparisons, the Bonferroni correction was applied for multiple comparisons. Finally, we conducted correlation analysis between the severity of nonmotor symptoms and regional ^{18}F-FP-CIT uptake in the iRBD group by applying partial correlation analysis controlling for age. We used SPSS software (version 19.0; IBM Corp., Armonk, NY, USA) for all statistical analyses, and the significance level was set at 0.05 (two-tailed).

RESULTS

Of the 33 eligible PD patients, 31 iRBD patients, and 20 controls, 3 PD, 1 iRBD, and 1 control subjects were excluded from the study for the following reasons: structural abnormalities on MRI, failure of image acquisition, or refusal to scan. The baseline characteristics of the cohorts are summarized in Table 1. There were no differences in age and sex distributions, general cognition status, or depression scores among the three groups.

Clinical assessments in three cohorts

Olfactory impairment was detected in 38.5% of iRBD patients and 50% of PD patients (Table 1). Because olfactory loss may be a risk factor for neurodegenerative diseases other than Lewy body diseases, we intentionally included only normal controls without hyposmia during the screening period. Analysis of nonmotor symptom items in the MDS-UPDRS part I revealed a significant group difference only in constipation (item 1.11). The mean scores of item 1.11 showed a linearly increasing tendency from the control to PD groups ($p = 0.027$). A similar but insignificant trend was found in items indicating anxiety (item 1.4), apathy (item 1.5), orthostatic dizziness (item 1.12), and fatigue (item 1.13) (Figure 2A). When we compared nonmotor symptoms by NMSS domain, the Mood/cognition and Gastrointestinal tract domains showed trends of linearly increasing scores from the control to PD groups ($p = 0.043$ and 0.010, respectively). Similar but insignificant trends were observed in the domains of sleep/fatigue, urinary, and sexual dysfunctions (Figure 2B). For the comparison of cognitive functions, we used z-scores of each cognitive test reflecting age and educational years. There were significant differences in the TMT-B and SVLT recognition scores ($p = 0.041$ and 0.019, respectively) and a tendency of differences in the RCFT copy ($p = 0.086$), in which the PD and iRBD groups showed lower scores than the control group. When we defined impairment in each cogni-

Table 1. Baseline characteristics of the study cohorts

Characteristics	Drug-naïve PD	iRBD	Healthy controls	*p*-value*
Age, yrs	69.2 ± 7.0	70.5 ± 5.9	70.1 ± 4.8	0.703
Sex, F/M (*n*)	14/19	14/17	12/7	0.323†
Duration of RBD, yrs	4.8 ± 3.9	4.3 ± 3.0	-	0.717
Duration of PD, yrs	1.1 ± 0.5	-	-	
Hoehn & Yahr stage	1.6 ± 0.5	-	-	
K-MMSE score	27.1 ± 2.6	27.6 ± 2.1	28.1 ± 1.8	0.234
GDS-15 score	6.9 ± 3.6	6.0 ± 3.1	5.5 ± 3.8	0.346
MDS-UPDRS score				
Part I	9.3 ± 7.2	7.1 ± 3.5	5.7 ± 3.8	0.081
Part II	8.6 ± 6.5	3.3 ± 3.3	2.6 ± 2.9	< 0.001§
Part III	25.0 ± 11.9	5.8 ± 4.9	0.7 ± 1.3	< 0.001§,‖
Hyposmia, %	50.0	38.5	0‡	0.002†,‖,¶
NMSS score, total	41.5 ± 50.7	24.3 ± 20.1	19.5 ± 11.6	0.069

Data are shown as the mean ± standard deviation unless otherwise indicated. *comparison among the three groups by the ANOVA test unless otherwise specified, †comparison among the three groups by the chi-square test, ‡only healthy subjects who were not confirmed to have hyposmia were included in the control group in this cohort study (see details in the Materials and Methods section), §significant difference in post hoc comparisons between the PD and each of the two other groups ($p < 0.016$), ‖significant difference in post hoc comparison between the iRBD and control groups ($p < 0.016$), ¶significant difference in post hoc comparison between the PD and control groups ($p < 0.016$). PD: Parkinson's disease, iRBD: idiopathic rapid eye movement sleep behavior disorder, K-MMSE: Korean version of Mini-Mental Status Exam, GDS: Geriatric Depression Scale, MDS-UPDRS: Movement Disorders Society Task Force-revised Unified PD Rating Scale, NMSS: Non-Motor Symptom Scale.

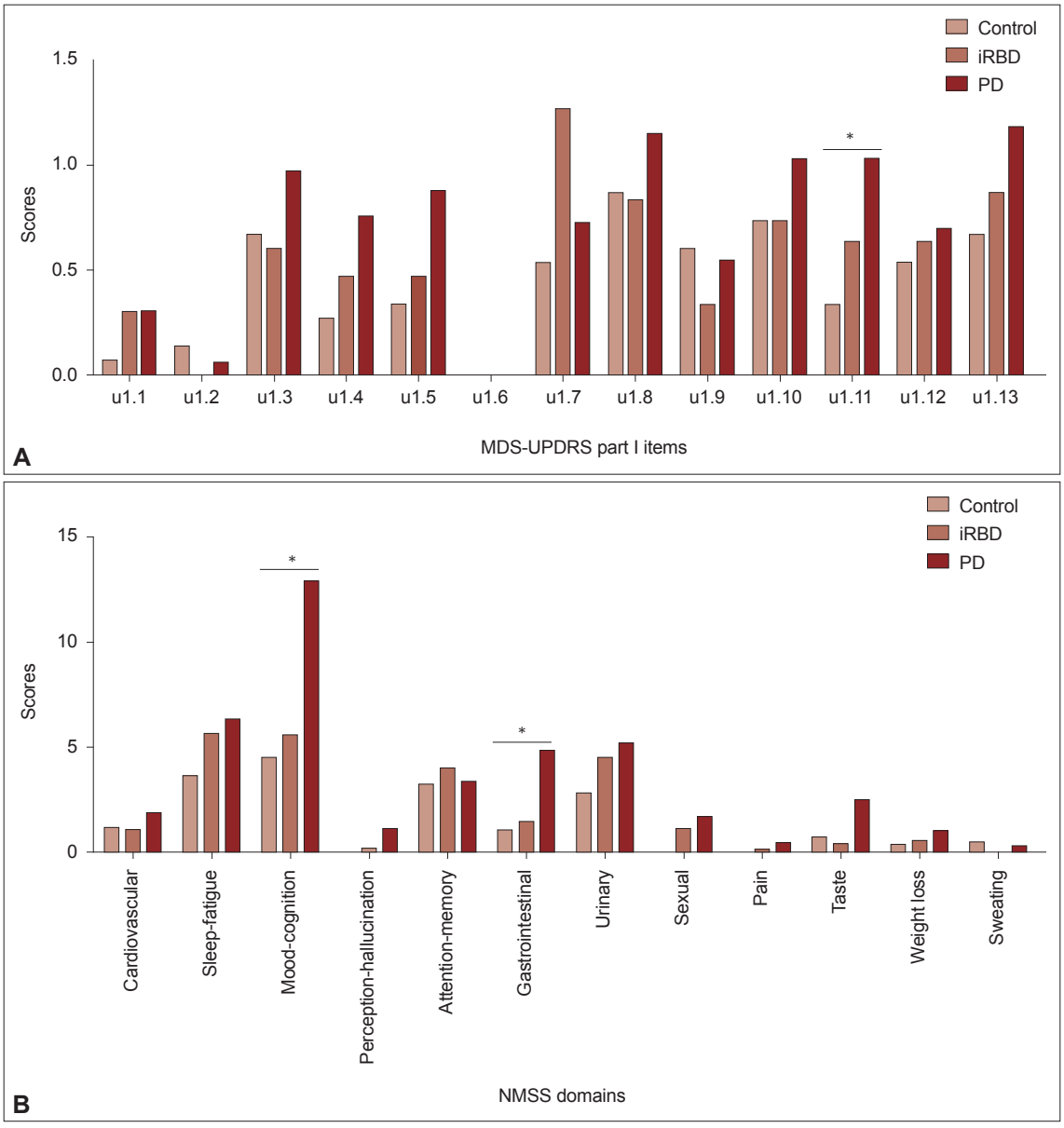


Figure 2. Comparison of nonmotor symptoms among the PD, iRBD, and healthy control groups in the MDS-UPRS part I items (A) and in the NMSS domains (B). PD: drug-naïve, newly diagnosed Parkinson's disease patients with probable rapid eye movement sleep behavior disorder, iRBD: idiopathic rapid eye movement sleep behavior disorder patients, HC: healthy controls, MDS-UPDRS: Movement Disorders Society Task Force-revised Unified PD Rating Scale; NMSS: Non-Motor Symptom Scale. The items of the MDS-UPDRS part 1 represent u1.1: cognitive impairment, u1.2: hallucinations and psychosis, u1.3: depressed mood, u1.4: anxious mood, u1.5: apathy, u1.6: features of dopamine dysregulation syndrome, u1.7: sleep problems, u1.8: daytime sleepiness, u1.9: pain and other sensations, u1.10: urinary problems, u1.11: constipation problems, u1.12: light headedness on standing, u1.13: fatigue. *indicates a significant group difference ($p < 0.05$).

tive test if the z-score was below 1.5 standard deviations (SD) of normative values, the PD and iRBD groups showed a higher frequency of impairments in the TMT-B and RCFT copy compared to the control group (N, numbers of subjects with impairment = 8, 9, and 0 for PD, RBD, and controls, $p = 0.034$, and $n = 7$, 14, and 3, $p = 0.029$, respectively). Details of the neuropsychological test results are depicted in Supplementary Table 1 (in the online-only Data Supplement).

^{18}F-FP-CIT uptakes in three cohorts

There was a prominent decrease in the DAT density measured by ^{18}F-FP-CIT uptake in the PD group compared to those in the iRBD and control groups in all regions, but uptake was indistinguishable in the raphe nuclei among the three groups and between any two groups. The mean ^{18}F-FP-CIT uptake of the iRBD group was intermediate between those of the PD and control groups (Table 2). In the post hoc comparisons with controls, the

iRBD group had reduced ^{18}F-FP-CIT uptake in the left posterior putamen (p = 0.014) and the bilateral substantia nigra (p = 0.008 and 0.005).

Analysis in iRBD patients with and without olfactory impairment

Demographic and clinical features, including the duration of RBD, the MDS-UPDRS total, part 2 and 3 scores, total NMSS score, K-MMSE, and GDS scores of the two iRBD subgroups, were similar between the two iRBD subgroups (for all $p > 0.05$, Supplementary Table 2 in the online-only Data Supplement), but the iRBD patients with olfactory impairment tended to be male and to have a high MDS-UPRDS part I score (p = 0.058 and 0.060, respectively) (Supplementary Table 2 in the online-only Data Supplement).

Table 2. Estimated ^{18}F-FP-CIT uptakes in volumes of interest in study cohorts

Regions	Drug-naïve PD	iRBD	Healthy controls	*p*-value*
Caudate nucleus				
Left	2.23 ± 0.93	3.46 ± 1.10	3.89 ± 0.78	< 0.001
Right	2.31 ± 0.85	3.40 ± 1.23	3.92 ± 0.85	< 0.001
Putamen, anterior				
Left	2.67 ± 0.74	4.91 ± 1.30	5.56 ± 0.89	< 0.001
Right	2.77 ± 0.84	4.90 ± 1.35	5.65 ± 0.88	< 0.001
Putamen, posterior				
Left	1.57 ± 0.62	4.23 ± 1.36	4.99 ± 0.88	< 0.001†
Right	1.69 ± 0.56	4.24 ± 1.39	4.90 ± 0.86	< 0.001
Substantia nigra				
Left	1.42 ± 0.28	1.84 ± 0.37	2.10 ± 0.31	< 0.001†
Right	1.40 ± 0.28	1.74 ± 0.38	2.02 ± 0.28	< 0.001†
Raphe nucleus				
Dorsal	1.37 ± 0.44	1.36 ± 0.46	1.48 ± 0.40	0.625
Median	1.33 ± 0.42	1.27 ± 0.42	1.30 ± 0.35	0.853

Data are shown as the mean ± standard deviation. *comparison among the three groups of PD, iRBD, and controls by the ANOVA test, †significant difference between iRBD and control groups by post hoc analysis (p = 0.008 and 0.005 for the left and right substantia nigra, and p = 0.014 for the left posterior putamen). PD: Parkinson's disease, iRBD: idiopathic rapid eye movement sleep behavior disorder.

Nonmotor, cognition, and parkinsonian symptoms

In the analysis of nonmotor symptoms, we found a significant difference only in constipation (i.e., item 1.11) of the MDS-UPDRS part I and in the gastrointestinal, urinary, and sexual symptom domains of the NMSS. The scores of these nonmotor symptoms were high in the iRBD-olfactory impairment group, but the scores in the iRBD without olfactory impairment group were indifferent from those in the control group (Table 3). Cognitive test scores and mild parkinsonian sign scores were not significantly different between the two iRBD subgroups (Supplementary Table 2 in the online-only Data Supplement). However, the TMT-B score tended to be lower (-2.03 ± 2.68 vs. -0.66 ± 1.34, p = 0.388), and the bradykinesia score tended to be higher in the olfactory impairment group than in the no impairment group (3.56 ± 2.64 vs. 2.88 ± 3.52, p = 0.162), but the difference was not statistically significant.

Dopamine transporter reductions

When we analyzed the DAT PET data, the iRBD with olfactory impairment group showed significant reductions in ^{18}F-FP-CIT uptake in the caudate nucleus, anterior and posterior putamen, and substantia nigra compared to the HC group (Figure 3). In contrast, the iRBD without olfactory impairment group showed no regions of significantly reduced ^{18}F-FP-CIT uptake (Figure 3). Relative DAT reductions averaged for both hemispheres in each iRBD subgroup in comparison to the HC and PD groups are depicted in Figure 4. DAT densities with reference to age-adjusted normative mean values were all above 0.8 in iRBD patients without olfactory impairment, whereas those ranged from 0.6 to 0.8 in all regions in iRBD patients with impairment (Figure 4).

When we conducted correlation analysis in iRBD patients for DAT with nonmotor symptoms, a significant negative correlation was detected between the constipation score and ^{18}F-FP-CIT uptakes in the bilateral anterior and posterior putamen and

Table 3. Characteristic nonmotor symptoms that have significant group differences among the iRBD patients with and without olfactory impairment and healthy controls

	iRBD		Healthy controls	*p*-value*
	Olfactory impairment	No olfactory impairment		
MDS-UPDRS I.11 (constipation)	1.08 ± 0.64	0.08 ± 0.29	0.33 ± 0.62	< 0.001†‡
NMSS domain 6 (gastrointestinal tract)	2.57 ± 2.03	0.25 ± 0.45	1.00 ± 2.27	0.002†‡
NMSS domain 7 (urinary)	6.00 ± 5.73	3.75 ± 3.94	2.80 ± 1.90	0.021†‡
NMSS domain 8 (sexual function)	3.00 ± 3.92	0.25 ± 1.00	0.00 ± 0.00	0.023†

Data are shown as the mean ± standard deviation. *comparison among the three groups by the Kruskal-Wallis test, †significant difference between the iRBD-olfactory impairment and control groups by the Mann-Whitney U test (p < 0.016), ‡significant difference between the two iRBD subgroups by the Mann-Whitney U test (p < 0.016). There was no significant difference between the iRBD-no olfactory impairment and control groups in any of the items and domains investigated. iRBD: idiopathic rapid eye movement sleep behavior disorder, MDS-UPDRS: Movement Disorders Society Task Force-revised Unified Parkinson's Disease Rating Scale, NMSS: Non-Motor Symptom Scale.

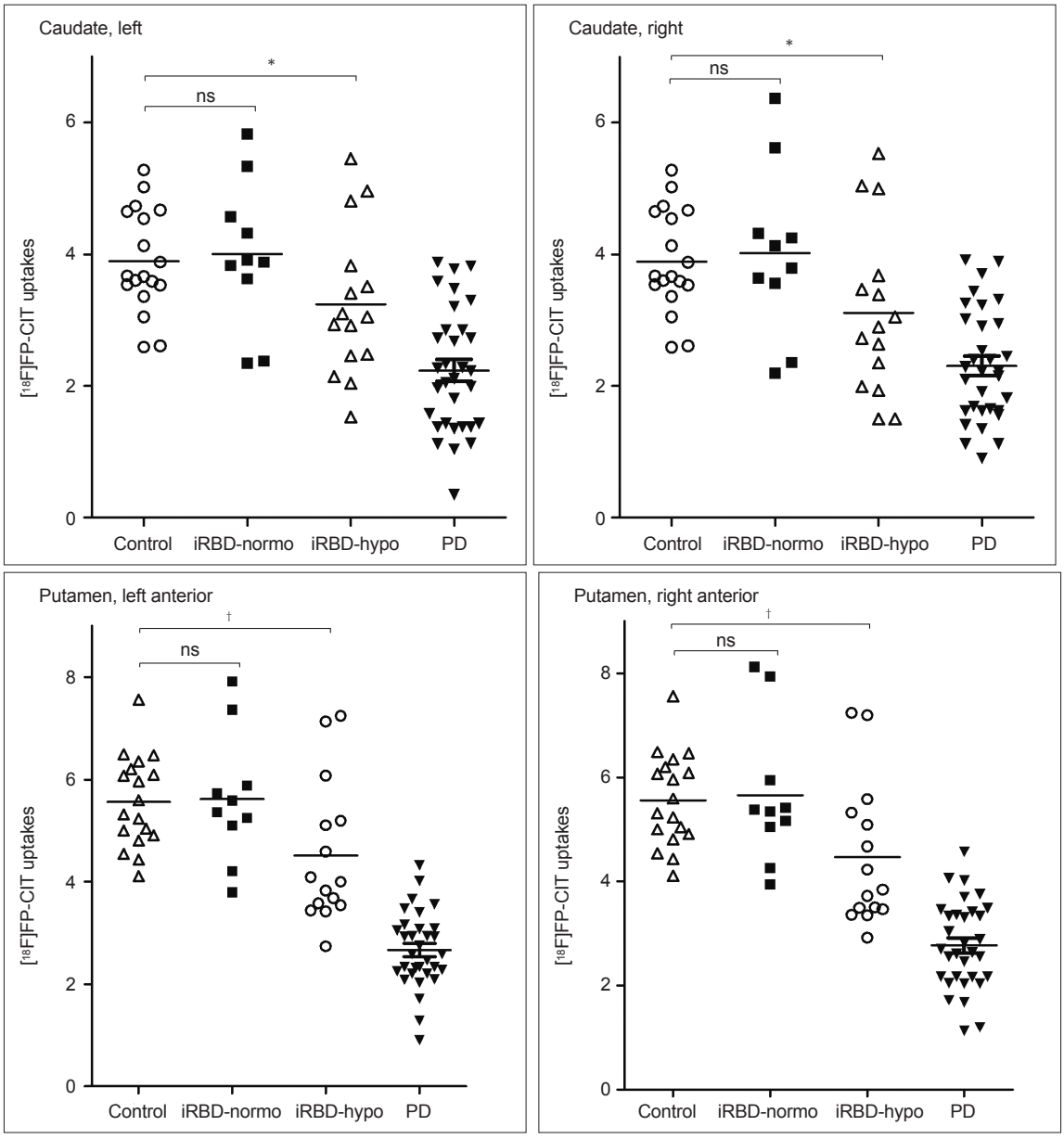


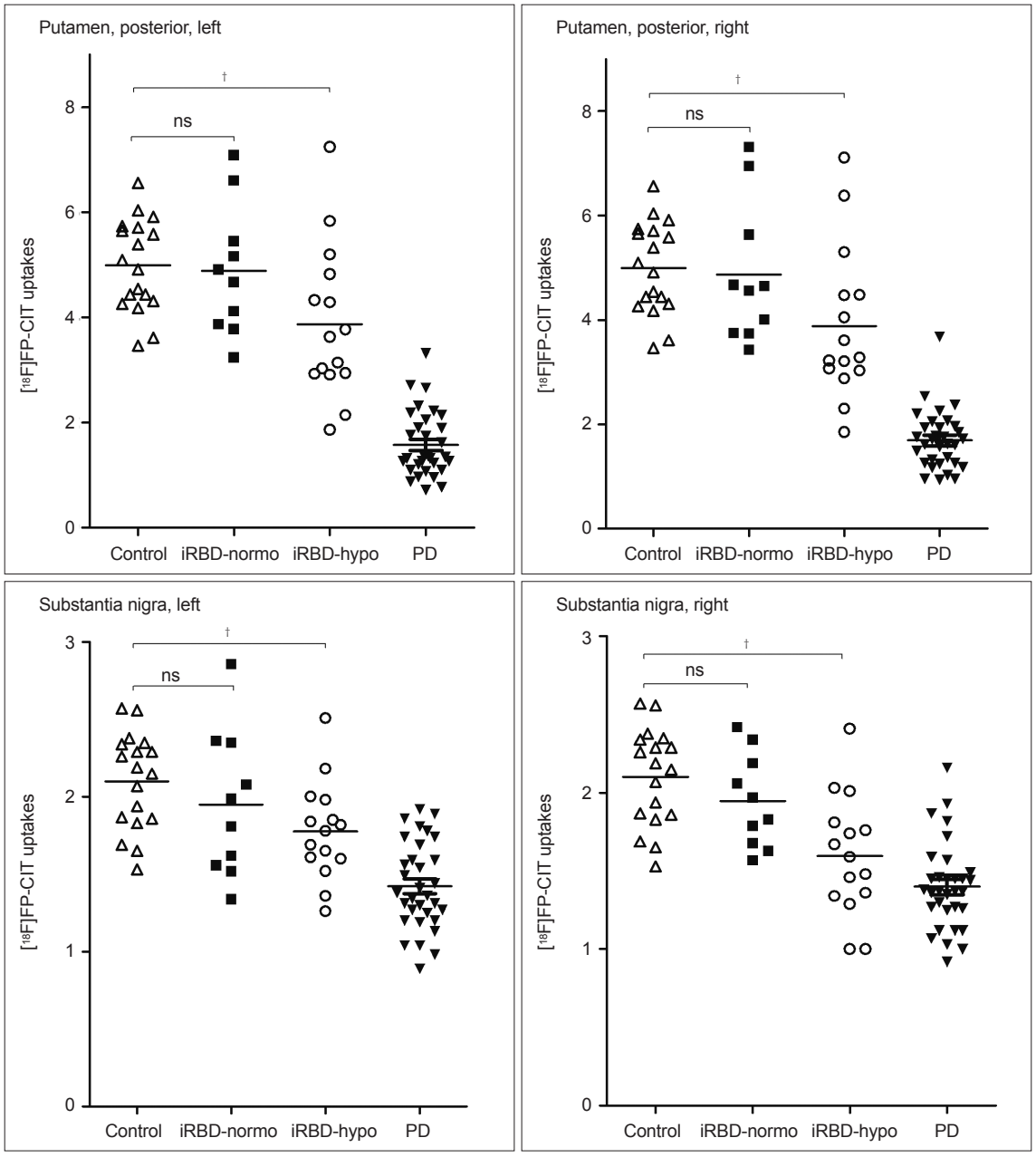
Figure 3. Dopamine transporter uptake in each iRBD subgroup. ^{18}F-FP-CIT uptakes in the caudate, anterior and posterior putamen, and the substantia nigra are depicted in healthy controls, iRBD-no olfactory impairment and iRBD-olfactory impairment groups, and PD group. Comparisons between the iRBD subgroups and the control group were adjusted for age. ns: no significant difference, iRBD: idiopathic rapid eye movement sleep behavior disorder patients, PD: drug-naïve Parkinson's disease patients. *if adjusted $p < 0.05$, †if adjusted $p < 0.01$.

substantia nigra (correlation coefficient ranged from -0.260 to -0.358, $p < 0.05$ for all, after controlling for age by partial correlation analysis). For other nonmotor symptoms and cognitive function scores, there were no significant correlations with DAT uptakes.

DISCUSSION

The present study revealed features of DAT changes in relation to olfactory impairment and other prodromal features that were assessed systematically in our iRBD cohort.

As shown in Figure 2, a trend of increasing severity from normal to disease conditions was observed in several nonmotor symptoms, including anxiety and apathy (or mood-cognition), constipation (gastrointestinal), some autonomic dysfunction (urinary, sexual, orthostatic dizziness), and fatigue. Although statistical significance was only detected in the gastrointestinal and mood-cognition symptoms, these nonmotor symptoms might be more disease-related than those without such trends. As reported in a large iRBD cohort,[27] there was a close relation-



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ship between hyposmia and constipation in our cohort. The constipation symptom score increased from normal to disease conditions, and that score correlated with the DAT uptake reduction. Follow-up analysis of our cohort is needed to reveal the temporal relationship between the emergence of nonmotor and motor parkinsonian features and the DAT reduction in iRBD.

By performing a quantitative assessment of DAT, we could clearly show the level of DAT reductions in the iRBD patients with olfactory impairment at 0.6−0.8 of age-adjusted normal values. There was also a distinctive pattern of DAT reduction in the putamen and caudate between the iRBD with olfactory impairment and drug-naïve PD groups. In the PD group, the DAT reduction in the posterior putamen was large, whereas that in the caudate was relatively small. In contrast, the DAT reductions in both the posterior putamen and the caudate were similar in the iRBD with olfactory impairment group. Therefore, it is suggested that neurodegeneration in iRBD patients with hyposmia may not be confined to a motor part of the basal gan-

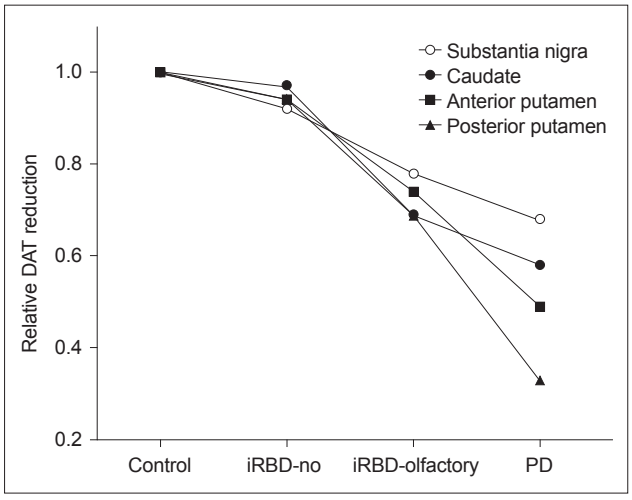

Figure 4. Relative reduction of dopamine transporter (DAT) binding in iRBD patients. Relative reductions of DAT binding in each region were estimated with reference to an age-normative value of ^{18}F-FP-CIT uptakes of each region in healthy controls. Average values from both hemispheres are plotted. iRBD group: idiopathic rapid eye movement sleep behavior disorder patients, PD group: drug-naïve, newly diagnosed Parkinson's disease patients.

glia. Combining DAT data with a high frequency of autonomic dysfunction and with the fact that common parkinsonism appearing in iRBD patients is known to be postural instability gait disturbance (PIGD) type,[28] it is necessary to follow-up with this cohort to confirm whether our hyposmic iRBD patients will eventually develop PIGD-type poor prognostic PD or DLB-type Lewy body disease.

We showed DAT reduction in the substantia nigra as well as in the striatum in our iRBD patients with olfactory impairment as well as in PD patients. The greatest statistical significance found in both substantia nigra might be affected by the variance difference in DAT data between the striatum and nigra. It is perceived that nigral neuronal loss starts at the distal axons,[29] and thus, greater variability in the striatum was expected. On the other hand, DAT regulation in the nigra in PD was shown in a pathological study, as there may be a shift into neurons that express a lower level of DAT.[10] However, studies are needed to reveal nigral DAT regulation in early stage PD, and further studies using a specific DAT tracer should be undertaken to replicate our findings.

Most of the ^{18}F-FP-CIT uptake in raphe nuclei reflects serotonin transporters in the serotonergic cell bodies.[28] We included raphe nuclei in this analysis as a reference region for serotonergic binding because of the cross-affinity of FP-CIT to the serotonin transporter. Our study revealed that both raphe nuclei uptakes were not different among the groups. As in our study, preservation of the serotonergic system in early PD has been observed with tracers binding to serotonin transporters.[30,31] However, compared to serotonin receptor imaging, serotonin transporter uptake may not provide a robust correlation with serotonergic function in the brain.[32] Thus, serotonergic involvement in iRBD needs to be further investigated in studies that use tracers binding to postsynaptic receptors.

Our data need to be interpreted with caution. First, we need to confirm the relationship between the nonmotor feature and regional neurodegenerative changes through a longitudinal follow-up. Second, the manually driven regions of interest for the substantia nigra might have reduced the power of detecting neurodegenerative changes because it had to be based on the axial MRI images, although the configurations of these structures are oblique. Third, the possibility that some of our iRBD patients will develop a neurodegenerative disease other than PD was not excluded. However, hyposmia is a specific premotor sign of Lewy body diseases rather than multiple system atrophy (MSA),[33] and our iRBD patients without olfactory impairment did not have symptoms suggesting autonomic dysfunctions or neurological signs of MSA.

This study demonstrated that hyposmia can predict the level of DAT reduction and the presence of prodromal nonmotor features in iRBD subjects. Longitudinal follow-up of our cohort would help to reveal whether neurodegeneration differs by hyposmia over time in iRBD and to elucidate the temporal relationship between the emergence of clinical features and DAT loss in iRBD.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.18061.

Conflicts of Interest

The authors have no financial conflicts of interest.

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ORCID iDs

Jee-Young Lee https://orcid.org/0000-0002-9120-2075
Yu Kyeong Kim https://orcid.org/0000-0002-3282-822X

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