

18F-FP-CIT Positron Emission Tomography for Correlating Motor and Cognitive Symptoms of Parkinson's Disease

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Background and Purpose The aim of this paper was to investigate the utility of 18F-N-(3-fluoropropyl)-2 β -carboxymethoxy-3 β -(4-iodophenyl) nortropane (FP-CIT) positron emission tomography (PET) for evaluating the severity of Parkinson's disease (PD) according to various clinical stages, and to identify the relationship between the striatal substructure and the Unified Parkinson's Disease Rating Scale (UPDRS) motor score, cognitive symptoms through 18F-FP-CIT PET.

Methods We retrospectively identified 542 patients with various clinical stages of PD who underwent an 18F-FP-CIT PET at our clinics. The difference between the 18F-FP-CIT PET according to the Hoehn-Yahr stage, correlation between 18F-FP-CIT PET and the UPDRS III grouped motor items, and the Korean Mini-Mental State Examination (K-MMSE) were investigated.

Results As disease progressed, the right caudate and both the anterior putamen and caudate/putamen ratios exhibited a significantly lower uptake. The uptake of all striatal substructures was significantly correlated with the UPDRS total motor score. The right caudate nucleus was significantly related to both the UPDRS tremor items and the right UPDRS akinesia-rigidity items. The left caudate nucleus was related to both the UPDRS tremor items and UPDRS akinesia-rigidity items. The right anterior putamen was related to the axial items, right tremor and akinesia-rigidity items; while the left anterior putamen was related to the right tremor and right akinesia-rigidity items. Both of the posterior putamens were related to the axial items, left tremor and left akinesia rigidity items. K-MMSE was not significantly related to any striatal substructures.

Conclusions The UPDRS total motor score was significantly correlated with the uptake of all striatal substructures. However, the 18F-FP-CIT uptake in specific striatal substructures was rather complexly correlated with the UPDRS motor grouped items and was not significantly related to K-MMSE. These results suggest the possibility of the complex pathophysiology of motor symptoms of PD and limitation of 18F-FP-CIT PET for the evaluation of the severity of PD motor and cognitive symptoms.

Key Words 18F-FP-CIT-positron emission tomography, Hoehn-Yahr, Korean mini-mental state examination, Parkinson's disease, unified Parkinson's disease rating scale.

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INTRODUCTION

The characteristic motor symptoms of Parkinson's disease (PD) triggers at least 40–50% of dopaminergic cell loss,¹ and

this cell loss is associated with the depletion of the striatal dopamine transporter (DAT) sites in the basal ganglia.² The introduction of brain imaging of the nigrostriatal dopaminergic system has provided an objective tool for the diagnosis and differential diagnosis of PD and searching methods for the differential diagnosis of Parkinsonian symptoms. To know the integrity of the nigrostriatal dopaminergic system, two main imaging methods have been used. The first developed method used 18F-dopa as a binding radiotracer in the

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striatum. It binds to the striatal dopaminergic terminal and displays the dopaminergic densities. However, because the loss of dopaminergic neurons can be compensated by increasing turnover in the dopamine terminals,²⁻⁴ the striatal dopaminergic terminal densities might be overestimated in an 18F-dopa imaging study especially in the early stages of PD. An alternative method to overcome this problem is using radiotracer binding at the DAT. Among various tracers, N-(3-fluoropropyl)-2 β -carboxymethoxy-3 β -(4-iodophenyl) nortropine (FP-CIT) is a cocaine analog that specifically binds to DATs. If FP-CIT is tagged by 18F, the outcome is high signal-to-noise ratios and fast kinetics. In addition, it is reasonably appropriate for nigrostriatal dopaminergic imaging.⁵⁻⁷

However, the use of DAT imaging as a marker for measuring the severity and progression of PD and the tools for examining the clinico-anatomic relationship have become controversial.⁸⁻¹¹ In cross-sectional studies for early PD, densities of DAT were inversely correlated with the severity of motor symptoms.^{8,12} On the other hand, both positron emission tomography (PET) and single photon emission computed tomography (SPECT) study using DAT demonstrated no statistically significant relationship between the degree of striatal uptake and the clinical severity change in PD.¹⁰ Moreover, there has been only one negative study examining the correlation between DAT imaging and the severity of cognitive dysfunction in IPD.¹³

The aim of this paper was to elucidate the utility of the 18F-FP-CIT PET for evaluating the severity of PD according to the various clinical stages, and to explore the correlation between the striatal substructure uptake and the Unified Parkinson's Disease Rating Scale (UPDRS) motor score through 18F-FP-CIT PET. Finally, we also evaluated whether cognitive functions were associated with 18F-FP-CIT PET.

METHODS

Patients

We enrolled the patients who visited the Seoul Veterans Health Service Hospital Movement Disorders Center between 2011 and 2015. Among them, 542 patients who met PD society brain bank step I and step II criteria¹³ and underwent 18F-FP-CIT PET scan were included in this study. All patients underwent a brain magnetic resonance image (MRI), and patients with organic brain disease were excluded from this study. The patients who had 1) atypical Parkinsonism, 2) history of brain tumor, stroke, traumatic encephalopathy, seizure disorder, or psychiatric problem, 3) obvious medical problems, and 4) farming as an occupation and history of pesticide exposure, were excluded from this study.

The Hoehn-Yahr (H-Y) staging and UPDRS III motor do-

main were used as a severity scale of motor symptom. These assessments were administered by a single neurologist immediately before 18F-FP-CIT PET scanning when the antiparkinsonian agents had been ceased for at least 6 hours. To simplify motor symptoms, seven grouped scores combining the similar UPDRS scores were used in this study. An axial score (items 18, 19, 20, 22, 27-30), right-sided tremor score (right side scores of items 20, 21), left-sided tremor score (left side scores of items 20, 21), right-sided akinesia-rigidity score (right side scores of items 22-26), and left-sided akinesia-rigidity score (left side scores of items 22-26), tremor score (items 20, 21 divided by 7), rigidity score (items 18, 19, 22, 27, 28, 29, 30, and 31 divided by 12), were calculated and applied in current study.¹⁴ These grouped scores and correlations of 18F-FP-CIT PET image were analyzed. The patients' general cognitive state and severity of dementia were assessed using the Korean Mini-Mental State Examination (K-MMSE).¹⁵

We retrospectively identified 10 normal subjects (8 males and 2 females; mean age, 70 years; range, 58-79 years) who were not diagnosed with PD, essential tremor, or organic brain disease that were examined by 18F-FP-CIT PET voluntarily for private reasons. The 18F-FP-CIT PET image data from these subjects were adopted as normal controls. This study was approved by the Institutional Review Board of the Veterans Health Service Medical Center (2017-09-008) and met the standards established by the Declaration of Helsinki.

18F-FP-CIT PET

All participants fasted for at least 12 hours and ceased all anti-parkinsonian drugs for at least 6 hours prior to the 18F-FP-CIT PET scanning. However, the medications that may affect DAT binding, such as D-amphetamine, benztropine, methylphenidate were stopped before the 18F-FP-CIT PET scanning. After a 90- and 210-minute intravenous injection of 149 MBq to 259 MBq of 18F-FP-CIT (3.7 MBq/kg) to participants, two sequential PET and computed tomography (CT) scans (dual time point) were taken using Discovery STE (GE Healthcare, Milwaukee, WI, USA). From the vertex to the skull base, CT scanning was conducted (30 mAs; 140 kVp; slice, 3.75 mm) and 18F-FP-CIT PET imaging progressed over the same region in 15-minute durations. For attenuation correction, images were reconstructed using the CT data applying the standard ordered subset expectation maximization (2 iterations, 8 subsets) algorithm. The data were acquired in the 3-dimensional mode. Additionally, the 18F-FP-CIT PET images of the 10 normal subjects were used for constructing the reference matrix (Fig. 1).

Image analysis

The regions of interest (ROI) (caudate, putamen, and cerebellum) were identified in both hemispheres on realigned MR images (1.5 T) according to the 18F-FP-CIT-PET image using the surface fitting method. The four serial images where the striatum was best delineated were adopted for the ROI assessment. Along its longitudinal axis, the putamen was divided into the anterior and posterior parts. The ROIs were then applied on the PET image and the uptake of 18F-FP-CIT at 120 minutes after the 18F-FP-CIT injection was determined by the (ROS-cerebellum)/cerebellum ratio.

The asymmetry index (AI) of putamen and caudate was determined by the following formula: $AI = [(ipsilateral - contralateral) / (ipsilateral + contralateral)] \times 100$. The uptake of the putamen/caudate ratio (PCR) was calculated according to a previous report.¹⁶

Statistical analysis

First, the baseline demographic features between the normal controls and patients with PD were assessed by Student's two-tailed *t*-tests. Second, the sex and frequency according

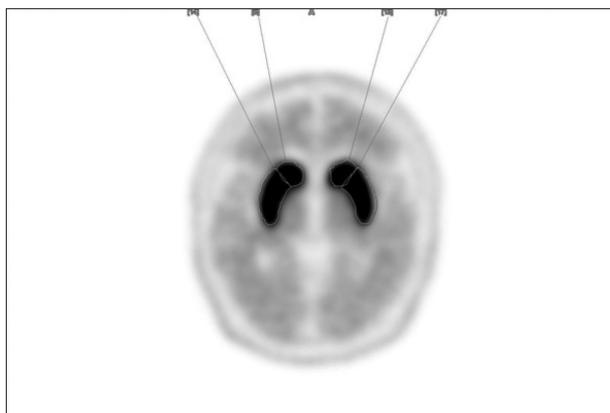


Fig. 1. Applications of the region of interest to 18F-FP-CIT positron emission tomography imaging showing right and left caudate, putamen at the level of striatum in a healthy control.

to the H-Y stage were assessed using chi-square-tests. Third, UPDRS grouped items and regional ROI were evaluated using a one-way analysis of variance test. Finally, Spearman's and Pearson correlation tests were adopted to identify the relationship between the location of the striatum and H-Y staging, UPDRS motor scores and K-MMSE. Statistical significance was identified as a *p*-value of less than 0.05. The Statistical Package for the Social Sciences, version 18.0 software (SPSS, Inc, Chicago, IL, USA) was used for statistical analyses.

RESULTS

Characteristics of the patients

The study included 542 patients with PD and 10 control patients. The demographic information of the patients is provided in Table 1. The age and sex were not significantly different between the control and PD patients. The mean H-Y stage was 1.5 in patients with PD (Table 1).

UPDRS motor grouped items according to the H-Y stage

Among UPDRS motor grouped items, the right UPDRS tremor, right UPDRS akinesia-rigidity, UPDRS tremor score, UPDRS rigidity score, and UPDRS motor scores exhibited

Table 1. Demographic and clinical features of study subjects (mean \pm standard deviation)

Characteristics	Controls (n=10)	PD (n=542)	<i>p</i> -value
Sex			
Male	8	502	
Female	2	40	0.706
Age (year)	70.2 \pm 7.9	69.9 \pm 6.3	0.814
Duration (month)		72.2 \pm 55.9	
K-MMSE		23.2 \pm 4.4 (4–30)	
H-Y stage		1.5 \pm 0.5	

p-value of less than 0.05 was considered statistically significant.

H-Y: Hoehn-Yahr, K-MMSE: Korean Mini-Mental State Examination, PD: Parkinson's disease.

Table 2. UPDRS motor grouped items according to H-Y stage (mean \pm standard deviation)

	H-Y1 (n=374)	H-Y2 (n=143)	H-Y \geq 3 (n=25)
UPDRS axial*	3.4 \pm 1.2	3.4 \pm 1.3	4.0 \pm 1.4
Right UPDRS tremor [†]	1.6 \pm 1.1	3.2 \pm 1.6	5.4 \pm 0.5
Left UPDRS tremor*	2.0 \pm 1.0	1.8 \pm 1.1	3.0 \pm 0.2
Right UPDRS akinesia-rigidity [†]	4.0 \pm 2.2	7.9 \pm 2.2	12.0 \pm 0.3
Left UPDRS akinesia-rigidity*	2.9 \pm 1.5	2.6 \pm 1.3	6.6 \pm 0.5
UPDRS tremor score [†]	0.55 \pm 0.17	0.63 \pm 0.23	1.21 \pm 0.08
UPDRS rigidity score [†]	0.60 \pm 0.15	0.66 \pm 0.17	0.95 \pm 0.14
UPDRS motor [†]	14.1 \pm 3.2	18.5 \pm 4.0	32.5 \pm 1.9

*Statistical difference was between H-Y stage 1, 2 and H-Y stage 3, [†]Statistical difference was between each H-Y stage.

H-Y: Hoehn-Yahr, UPDRS: Unified Parkinson's Disease Rating Scale.

Table 3. Regional 18F-FP-CIT uptake among study subjects (mean±standard deviation)

FP-CIT PET	Controls	H-Y1 (n=374)	H-Y2 (n=143)	H-Y≥3 (n=25)
Rt. caudate*	7.92±0.81	3.82±1.17	3.13±0.98	1.81±0.71
Lt. caudate†	8.01±0.74	3.10±1.00	3.32±0.80	1.89±1.19
Rt. anterior putamen*	10.40±0.91	3.29±1.17	2.95±0.91	2.03±1.07
Lt. anterior putamen*	10.35±0.86	3.82±1.11	3.03±0.98	2.50±1.10
Rt. posterior putamen†	9.35±0.63	2.74±1.05	3.00±0.77	1.93±0.65
Lt. posterior putamen‡	9.23±0.61	2.72±1.01	2.76±0.69	1.87±1.33
Asymmetry index CN	3.29±2.28	21.67±14.55	20.29±9.27	17.79±17.82
Asymmetry index AP§	3.77±3.73	26.85±20.44	17.69±13.06	26.36±12.28
Asymmetry index PP*	6.45±3.76	15.96±11.17	19.64±9.38	25.35±18.16
Caudate/putamen ratio‡	0.40±0.03	0.56±0.13	0.54±0.08	0.46±0.06

Compared to patients with IPD, controls displayed a higher uptake in all of the basal ganglia areas, lower asymmetry indices and caudate/putamen ratios.

*Statistical difference occurred more frequently with advancing H-Y stages, †Statistical difference was found among each H-Y stage (H-Y2 > H-Y1 > H-Y≥3), ‡Statistical difference was found between H-Y stage 1, 2 and H-Y stage≥3, §Statistical difference was found between H-Y stage 2 and H-Y stage 1, H-Y stage≥3.

AP: anterior putamen, CN: caudate nucleus, H-Y: Hoehn-Yahr, PET: positron emission tomography, PP: posterior putamen.

Table 4. Correlation analysis of UPDRS motor grouped items and K-MMSE with 18F-FP-CIT PET

	Right caudate	Left caudate	Right anterior putamen	Left anterior putamen	Right posterior putamen	Left posterior putamen
UPDRS axial	-0.067	-0.131†	-0.114†	-0.082	-0.148†	-0.147†
Right UPDRS tremor	-0.385†	-0.123†	-0.112†	-0.252†	0.025	-0.008
Left UPDRS tremor	0.104	-0.114†	-0.028	0.117	-0.182†	-0.131†
Right UPDRS akinesia-rigidity	-0.412†	-0.122†	-0.129†	-0.280†	0.055	-0.031
Left UPDRS akinesia-rigidity	0.040	-0.179†	-0.078	0.044	-0.257†	-0.174†
UPDRS tremor score	-0.309†	-0.204†	-0.129†	-0.166†	-0.106*	-0.100*
UPDRS rigidity score	-0.263†	-0.166†	-0.125†	-0.170†	-0.076*	-0.127†
UPDRS motor	-0.387†	-0.246†	-0.193†	-0.246†	-0.128†	-0.155†
H-Y stage	-0.373†	-0.014	-0.217†	-0.384†	0.162	-0.057
K-MMSE	-0.022	-0.058	-0.071	0.038	-0.056	-0.047

*p<0.05, †p<0.01.

H-Y: Hoehn-Yahr, K-MMSE: Korean Mini-Mental State Examination, PET: positron emission tomography, UPDRS: Unified Parkinson's Disease Rating Scale.

significantly higher scores according to the H-Y stage. The UPDRS axial, left UPDRS tremor, and left UPDRS akinesia-rigidity scores were significantly higher in patients with a H-Y stage of 3 or higher compared to those with a H-Y stage of less than 3 (Table 2).

Difference in the regional 18F-FP-CIT uptake according to the H-Y stage

Compared to the control group, the all striatal areas (both caudate nucleus, anterior and posterior putamen) displayed a lower 18F-FP-CIT uptake in patients with PD. The patients with H-Y stage 3 or higher exhibited the lowest uptake in all striatal areas. According to the advancing H-Y stage, the right caudate, both anterior putamens, and the caudate/putamen ratio demonstrated a significantly lower uptake. In pa-

tients with H-Y stage 2, the left caudate and right posterior putamen exhibited a higher uptake compared to the patients with H-Y stage 1 (Table 3).

Correlation analysis among UPDRS motor grouped items, H-Y stage, K-MMSE and regional 18F-FP-CIT uptake

The H-Y stage was significantly correlated with the right caudate nucleus, both anterior putamens. UPDRS motor score, UPDRS tremor score and UPDRS rigidity score. They were also all significantly correlated with all of the striatal areas. The right caudate nucleus was significantly related to the right UPDRS tremor and right UPDRS akinesia-rigidity items. The left caudate nucleus was related to both the UPDRS tremor and UPDRS akinesia-rigidity items. The right

anterior putamen was related to the UPDRS axial, right UPDRS tremor, and right UPDRS akinesia-rigidity items; while, left anterior putamen was related to the right UPDRS tremor and right UPDRS akinesia-rigidity items. Both of the posterior putamens were related to the UPDRS axial items, left UPDRS tremor, items, left UPDRS akinesia-rigidity items, UPDRS tremor, and UPDRS rigidity scores (Table 4). K-MMSE was not significantly related to any of the striatal substructure 18F-FP-CIT uptakes.

DISCUSSION

The most characteristic pathological abnormality of PD is the specific degeneration of dopamine neurons in the ventrolateral substantia nigra pars compacta and posterior putamen, which is most pronounced in dorsal area. In a PET study for patients with early stages of PD, the anterior-posterior striatal uptake gradient as well as the more affected-less affected striatal uptake gradient was identified¹⁷ and they were compatible with the previous pathological findings for PD.

This study also suggests a pathological sequence in patients with PD. Compared to controls, the 18F-FP-CIT uptake was reduced by 48.2, 38.7, 31.6, 36.9, 29.3, and 29.5% in the right caudate, left caudate, right anterior putamen, left anterior putamen, right posterior putamen, and left posterior putamen, respectively, in the patient with H-Y stage 1. These results are similar to a previous study, except for the rather lower 18F-FP-CIT uptake in the caudate nucleus (48.2% vs. 70.9%).¹⁸ These results suggest that a substantial degeneration of dopaminergic neuron in the striatum was responsible for the initial clinical manifestations of PD. However, the pathological abnormalities of PD are not exclusively found in the nigrostriatal pathway; these abnormalities are also found in many other dopaminergic and non-dopaminergic systems.¹⁹

In patients with PD, we demonstrated that the 18F-FP-CIT uptake was significantly related to the UPDRS total motor scores regardless of the striatal anatomic locations. However, the complex associations between the regional 18F-FP-CIT uptake pattern and each motor grouped item suggested complex pathophysiology of these motor symptoms.

The uptakes of the right caudate nucleus, both anterior putamens, and the asymmetry index of the posterior putamen significantly decreased as the disease progressed (symbolized as the H-Y stage). However, compared to the patients with H-Y stage 1, the higher 18F-FP-CIT uptake in the left caudate nucleus and right posterior putamen and the similar uptake in the left posterior putamen was found in patients with H-Y stage 2. The reason for these discordant results between the H-Y stage of PD and the 18F-FP-CIT uptake is not

certain. One possible hypothesis is that this finding might be the result from the characteristics of the 18F-FP-CIT PET. In patients in the early stages of PD, the 18F-dopa uptake is characteristically increased compared to the degree of denervation, which likely reflects the compensatory upregulation; while the 18F-FP-CIT uptake decreases compared to the degree of denervation which also reflects the downregulation of DAT as a compensatory change.²⁰ Therefore, an 18F-dopa image study might underestimate the degrees of dopaminergic denervation; whereas an 18F-FP-CIT image study might overestimate the degree of dopaminergic denervation in patients in the early stages of PD. Another possibility can be deduced from the fact that the 18F-FP-CIT uptake in all of the striatal substructures (especially the posterior putamen) is already tending to level off when clinical motor symptoms are initially manifested in PD. In an 18F-dopa PET study,²¹ though the decline rate of 18F-dopa uptake in putamen was inversely correlated with the disease duration, it was faster and maximal at the beginning of PD than at later time points and slowed down as disease duration increased. Therefore, the differentiation of the severity of radiotracer uptake deficits may not be accurately measured in patients with a previously marked denervated striatum. However, as the disease progressed, the question remains of why certain striatal substructure sequentially decreases while the other remains uncertain. Early incongruent striatal involvement may affect these findings; therefore, these hypotheses should be tested.

Generally, dopaminergic degeneration is thought to be more strongly related to the entire striatum or putamen than the caudate nucleus in PD^{7,22,23} and most previous FP-CIT studies for patients with PD have reported consistent results.^{5,12,18,24} A [123I] FP-CIT SPECT study reported a significant relationship between the bradykinesia and striatal uptake but not with tremor or rigidity.¹² Another study reported that akinetic-rigidity (compared to tremors) was significantly correlated with the FP-CIT uptake in the putamen and caudate.²⁴ However, other studies reported different results and demonstrated that the correlation between the motor symptoms of the PD and FP-CIT uptake was not statistically significant.^{25,26} These inconsistent results might be explained by the pattern of dopaminergic degeneration and declining rate difference. Moreover, the clinical symptoms of PD may not manifest until the striatal uptake is considerably reduced.¹⁶

Our study showed that tremor grouped items were correlated with FP-CIT uptake of both caudate nucleus. Contrast bradykinesia and rigidity, many studies questioned about the association between tremor symptoms of PD and FP-CIT uptake.^{18,23-25} The exact pathophysiological mechanism of PD resting tremor is not clear yet. The nigrostriatal dopaminergic

gic degeneration might reduce segregation among basal ganglia circuits, thus induction of triggering anomalous rhythmic firing by tremor cells result in parkinsonian tremor.¹⁵ Our study showed right tremor was related with both caudate nucleus and both anterior putamen and left tremor was related with left caudate nucleus and both posterior putamen. These data supported the hypothesis that Parkinsonian tremor was also dependent on dopaminergic loss and that it was related to the striatal reduced uptake.²⁷

Whether the caudate nucleus is related with the development of tremor has been controversial. In tremor-dominant PD patients, decline rate of F-DOPA uptake was significantly slow in caudate nucleus than in other type PD patients (0.6–1.3% vs. 4.3–6.5%).²¹ In animal model, bretteylium, tetrabenazine or mescaline injection into caudate nucleus triggered tremor and whereas catecholamines injection into caudate nucleus suppressed tremor.²⁸ These results demonstrated that the disturbance of dopamine balance in caudate nucleus might lead to tremor development.¹⁸

Asymmetry of parkinsonian symptoms is characteristics clinical diagnostic feature of PD.²⁹ Previous study showed the asymmetric degree between more and less affected putamen became less prominent as the disease progressed,³⁰ however other study showed that the absolute [18F]CFT putamen uptake was lower in the ipsilateral side of the predominant symptoms than in the contralateral side after average 2.2 year follow up period.¹⁰ Our study also found an asymmetry of posterior putamen was maintained (or increased) at advanced stage of PD. These results suggested that disease initiation may differently affect striatal substructure, and these initiating factors may influence for considerable duration of disease progression.

However, the significant overlap of the range of striatal uptakes between the right and left side even in the absence of overlap in UPDRS values may suggested that other factors may be responsible for the severity and the laterality of the clinical manifestations. The pathology of PD is not restricted in striatal area, other diverse brain region may be related with symptoms of PD. The imaging of the substructure of striatum may not related with specific symptoms, rather these low uptakes may reflect thalamic or subthalamic lesions, which are closely associated with striatal substructure.¹⁵ In addition, our study confirmed the previous study showing limited evidence for cognitive function and FP-CIT imaging.³¹

The present study had several limitations. First, the most of study populations were mild patients and as a result, this study was biased for mild cases (mean H-Y stage 1.5). Second, study populations were not naïve to dopaminergic drugs at the time of 18F-FP-CIT PET study, allowing for potential influ-

ence of dopaminergic therapy on 18F-FP-CIT PET imaging. Finally, present study was a hospital based cross-sectional study in a single medical center, so this study did not represent the real populations and identifying causal relationship between uptake and specific symptoms were difficult. For example, low proportion of female study subjects reflect the characteristics of veterans hospital.

This study showed a prediction of the PD course according to imaging of the nigrostriatal dopaminergic system and pure motor symptomatology was difficult and lately affected striatal substructure (i.e. caudate nucleus) might better reflect the progression of disease. And motor symptoms of PD were complexly associated with striatal substructure. In conclusion, the present study demonstrated both the potential value and limitation of 18F-FP-CIT images for surrogating severity biomarker and exploring the mechanisms of PD motor symptoms.

Conflicts of Interest

The authors have no financial conflicts of interest.

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