




Lack of association between dopamine transporter loss and non-motor symptoms in patients with Parkinson's disease: a detailed PET analysis of 12 striatal subregions

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Abstract

Introduction Patients with Parkinson's disease (PD) present a variety of non-motor symptoms. However, it remains unclear whether dopamine depletion is related to non-motor symptoms, and which non-motor symptoms are significantly dependent on dopaminergic deficit.

Methods Forty-one patients with PD who underwent positron emission tomography imaging of dopamine transporters (DATs) were recruited for this study. The striatum was divided into 12 subregions, and DAT activity, as striatal dopaminergic concentration, was calculated in each subregion. In addition to measuring motor symptoms using the Unified Parkinson's Disease Rating Scale-part III (UPDRS-III), various non-motor symptoms were assessed using the Montreal cognitive assessment, frontal assessment battery, Beck depression inventory (BDI), Beck anxiety inventory, PD sleep scale (PDSS), PD fatigue scale, and non-motor symptoms scale (NMSS) for PD.

Results For simple linear regression analyses, dopaminergic depletion in all striatal subregions was negatively correlated with the UPDRS-III score. The most relevant non-motor symptom assessment related to dopaminergic loss in the 12 subregions was NMSS, followed by BDI and PDSS. However, following multiple linear regression analyses, dopaminergic depletion in the 12 striatal subregions was not related with any of the non-motor symptoms. Conversely, dopaminergic deficit in the right anterior and posterior putamen was associated with the UPDRS-III score.

Conclusions Striatal dopaminergic depletion was not significantly correlated with any of the various non-motor symptoms in PD. Our findings suggest that non-dopaminergic systems are significantly implicated in the pathogenesis of non-motor symptoms in patients with PD.

Keywords 18F-FP-CIT PET · Dopamine depletion · Dopamine transporter imaging · Non-motor symptom · Parkinson's disease

Introduction

The pathologic hallmark of Parkinson's disease (PD) is characterized by progressive neurodegeneration which includes

the loss of dopaminergic neurons in the pars compacta of substantia nigra with decreased dopamine release in the striatum, resulting in motor symptoms including tremor, rigidity, and bradykinesia. Abnormal accumulation of misfolded α -

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synuclein—Lewy bodies and Lewy neurites—further leads to progressive neuronal loss in both central and peripheral nervous systems with neuronal selectivity. Recently, Goedert et al. suggested that Lewy pathology begins in the enteric nervous system and/or the olfactory bulb, with subsequent propagations of Lewy pathology occurring in the lower brain stem, the upper brain stem, and cerebral cortex [1]. Parkinsonian motor symptoms start to develop after significant dopaminergic reduction (at least 40–50%) in the striatum [2, 3]. Dopamine transporter (DAT) imaging with positron emission tomography (PET) using a radiotracer such as ^{18}F -radiolabeled N-(3-fluoropropyl)-2 β -carboxymethoxy-3 β -(4-iodophenyl) nortropane (^{18}F -FP-CIT) can be used to assess the dopaminergic degeneration of the striatum [4]. The characteristic finding detected by DAT imaging is dopaminergic reduction in the posterior putamen, which is known to be involved in basal ganglia circuits of parkinsonian motor symptoms. Furthermore, recent studies have shown significant negative correlations between striatal dopaminergic uptake on DAT imaging and the severity of motor symptoms in patients with PD [3, 5].

Patients with PD present with various non-motor features. Some non-motor symptoms including REM sleep behavior disorder (RBD), constipation, depression, or hyposmia, which may occur even in the premotor stage of PD [6, 7]. As PD progresses, non-motor features such as pain, fatigue, orthostatic hypotension, urinary difficulty, psychiatric symptom, or dementia may be present in varying degrees of severity [7, 8]. Unlike motor symptoms, it remains controversial whether non-motor symptoms are linked to dopaminergic deficits of the striatum. Since non-motor symptoms in PD are diverse and connected with each other, a comprehensive analysis is required for exploring the detailed relationships between the level of striatal dopamine depletion and the severity of various non-motor symptoms.

Accordingly, we aimed to investigate correlations between non-motor symptoms and striatal dopaminergic deficits measured by ^{18}F -FP-CIT PET. In this study, various scales for different non-motor symptoms including depression, anxiety, fatigue, sleep quality, global cognition, and frontal executive function were assessed. Furthermore, the striatum was divided into 12 subregions to uncover which areas of the striatum correlate with non-motor symptoms.

Methods

Patient selection and clinical assessment of motor and non-motor symptoms

A total of 151 patients with parkinsonism visited and registered in the hospital between 2013 and 2016. We consecutively reviewed PD patients who underwent both brain magnetic

resonance imaging (MRI) and ^{18}F -FP-CIT PET in our hospital. PD was diagnosed according to not only the UK Brain Bank Criteria [8, 9], but also the typical pattern of dopaminergic depletion on the DAT scans with ^{18}F -FP-CIT [10]. Since this study was designed as a retrospective analysis to investigate correlations between striatal dopamine depletion and non-motor symptoms, we applied more strict criteria to include appropriate patients in the scope of the study. We excluded patients based on the following: (1) any evidence of considerable brain damage including cerebral ischemia, stroke, or encephalomalacia by reviewing brain MRI of each patient; (2) equivocal findings of ^{18}F -FP-CIT PET to rule out the possibility of secondary parkinsonism or scans without evidence of dopamine deficit; (3) any serious medical illness including renal insufficiency, hepatic failure, infection, or cancer; (4) any previous history of neuropsychological medication for depression, anxiety, insomnia, or dementia to exclude a potential possibility of medication effect for non-motor symptoms; (5) below 20-point score on the Korean version of Mini-Mental State Examination (K-MMSE) indicating moderate to severe dementia; (6) a possibility of uncertain diagnosis with poor levodopa responsiveness or any atypical feature during the follow-ups in our hospital; and (7) any patient with insufficient or inappropriate data in their medical records. Following screening, 41 patients with PD were enrolled in the study. This study was approved by the hospital's institutional review board (IRB) committee (IRB no. 2017-07-020).

Parkinsonian motor symptoms were evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS) part III and the Hoehn and Yahr (H&Y) stage. In addition, levodopa equivalent daily dose (LEDD) was calculated for each subject. Cognitive function was assessed using the Korean version of the Montreal cognitive assessment (MoCA-K) as a parameter of global cognition [11], and the frontal assessment battery (FAB) was used to assess frontal executive function [12]. Other non-motor symptoms were investigated using the Beck depression inventory (BDI) [13], the Beck anxiety inventory (BAI) [14], the Parkinson's disease sleep scale (PDSS) [15], the Parkinson fatigue scale (PFS) [16], and the non-motor symptoms scale (NMSS) [17].

PET image acquisition and quantitative analysis of striatal subregions

DAT scans using ^{18}F -FP-CIT were completed using a PET/computed tomography (CT) scanner (Biograph Duo, Siemens Healthcare, Erlangen, Germany), which provides an in-plane spatial resolution of 2.0-mm full width at half maximum from the center of the field of view. Prior to PET/CT scanning, all subjects discontinued all medications for at least 12 h. Image acquisition was obtained 2 h after intravenous injection of 185 MBq of ^{18}F -FP-CIT. CT images were acquired using a continuous spiral technique on a two-slice helical CT with

110 KV and 50 mA adjusted to body weight (section width, 2.0 mm). Emission scans were then obtained for 10 min. Attenuation-corrected PET images with a voxel size of $1.3 \times 1.3 \times 3.4$ mm were reconstructed using 2D ordered-subsets expectation maximization algorithms.

Image processing was performed using SPM8 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UCL, London, UK) and Matlab 2013a for Windows (Math Works, Natick, MA, USA) and MRIcro version 1.37 (Chris Rorden, Columbia, SC, USA). Quantitative analyses were based on volumes of interest (VOIs), as previously described [10]. To remove inter-subject anatomical variability, individual PET images were spatially normalized to the Montreal Neurology Institute (MNI) template space using a standard 18F-FP-CIT PET template. The 18F-FP-CIT PET template was constructed using the T1-weighted MRI and 18F-FP-CIT PET images of 13 normal controls [18].

Twelve VOIs of bilateral striatal subregions were drawn including right/left-sided anterior caudate nucleus (AC), posterior caudate nucleus (PC), anterior putamen (AP), posterior putamen (PP), ventral putamen (VP), and ventral striatum (VS), in addition to one occipital VOI as a reference. Regions were drawn on a co-registered spatially normalized single T1 MR and 18F-FP-CIT PET template as done in previous studies [10, 18]. The VOI for the VS was defined on the basis of previously defined criteria [19]. The AP-PC boundary point and AP-PP boundary point were the anterior commissure coronal planes. The PP-VP boundary point was the anterior–posterior commissure transaxial plane. The outer boundaries of the striatal subregions were visually determined based on increased activity of the striatum, which can distinguish these subregions from extrastriatal structures. These VOIs were then automatically applied directly to the spatially normalized individual PET images with manual adjustment by our in-house editing software to ensure registration accuracy. We evaluated dopaminergic degeneration by measuring DAT activity concentration in each VOI. The DAT activity was calculated by the non-displaceable binding potential (BP_{ND}), which was defined as (mean standardized uptake value (SUV) of the striatal subregion VOI – mean SUV of the occipital VOI)/mean SUV of the occipital VOI.

Statistics

Simple linear regression analysis was used for simple correlation between BP_{ND} of striatal subregions and each parameter including demographics, motor, and non-motor symptoms. Next, multiple linear regression analysis was performed to determine which specific parameter might be independently associated with dopaminergic depletion of striatum. SPSS 20.0 (IBM Corporation, Armonk, NY, USA) for Windows was used for statistical analysis. $P < 0.05$ was set for statistical significance.

Results

Baseline demographics and clinical characteristics in patients with Parkinson's disease

Baseline characteristics and motor/non-motor severities of the participants are displayed in Table 1. Mean age of 41 patients with PD was 67.5 years and 53.7% of patients were male. Mean disease duration was 2.3 years. Mean scores of the various non-motor symptoms were as follows: MoCA-K, 21.3; FAB, 14.0; BDI, 12.9; BAI, 14.4; PDSS, 100.2; PFS, 41.2; and NMSS, 50.0.

Simple linear regression analysis of dopamine deficiency in patients with Parkinson's disease

In Supplementary Table 1, a simple linear regression assay was performed between dopaminergic depletion of 12 striatal subregions and demographics or motor symptoms. Age was significantly associated with all striatal subregions, with the exception of the right anterior putamen. Education level was not correlated with any striatal subregions, and disease duration was associated only with the left anterior caudate nucleus. Conversely, both the UPDRS-III and LEDD showed significant relationships with all striatal subregions.

Table 1 Participant characteristics

	Patients with Parkinson's disease ($n = 41$)
Male, n (%)	22 (53.7)
Age (yr)	67.5 \pm 7.7
Disease duration (yr)	2.3 \pm 2.5
Level of education (yr)	10.5 \pm 5.3
K-MMSE	25.6 \pm 2.6
UPDRS-III score (motor)	22.8 \pm 12.5
Hoehn and Yahr stage	1.7 \pm 0.6
LEDD (mg)	258.6 \pm 277.1
Assessment tests for non-motor symptom	
MoCA-K (global cognitive function)	21.3 \pm 4.8
FAB (frontal lobe function)	14.0 \pm 3.2
BDI (depression)	12.7 \pm 9.0
BAI (anxiety)	14.4 \pm 10.2
PDSS (sleep)	100.2 \pm 31.5
PFS (fatigue)	41.2 \pm 18.2
NMSS (global non-motor symptoms)	50.0 \pm 29.0

Data represent mean \pm SD

K-MMES, Korean version of Mini-Mental State Examination; *UPDRS-III*, Unified Parkinson's Disease Rating Scale-part 3; *LEDD*, levodopa equivalent daily dose; *MoCA-K*, Korean version of Montreal cognitive assessment; *FAB*, frontal assessment battery; *BDI*, Beck depression inventory; *BAI*, Beck anxiety inventory; *PDSS*, Parkinson's disease sleep scale; *PFS*, Parkinson's disease fatigue scale; *NMSS*, non-motor symptoms scale for Parkinson's disease

In Supplementary Table 2, a simple linear regression test was conducted between dopaminergic depletion of 12 striatal subregions and various non-motor symptoms. MoCA-K did not show any association with striatal subregions. FAB revealed a correlation only with the right posterior caudate nucleus ($\beta = 0.311$, $P = 0.049$). BDI was significantly correlated to the bilateral posterior caudate nucleus (right $\beta = -0.343$, $P = 0.028$; left $\beta = -0.410$, $P = 0.008$), the left anterior putamen ($\beta = -0.382$, $P = 0.014$), the bilateral posterior putamen (right $\beta = -0.346$, $P = 0.027$; left $\beta = -0.413$, $P = 0.007$), and the bilateral ventral putamen (right $\beta = -0.332$, $P = 0.034$; left $\beta = -0.431$, $P = 0.005$). BAI was significantly associated with the left posterior putamen ($\beta = -0.348$, $P = 0.026$) and the left ventral putamen ($\beta = -0.336$, $P = 0.032$). PDSS showed significant correlations with the left AC ($\beta = 0.316$, $P = 0.044$), bilateral PC (right $\beta = 0.418$, $P = 0.007$; left $\beta = 0.398$, $P = 0.010$), and bilateral PP (right $\beta = 0.348$, $P = 0.026$; left $\beta = 0.318$, $P = 0.014$). PFS did not reveal any association with any striatal subregions. NMSS was negatively correlated with left AC ($\beta = -0.336$, $P = 0.032$), bilateral PC (right $\beta = -0.357$, $P = 0.022$; left $\beta = -0.450$, $P = 0.003$), bilateral AP (right $\beta = -0.360$, $P = 0.021$; left $\beta = -0.428$, $P = 0.005$), bilateral PP (right $\beta = -0.418$, $P = 0.006$; left $\beta = -0.427$, $P = 0.005$), bilateral VP (right $\beta = -0.407$, $P = 0.008$; left $\beta = -0.451$, $P = 0.003$), and left VS ($\beta = -0.363$, $P = 0.020$).

Multiple linear regression analysis of dopamine depletion in patients with Parkinson's disease

After simple linear regression analysis, multiple linear regression analyses were conducted with significant factors for each striatal subregion (Table 2). We found that UPDRS-III was significantly related with dopaminergic degeneration in the right AP and PP. However, no non-motor symptoms were correlated with dopaminergic depletion of the 12 striatal subregions.

Discussion

For assessment of cerebral alterations in patients with brain disorders, researchers have used various imaging tools including diffusion-weighted imaging and magnetic resonance spectroscopy. Diffusion-weighted imaging with ADC values indicating the random movement of water molecules demonstrates cytotoxicity-related brain abnormality [20, 21], whereas magnetic resonance spectroscopy reveals metabolic changes [22]. Conversely, FP-CIT PET scans enable us to measure the amount of presynaptic striatonigral dopaminergic neurons. Therefore, the FP-CIT PET method is more directly associated with understanding the pathophysiology of PD.

A recent meta-analysis demonstrated that the loss of putaminal dopamine negatively correlates with the severity of motor symptoms in PD [2]. Similarly, our data also revealed that dopaminergic depletion in the AP and PP of the right

striatum negatively correlated to the total motor symptoms of PD. However, we did not conduct further analysis on detailed motor features such as subtype or subscore, as this study was designed to focus on non-motor symptoms.

We investigated to explore whether striatal dopaminergic uptake using ^{18}F -FP-CIT PET is significantly related with non-motor symptoms of patients with PD. Since PET has higher sensitivity and resolution than single photon emission computed tomography (SPECT), we divided the striatum into 12 subregions on PET images. Moreover, we assessed many non-motor symptoms including depression, anxiety, global cognitive function, frontal executive function, depression, anxiety, sleep, fatigue, and global non-motor symptom, as described in the methods. To the best of our knowledge, this study was performed with the most segmentalized subdivisions of the striatum as well as the most numerous non-motor symptoms. Accordingly, we could thoroughly investigate detailed associations between non-motor symptoms and striatal dopaminergic deficits in patients with PD.

Previous work has investigated the association between non-motor symptoms and dopamine depletion using DAT scans. Mild cognitive impairment in PD has shown to be associated with significant reduction of striatal dopamine [23, 24], and global cognitive function with MoCA being negatively correlated to striatal depletion [25]. In addition, among several cognitive domains, frontal executive dysfunction was significantly related to striatal dopaminergic depletion [25–27]. Further, several studies have found depression and/or anxiety to be significantly associated with the dopaminergic depletion of the striatum in patients with PD [28–33]. When investigating apathy and dopamine depletion however, two different research groups found opposite results regarding their association [34, 35]. Yousaf et al. showed daytime sleepiness was related to dopamine depletion of the caudate nucleus [36]. However, the previous studies showing a positive result between dopamine depletion and non-motor symptoms focused only on a few of non-motor features, thereby leading to limitations in the interpretation and generalizability of these findings. Our results failed to provide strong evidence for a correlation between dopaminergic depletion and various non-motor symptoms in PD. Such a difference between our data and other studies might be associated in part with methods, as described in the previous paragraph. Furthermore, to obtain more exact and accurate results, we applied strict and rigorous statistics. Although simple correlation analysis revealed some significant correlations between dopaminergic depletion and non-motor symptoms including depression and sleep quality along with motor symptoms, multiple linear regression analysis showed no significant association of dopaminergic depletion with various non-motor symptoms in patients with PD. In line with our findings, a recent study demonstrated that striatal dopamine depletion was not related to non-motor burden of NMSS in the early stages of PD [37]. Taken together, it may indicate that non-dopaminergic

Table 2 Multiple linear regression analysis on dopamine depletion in relation to non-motor symptoms among patients with Parkinson's disease

Region of interest	Variable	β	<i>t</i> value [95% CI]	<i>P</i> value
Left anterior caudate nucleus	Age	-0.034	-1.913 [-0.070, 0.002]	0.064
	Disease duration	-0.039	-0.798 [-0.139, 0.060]	0.430
	UPDRS-III	-0.015	-1.369 [-0.038, 0.007]	0.180
	LEDD	0.000	-0.506 [-0.001, 0.001]	0.616
	PDSS	0.002	0.541 [-0.007, 0.012]	0.592
	NMSS	0.002	0.375 [-0.010, 0.014]	0.710
Right posterior caudate nucleus	Age	-0.018	-1.368 [-0.046, 0.009]	0.180
	UPDRS-III	-0.006	-0.742 [-0.022, 0.010]	0.463
	LEDD	0.000	-0.626 [-0.001, 0.001]	0.536
	FAB	0.010	0.313 [-0.057, 0.077]	0.757
	BDI	-0.011	-0.940 [-0.035, 0.013]	0.354
	PDSS	0.004	1.207 [-0.003, 0.011]	0.236
Left posterior caudate nucleus	NMSS	0.003	0.588 [-0.006, 0.012]	0.560
	Age	-0.022	-2.112 [-0.044, -0.001]	0.042
	UPDRS-III	-0.004	-0.629 [-0.018, 0.009]	0.534
	LEDD	-3.426×10^{-5}	-0.102 [-0.001, 0.001]	0.919
	BDI	-0.011	-1.185 [-0.031, 0.008]	0.244
	PDSS	0.003	1.155 [-0.002, 0.009]	0.256
Right anterior putamen	NMSS	0.000	-0.030 [-0.008, 0.007]	0.976
	UPDRS-III	-0.025	-2.342 [-0.046, -0.003]	0.025
	LEDD	0.000	-0.637 [-0.001, 0.001]	0.528
Left anterior putamen	NMSS	-0.004	-0.714 [-0.014, 0.007]	0.480
	Age	-0.027	-1.385 [-0.067, 0.013]	0.175
	UPDRS-III	-0.017	-1.452 [-0.042, 0.007]	0.155
Right posterior putamen	LEDD	0.000	-0.256 [-0.001, 0.001]	0.799
	BDI	-0.019	-1.059 [-0.055, 0.017]	0.297
	NMSS	-0.002	-0.324 [-0.016, 0.012]	0.748
	Age	-0.012	-0.825 [-0.041, 0.017]	0.416
	UPDRS-III	-0.019	-2.041 [-0.037, 0.000]	0.049
	LEDD	0.000	-0.543 [-0.001, 0.001]	0.590
Left posterior putamen	BDI	-0.008	-0.624 [-0.035, 0.018]	0.537
	PDSS	0.001	0.370 [-0.006, 0.009]	0.714
	NMSS	-0.001	-0.213 [-0.011, 0.009]	0.833
	Age	-0.016	-1.052 [-0.048, 0.015]	0.301
	UPDRS-III	-0.014	-1.467 [-0.034, 0.006]	0.152
	LEDD	0.000	-0.240 [-0.001, 0.001]	0.812
Right ventral putamen	BDI	-0.014	-0.788 [-0.052, 0.023]	0.436
	BAI	-0.004	-0.240 [-0.036, 0.028]	0.812
	PDSS	0.001	0.305 [-0.007, 0.009]	0.762
	NMSS	-0.001	-0.142 [-0.012, 0.011]	0.888
	Age	-0.018	-1.590 [-0.042, 0.005]	0.121
	UPDRS-III	-0.014	-1.902 [-0.029, 0.001]	0.066
Left ventral putamen	LEDD	0.000	-0.498 [-0.001, 0.01]	0.622
	BDI	-0.006	-0.622 [-0.028, 0.015]	0.539
	PDSS	0.001	0.443 [-0.005, 0.007]	0.660
	NMSS	0.000	0.086 [-0.008, 0.009]	0.932
	Age	-0.019	-1.600 [-0.043, 0.005]	0.119
	UPDRS-III	-0.010	-1.312 [-0.025, 0.005]	0.199
Left ventral putamen	LEDD	0.000	-0.442 [-0.001, 0.001]	0.661

Table 2 (continued)

Region of interest	Variable	β	<i>t</i> value [95% CI]	<i>P</i> value
Left ventral striatum	BDI	− 0.014	− 1.022 [− 0.043, 0.014]	0.314
	BAI	0.000	0.039 [− 0.024, 0.025]	0.969
	PDSS	0.002	0.647 [− 0.004, 0.008]	0.522
	NMSS	0.000	0.039 [− 0.009, 0.009]	0.969
	Age	− 0.022	− 1.816 [− 0.047, 0.003]	0.078
	UPDRS-III	− 0.011	− 1.435 [− 0.026, 0.004]	0.160
	LEDD	0.000	− 0.470 [− 0.001, 0.001]	0.641
	NMSS	− 0.001	− 0.245 [− 0.009, 0.007]	0.808

FAB, frontal assessment battery; *BDI*, Beck depression inventory; *BAI*, Beck anxiety inventory; *PDSS*, Parkinson's disease sleep scale; *NMSS*, non-motor symptoms scale for Parkinson's disease

dysfunctions including serotonergic degeneration provide greater contributions to non-motor symptoms in PD, compared with dopaminergic dysfunction. There is some evidence that serotonergic deficit is involved in the pathogenesis of apathy, fatigue, depression, and anxiety from the previous studies of patients with PD [38–40].

This study has some limitations. First, we enrolled PD patients taking dopaminergic medications. Such dopaminergic drugs do not influence dopamine depletion of FP-CIT PET. However, we could not exclude a possibility of the effect of dopaminergic medication on various non-motor symptoms evaluated in the current study. To minimize the effect of medication on non-motor symptoms, we excluded those who took any previous neuropsychiatric medicines including anti-depressants, anti-anxiolytics, and anti-dementia drug. Second, we did not assess precise measurements of apathy and pain which are not uncommon in patients with PD, although apathy and pain could be calculated as a subscore of NMSS (data not shown). Lastly, this study utilized a retrospective design and the sample size was relatively small. Accordingly, a prospective study with a larger sample size is required to confirm our findings.

In conclusion, our results showed a lack of evidence supporting associations between striatal dopaminergic depletion and non-motor symptoms in patients with PD. This highlighted that non-dopaminergic dysfunctions might play a larger role in non-motor symptoms in PD than dopaminergic deficits. Non-dopaminergic dysfunction may be crucial not only in understanding the pathophysiology of non-motor symptoms of PD, but also in treating various non-motor symptoms in patients with PD.

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Compliance with ethical standards

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.

Conflict of interest The authors declare that they have no conflicts of interest.

References

- Goedert M, Spillantini MG, Del Tredici K, Braak H (2013) 100 years of Lewy pathology. *Nat Rev Neurol* 9(1):13–24
- Kaasinen V, Vahlberg T (2017) Striatal dopamine in Parkinson disease: a meta-analysis of imaging studies. *Ann Neurol* 82(6):873–882
- Cheng HC, Ulane CM, Burke RE (2010) Clinical progression in Parkinson disease and the neurobiology of axons. *Ann Neurol* 67(6):715–725
- Ravina B, Eidelberg D, Ahlskog JE, Albin RL, Brooks DJ, Carbon M, Dhawan V, Feigin A, Fahn S, Guttman M, Gwinn-Hardy K, McFarland H, Innis R, Katz RG, Kieburtz K, Kish SJ, Lange N, Langston JW, Marek K, Morin L, Moy C, Murphy D, Oertel WH, Oliver G, Palesch Y, Powers W, Seibyl J, Sethi KD, Shults CW, Sheehy P, Stoessl AJ, Holloway R (2005) The role of radiotracer imaging in Parkinson disease. *Neurology* 64(2):208–215
- Seibyl JP, Marek KL, Quinlan D, Sheff K, Zoghbi S, Zea-Ponce Y, Baldwin RM, Fussell B, Smith EO, Charney DS, van Dyck C et al (1995) Decreased single-photon emission computed tomographic [123I]beta-CIT striatal uptake correlates with symptom severity in Parkinson's disease. *Ann Neurol* 38(4):589–598
- Reichmann H, Brandt MD, Klingelhofer L (2016) The nonmotor features of Parkinson's disease: pathophysiology and management advances. *Curr Opin Neurol* 29:467–473
- Lee HM, Koh SB (2015) Many faces of Parkinson's disease: non-motor symptoms of Parkinson's disease. *J Mov Disord* 8(2):92–97
- Pont-Sunyer C, Hotter A, Gaig C, Seppi K, Compta Y, Katzenschlager R, Mas N, Hofeneder D, Brucke T, Bayes A, Wenzel K, Infante J, Zach H, Pirker W, Posada IJ, Alvarez R, Isperto L, De Fabregues O, Callen A, Palasi A, Aguilar M, Marti MJ, Valldeoriola F, Salamero M, Poewe W, Tolosa E (2015) The onset of nonmotor symptoms in Parkinson's disease (the ONSET PD study). *Mov Disord* 30(2):229–237
- Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinicopathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 55(3):181–184
- Oh M, Kim JS, Kim JY, Shin KH, Park SH, Kim HO, Moon DH, Oh SJ, Chung SJ, Lee CS (2012) Subregional patterns of preferential striatal dopamine transporter loss differ in Parkinson disease, progressive supranuclear palsy, and multiple-system atrophy. *J Nucl Med* 53(3):399–406

11. Lee JY, Dong Woo L, Cho SJ, Na DL, Hong Jin J, Kim SK, You Ra L, Youn JH, Kwon M, Lee JH, Maeng Je C (2008) Brief screening for mild cognitive impairment in elderly outpatient clinic: validation of the Korean version of the Montreal Cognitive Assessment. *J Geriatr Psychiatry Neurol* 21(2):104–110
12. Kim TH, Huh Y, Choe JY, Jeong JW, Park JH, Lee SB, Lee JJ, Jho JH, Lee DY, Woo JI, Kim KW (2010) Korean version of frontal assessment battery: psychometric properties and normative data. *Dement Geriatr Cogn Disord* 29(4):363–370
13. Jo SA, Park MH, Jo I, Ryu SH, Han C (2007) Usefulness of Beck Depression Inventory (BDI) in the Korean elderly population. *Int J Geriatr Psychiatry* 22(3):218–223
14. Lee K, Kim D, Cho Y (2018) Exploratory factor analysis of the Beck anxiety inventory and the Beck depression inventory-II in a psychiatric outpatient population. *J Korean Med Sci* 33(16):e128
15. Chaudhuri KR, Pal S, DiMarco A, Whately-Smith C, Bridgman K, Mathew R, Pezzella FR, Forbes A, Hogg B, Trenkwalder C (2002) The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 73:629–635
16. Brown RG, Dittner A, Findley L, Wessely SC (2005) The Parkinson fatigue scale. *Parkinsonism Relat Disord* 11:49–55
17. Koh SB, Kim JW, Ma HI, Ahn TB, Cho JW, Lee PH, Chung SJ, Kim JS, Kwon DY, Baik JS (2012) Validation of the Korean-version of the nonmotor symptoms scale for Parkinson's disease. *J Clin Neurol* 8:276–283
18. Kim HW, Kim JS, Oh M, Oh JS, Lee SJ, Oh SJ, Chung SJ, Lee CS (2016) Different loss of dopamine transporter according to subtype of multiple system atrophy. *Eur J Nucl Med Mol Imaging* 43:517–525
19. Mawlawi O, Martinez D, Slifstein M, Broft A, Chatterjee R, Hwang DR, Huang Y, Simpson N, Ngo K, Van Heertum R, Laruelle M (2001) Imaging human mesolimbic dopamine transmission with positron emission tomography: I. Accuracy and precision of D(2) receptor parameter measurements in ventral striatum. *J Cereb Blood Flow Metab* 21:1034–1057
20. Razek AA, Elmongy A, Hazem M, Zakareya S, Gabr W (2011) Idiopathic Parkinson disease effect of levodopa on apparent diffusion coefficient value of the brain. *Acad Radiol* 18(1):70–73
21. Abdel Razek AA, Abd El-Gaber N, Abdalla A, Fathy A, Azab A, Rahman AA (2009) Apparent diffusion coefficient value of the brain in patients with Gaucher's disease type II and type III. *Neuroradiology* 51(11):773–779
22. El-mewafy Z, Abdel Razek A, El-Eshrawy M, Abo El-Eneen N, EL-Biaomy A (2018) MR spectroscopy of the frontal region in patients with metabolic syndrome: correlation with anthropometric measurement. *Polish J Radiol* 83:e215–e219
23. Chung SJ, Yoo HS, Oh JS, Kim JS, Ye BS, Sohn YH, Lee PH (2018) Effect of striatal dopamine depletion on cognition in de novo Parkinson's disease. *Parkinsonism Relat Disord* 51:43–48
24. Pellecchia MT, Picillo M, Santangelo G, Longo K, Moccia M, Erro R, Amboni M, Vitale C, Vicidomini C, Salvatore M, Barone P, Pappata S (2015) Cognitive performances and DAT imaging in early Parkinson's disease with mild cognitive impairment: a preliminary study. *Acta Neurol Scand* 131(5):275–281
25. Kubler D, Schroll H, Buchert R, Kuhn AA (2017) Cognitive performance correlates with the degree of dopaminergic degeneration in the associative part of the striatum in non-demented Parkinson's patients. *J Neural Transm (Vienna)* 124(9):1073–1081
26. Siepel FJ, Bronnick KS, Booij J, Ravina BM, Lebedev AV, Pereira JB, Gruner R, Aarsland D (2014) Cognitive executive impairment and dopaminergic deficits in de novo Parkinson's disease. *Mov Disord* 29(14):1802–1808
27. Rinne JO, Portin R, Ruottinen H, Nurmi E, Bergman J, Haaparanta M, Solin O (2000) Cognitive impairment and the brain dopaminergic system in Parkinson disease: [18F]fluorodopa positron emission tomographic study. *Arch Neurol* 57(4):470–475
28. Weintraub D, Newberg AB, Cary MS, Siderowf AD, Moberg PJ, Kleiner-Fisman G, Duda JE, Stern MB, Mozley D, Katz IR (2005) Striatal dopamine transporter imaging correlates with anxiety and depression symptoms in Parkinson's disease. *J Nucl Med* 46(2):227–232
29. Erro R, Pappata S, Amboni M, Vicidomini C, Longo K, Santangelo G, Picillo M, Vitale C, Moccia M, Giordano F, Brunetti A, Pellecchia MT, Salvatore M, Barone P (2012) Anxiety is associated with striatal dopamine transporter availability in newly diagnosed untreated Parkinson's disease patients. *Parkinsonism Relat Disord* 18(9):1034–1038
30. Ceravolo R, Frosini D, Poletti M, Kiferle L, Pagni C, Mazzucchi S, Volterrani D, Bonuccelli U (2013) Mild affective symptoms in de novo Parkinson's disease patients: relationship with dopaminergic dysfunction. *Eur J Neurol* 20(3):480–485
31. Vriend C, Raijmakers P, Veltman DJ, van Dijk KD, van der Werf YD, Foncke EM, Smit JH, Berendse HW, van den Heuvel OA (2014) Depressive symptoms in Parkinson's disease are related to reduced [123I]FP-CIT binding in the caudate nucleus. *J Neurol Neurosurg Psychiatry* 85(2):159–164
32. Felicio AC, Moriyama TS, Godeiro-Junior C, Shih MC, Hoexter MQ, Borges V, Silva SM, Amaro-Junior E, Andrade LA, Ferraz HB, Bressan RA (2010) Higher dopamine transporter density in Parkinson's disease patients with depression. *Psychopharmacology* 211(1):27–31
33. Rektorova I, Srovnalova H, Kubikova R, Prasek J (2008) Striatal dopamine transporter imaging correlates with depressive symptoms and tower of London task performance in Parkinson's disease. *Mov Disord* 23(11):1580–1587
34. Santangelo G, Vitale C, Picillo M, Cuoco S, Moccia M, Pezzella D, Erro R, Longo K, Vicidomini C, Pellecchia MT, Amboni M, Brunetti A, Salvatore M, Barone P, Pappata S (2015) Apathy and striatal dopamine transporter levels in de-novo, untreated Parkinson's disease patients. *Parkinsonism Relat Disord* 21(5):489–493
35. Chung SJ, Lee JJ, Ham JH, Lee PH, Sohn YH (2016) Apathy and striatal dopamine defects in non-demented patients with Parkinson's disease. *Parkinsonism Relat Disord* 23:62–65
36. Yousaf T, Pagano G, Niccolini F, Politis M (2018) Excessive daytime sleepiness may be associated with caudate denervation in Parkinson disease. *J Neurol Sci* 387:220–227
37. Chung SJ, Lee JJ, Ham JH, Ye BS, Lee PH, Sohn YH (2016) Striatal dopamine depletion patterns and early non-motor burden in Parkinson's disease. *PLoS One* 11(8):e0161316
38. Maillet A, Krack P, Lhomme E, Metereau E, Klinger H, Favre E, Le Bars D, Schmitt E, Bichon A, Pelissier P, Fraix V, Castrioto A, Sgambato-Faure V, Broussolle E, Tremblay L, Thobois S (2016) The prominent role of serotonergic degeneration in apathy, anxiety and depression in de novo Parkinson's disease. *Brain* 139(Pt 9):2486–2502
39. Boileau I, Warsh JJ, Guttman M, Saint-Cyr JA, McCluskey T, Rusjan P, Houle S, Wilson AA, Meyer JH, Kish SJ (2008) Elevated serotonin transporter binding in depressed patients with Parkinson's disease: a preliminary PET study with [11C]DASB. *Mov Disord* 23(12):1776–1780
40. Pavese N, Metta V, Bose SK, Chaudhuri KR, Brooks DJ (2010) Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction. *Brain* 133(11):3434–3443