Correlation of Parkinson Disease Severity and $^{18}$F-DTBZ Positron Emission Tomography

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**IMPORTANCE** Currently, diagnosis of Parkinson disease is mainly based on clinical criteria characterized by motor symptoms including bradykinesia, rigidity, resting tremor, and postural instability. Reliable in vivo biomarkers to monitor disease severity and reflect the underlying dopaminergic degeneration are important for future disease-modifying therapy in Parkinson disease.

**OBJECTIVES** To use $^{18}$F-9-fluoropropyl-(-)-dihydrotetrabenazine ($^{18}$F-DTBZ, [18F]AV-133) positron emission tomography (PET) to explore the characteristics of vesicular monoamine transporter type 2 imaging in patients with Parkinson disease (PD) with different severity levels as well as to investigate its capability in monitoring clinical severity.

**DESIGN, SETTING, AND PARTICIPANTS** Regional uptakes for $^{18}$F-DTBZ PET of different disease stages were measured. Seventeen healthy control participants and 53 patients in 3 groups of mild, moderate, and advanced stages of PD were recruited for $^{18}$F-DTBZ PET scans from the Movement Disorders Clinic in the Chang Gung Memorial Hospital, Taiwan.

**MAIN OUTCOMES AND MEASURES** The severity of disease in patients with PD was quantified by modified Hoehn-Yahr Scale, Unified Parkinson Disease Rating Scale total scores and subscores of posture instability and gait disturbance, tremor, akinesia, and rigidity while not taking medication. Both voxelwise- and volume of interest–based image analyses were performed. The specific uptake ratio (SUR) of each volume of interest and voxel was calculated as (target uptake − reference uptake) / reference uptake using the occipital reference region from magnetic resonance imaging–based spatially normalized $^{18}$F-DTBZ images for each participant. Average SUR images were displayed as 2-dimensional and 3-dimensional to illustrate the image patterns in each group. The nonparametric Kruskal-Wallis test on regional SUR was used for group comparison between healthy control participants and patients with PD at different stages. Quantitative parameters were correlated with severity of disease and disease duration by Spearman correlation. Voxelwise analysis for evaluating dopaminergic neuron decline of different PD stages was performed by SPM5.

**RESULTS** The 2-dimensional and 3-dimensional $^{18}$F-DTBZ PET images demonstrated that the reduction of vesicular monoamine transporter type 2 availability was obviously correlated with the severity of disease in patients with PD. The mean reductions of vesicular monoamine transporter type 2 density for the caudate, putamen, and substantia nigra were 21.50%, 58.20%, and 21.10% for mild PD; 60.75%, 79.49%, and 39.87% for moderate PD; and 63.94%, 83.20%, and 44.00% for advanced PD, respectively. The SURs of bilateral striatal regions exhibited significantly exponential correlations to stage; disease duration; Unified Parkinson Disease Rating Scale motor score; posture instability and gait disturbance; and akinesia, rigidity, and tremor scores.

**CONCLUSIONS AND RELEVANCE** In PD, $^{18}$F-DTBZ PET is a potential imaging biomarker for measuring dopaminergic degeneration in vivo and monitoring the severity of disease.
Parkinson disease (PD) is a neurodegenerative disorder with the major pathological feature of dopaminergic neuron loss in the substantia nigra (SN) and, subsequently, decreased axons projected to the striatum. Currently, diagnosis of PD is mainly based on clinical criteria characterized by motor symptoms including bradykinesia, rigidity, resting tremor, and postural instability. Developing reliable in vivo biomarkers to monitor disease severity and reflect the underlying dopaminergic degeneration is important for future disease-modifying therapy in PD.

A noninvasive neuroimaging technique with radiotracers targeting the dopaminergic system from both positron emission tomography (PET) and single-photon emission computed tomography is an ideal method to monitor disease severity and investigate neural degeneration in PD. To serve as an objective biomarker for disease progression in PD, study of the correlation of imaging patterns and quantitation for an imaging tracer to clinical measures of disease severity is important. Previous studies have been conducted on the correlation of the striatal uptake of [18F]fluorodopa PET, for measuring aromatic amino acid decarboxylase activity, to disease severity. The correlations of dopaminergic transporter loss using iodine I 123-labeled 2β-carbomethoxy-3β-(4-iodophenyl) tropane and Tc-labeled tropane derivative single-photon emission computed tomography with PD stage and severity have been reported. Nevertheless, both aromatic amino acid decarboxylase activity and dopamine transporter density are regulated by disease and antiparkinsonian medications, which greatly limit their applications in measuring the dopaminergic degeneration precisely.

Vesicular monoamine transporter type 2 (VMAT2) is the protein responsible for pumping monoamines from cytosol into synaptic vesicles. Vesicular monoamine transporter type 2 imaging using PET tracer [11C]dihydrorotenabenazine ([11C-DTBZ]) has been proven to be an objective marker of nigrostriatal terminal integrity. Although VMAT2 availability may be sensitive to vesicular dopamine levels, previous studies have suggested there is no long-term regulation effect on the VMAT2 binding sites by dopaminergic drugs for PD. Using [11C]-DTBZ PET, an age-dependent VMAT2 decline in normal individuals was observed along with the significant correlation of striatal binding reduction to disease duration in PD. The asymmetry of VMAT2 binding was also highly correlated with clinical asymmetry. Another study reported the effectiveness of [11C]-DTBZ imaging for evaluating the evolution of dopamine neuron loss in a nonhuman primate model of PD at different stages.

A novel tracer of [18F]9-fluoropropyl-(+)-dihydrotetrabenazine ([18F]-DTBZ) for VMAT2 imaging with a longer half-life (t1/2 = 110 minutes compared with 20 minutes of C-11) has been recently developed. In patients with PD, [18F]-DTBZ PET imaging studies have demonstrated a high sensitivity for detecting monoaminergic terminal reductions. Recently, the image features of [18F]-DTBZ imaging in normal human brains were investigated. Yet, to our knowledge, the detailed imaging pattern and the correlation of VMAT2 availability to disease severity acquired by [18F]-DTBZ have not been well studied. Thus, it is of importance to use [18F]-DTBZ to provide in vivo dopaminergic integrity in different stages of PD for monitoring disease progression and for future clinical trials of disease-modifying therapy.

The goal of this study was to explore the image features of VMAT2 distribution by [18F]-DTBZ PET in patients with PD of different stages and compare with healthy control (HC) individuals. To demonstrate the spatial and progressive change of dopaminergic degeneration, the 2-dimension (2-D) and 3-dimension (3-D) distribution patterns of VMAT2 in patients with PD with mild, moderate, and advanced stages of disease were further investigated. In patients with PD, the correlations between clinical motor disability and the reduction of VMAT2 availability were also analyzed.

### Methods

#### Participants

Seventy participants were included in this study (17 HC and 53 PD). According to the modified Hoehn-Yahr (mH-Y) stage, the patients with PD were further divided into 3 subgroups of mild (score range, 1-2, n = 22), moderate (2.5-3, n = 20), and advanced (4-5, n = 11) stages. The study protocol was approved by the institutional review board of the Chang Gung Memorial Hospital and the Governmental Department of Health. Neurologic examinations were performed on all participants. In patients with PD, the severity of disease was assessed by mH-Y stage and the Unified Parkinson Disease Rating Scale (UPDRS) when patients were not taking medication (individuals should not take any antiparkinsonian medication at least 12 hours before the tests). Subscores of the UPDRS were analyzed as follows: tremor = arm and leg rest and action tremor (scores No. 20 + 21); akinesia = finger taps, hand movements, rapid alternating movements of the hands, and leg agility (scores No. 23 + 24 + 25 + 26); rigidity = arm and leg rigidity (score No. 22); and postural instability/gait disorder (PI/GD) = walking, freezing, and falling from UPDRS II scores + gait and postural stability (scores No. 13 + 14 + 15 + 29 + 30). To avoid the transient effects of dopamine-mimic drugs on vesicular dopamine levels and VMAT2 availability, all PET scans were performed while patients were not taking medication.

#### Data Acquisition

[18F]-DTBZ was prepared and synthesized at the cyclotron facility of Chang Gung Memorial Hospital. All participants were studied in a Biograph mCT PET/computed tomography system (Siemens Medical Solutions). All participants underwent magnetic resonance imaging (MRI) for screening of other diseases and performing spatial normalization with PET images. Participants were imaged on a 3-T Siemens Magnetom TIM Trio scanner (Siemens Medical Solutions).

After injection of a mean (SD) of 386 (11) MBq of [18F]-DTBZ, a single 10-minute PET scan was acquired 90 minutes postinjection in 3-D mode. Positron emission tomographic images were then reconstructed using 3-D ordered-subset expectation maximization algorithm (4 iterations, 24 subsets;...
Table 1. Demographic and Clinical Profiles of All Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy Control (n = 17)</th>
<th>Mild PD (n = 22)</th>
<th>Moderate PD (n = 10)</th>
<th>Advanced PD (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) [range], y</td>
<td>61.4 (5.0) [53-71]</td>
<td>60.8 (5.4) [54-71]</td>
<td>61.1 (7.6) [53-77]</td>
<td>66.1 (5.0) [59-72]</td>
</tr>
<tr>
<td>Sex, No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>13</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>9</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>5.2 (4.5)ab</td>
<td>14.0 (5.7)</td>
<td>15.5 (5.5)</td>
<td></td>
</tr>
<tr>
<td>UPDRS total</td>
<td>12.9 (9.2)ab</td>
<td>48.7 (15.4)c</td>
<td>75.8 (18.9)</td>
<td></td>
</tr>
<tr>
<td>UPDRS III</td>
<td>7.6 (5.5)ab</td>
<td>28.7 (10.1)c</td>
<td>45.7 (12.9)</td>
<td></td>
</tr>
<tr>
<td>PI/GD</td>
<td>1.4 (1.3)ab</td>
<td>5.8 (2.5)c</td>
<td>10.8 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Akinesia</td>
<td>2.9 (2.0)ab</td>
<td>10.9 (5.3)d</td>
<td>20.1 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Rigidity</td>
<td>1.7 (2.3)b</td>
<td>4.4 (3.5)</td>
<td>5.0 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>1.0 (1.6)</td>
<td>2.9 (4.0)</td>
<td>4.4 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Modified Hoehn-Yahr stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) [range]</td>
<td>1.2 (0.3) [1-2]ab</td>
<td>2.9 (0.2) [2-5]c</td>
<td>4.6 (0.5) [4-5]</td>
<td></td>
</tr>
</tbody>
</table>

Results

Table 1 shows the demographic data of all participants. In the mild PD group, the parameters, including disease duration, mH-Y stage, UPDRS total scores, UPDRS motor scores (UPDRS III), PI/GD, and akinesia scores, were significantly lower than those of the moderate and advanced PD groups (P < .001). Figure 1 illustrates the average 18F-DTBZ uptakes in 2-D and 3-D images from HC individuals and patients with PD. Images in HC individuals revealed a symmetric distribution pattern with the highest uptake in striatal regions and moderate uptake in the SN, raphe, hippocampus, amygdala, and hypothalamus (Figure 1A and B). The caudate nucleus and putamen could be easily separated by visual assessment in 2-D images. The 3-D image of HC individuals represented an integral and visible functional anatomy of dopaminergic, serotonergic, and noradrenergic innervations.

The VMAT2 availability in nigrostriatal regions was obviously decreased with the progression of clinical severity in PD. Figure 1C and D demonstrate a typical pattern of selective dopaminergic degeneration in mild PD as an obviously asymmetric activity decline in nigrostriatum with the greatest loss in contralateral PPU. In moderate PD (Figure 1E and F), the uptake reduction in the caudate, APu, and SN was more obvious. At this stage, the asymmetry of striatal uptake became less discernible. The characteristic of VMAT2 distribution in the advanced PD group (Figure 1G and H) was similar to that of moderate PD but with a more severe uptake decline in all regions. The correlation between dopamine neuron loss and disease progression from HC individuals to patients with advanced PD could be better visualized in 3-D views. The decline of VMAT2 began from the contralateral PPu, followed by the ipsilateral PPu, and then extended to
the APu and caudate. In advanced PD, the striatal VMAT2 activity could be observed only in the NAc and head of the caudate, whereas the activity was relatively preserved in the extrastriatal regions including the hippocampus, amygdala, raphe, and LC (Video).

**Table 2** shows the regional 18F-DTBZ SUR values for the HC individuals and patients with PD. As demonstrated, regional SUs of the striatum and SN in both the moderate and advanced PD groups were significantly lower than those in the HC group. Only the SUs of contralateral APu and PPU in mild PD were different from those of HC individuals. Specific uptake ratios of all striatal regions in moderate and advanced PD revealed a significant difference ($P < .05$) from those with mild PD. Nevertheless, there were no significant SUR differences in the raphe, hippocampus, and amygdala among HC individuals and patients with PD for all stages.

Percentage declines of regional uptake in the bilateral nigrostriatal regions for PD at different stages compared with HC individuals are also displayed in Table 2. In the nigrostriatal pathway, VMAT2 activities were reduced markedly in the PPU, followed by the APu and caudate, but less affected in the SN. Activity reduction in the PPU was greater than 60% for all stages of PD. There was no sex difference for regional SUs except in the contralateral SN for PD ($P = .03$) and hypothalamus for HC individuals ($P = .03$). The results of voxelwise analysis from statistical parametric mapping for discriminating 3 different PD

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**Figure 1.** Averaged 2-Dimensional and 3-Dimensional [18F]9-fluoropropyl-(+)-Dihydrotetrabenazine Specific Uptake Ratio Images of Normal Participants and Patients With Parkinson Disease (PD) of Varying Severity

Averaged [18F]9-fluoropropyl-(+)-dihydrotetrabenazine specific uptake ratio 2-dimensional images of healthy control participants (A) and patients with mild PD (C), moderate PD (E), and advanced PD (G). Symmetric and bilateral vesicular monoamine transporter type 2 (VMAT2) binding in dopamine innervation is illustrated in healthy control participants. Asymmetric pattern of nigrostriatal VMAT2 uptake loss is visible in mild PD, while less obvious in moderate PD, and asymmetry almost disappears, but with severe VMAT2 binding decline, in advanced PD. Posterior-to-anterior 3-dimensional views of VMAT2 binding images of dopamine innervation are illustrated for healthy control participants (B), mild PD (D), moderate PD (F), and advanced PD (H). The frame wire in 3-dimensional images indicates the complete volumes of interest of the caudate nuclei, putamen, substantia nigra, and midbrain.
groups from the HC group are shown in eAppendices 1 and 2 and the eFigure in Supplement.

The correlations between nigrostriatal SURs and clinical characteristics of patients with PD were calculated by an exponential regression model as shown in eAppendices 1 and 2 and eTable 1 in Supplement.

Figures 2 and 3 illustrate the scatterplots and fitted exponential curves of SURs against disease stage, duration, and clinical scores in the bilateral PPU.36,37 The SURs of the bilateral striatum exhibited significant correlations to mH-Y stage; disease duration; and UPDRS III, PI/GD, akinesia, rigidity, and tremors scores, while the SUR in the SN displayed significant correlation only to stage, disease duration, UPDRS III, and PI/GD scores (eAppendix 2 and eTable 1 in Supplement). No statistically significant correlation between quantitative values and clinical characteristics in the hippocampus, amygdala, and raphe was observed. The SURs in the ipsilateral PPU were obviously higher than those of the contralateral PPU as shown in Figure 2. As the disease progressed to the moderate and to the advanced stages (mH-Y ≥3), the uptake in the bilateral PPU became similar. In addition, SURs in bilateral nigrostriatal regions were exponentially correlated with disease stages with a statistical significance of P < .05 as shown in eTable 1 in Supplement and that indicated 2 phase declines: rapid decline (mild stage) and slower decline (moderate and advanced stages).

### Discussion

The present study provided the 2-D and 3-D imaging of VMAT2 distributions in the dopaminergic, serotoninergic, and noradrenergic pathways using 18F-DTBZ PET for HC individuals and patients with mild, moderate, and advanced stages of PD. The correlation between clinical severity and the quantitative measurement of VMAT2 integrity in PD was further explored.

### VMAT2 Imaging Feature of HC and PD Groups

The distribution pattern of VMAT2 could be clearly illustrated for HC individuals and patients with PD by both 2-D and 3-D images of 18F-DTBZ PET (Figure 1). As was similarly reported by Lin et al,35 high uptakes in the SN, striatum (nigrostriatal pathway), NAc, hippocampus, and amygdala (mesolimbic pathway), as well as the raphe (serotonin system) and

### Table 2. Mean Regional SURs and Percentage Decline Rate of Different Disease Groups

<table>
<thead>
<tr>
<th>Region</th>
<th>HC Mild PD</th>
<th>HC Moderate PD</th>
<th>HC Advanced PD</th>
<th>Sex Effect, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>2.3 (0.5)</td>
<td>1.7 (0.8)</td>
<td>0.8 (0.4)c</td>
<td>.43 .24</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>2.3 (0.5)</td>
<td>1.9 (0.8)</td>
<td>1.0 (0.5)c</td>
<td>.43 .26</td>
</tr>
<tr>
<td>Anterior putamen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>2.8 (0.5)</td>
<td>1.3 (0.6)d</td>
<td>0.7 (0.2)d</td>
<td>.29 .22</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>2.8 (0.5)</td>
<td>1.6 (0.7)d</td>
<td>0.9 (0.4)d</td>
<td>.29 .44</td>
</tr>
<tr>
<td>Posterior putamen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>2.7 (0.5)</td>
<td>0.6 (0.4)</td>
<td>0.3 (0.1)d</td>
<td>.11 .03</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>2.7 (0.5)</td>
<td>1.0 (0.6)</td>
<td>0.4 (0.3)d</td>
<td>.11 .46</td>
</tr>
<tr>
<td>Substantia nigra</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Contralateral</td>
<td>1.1 (0.3)</td>
<td>0.8 (0.4)f</td>
<td>28.8</td>
<td>.56 .85</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>1.1 (0.3)</td>
<td>0.9 (0.4)</td>
<td>13.4</td>
<td>.56 .86</td>
</tr>
<tr>
<td>Accumbens</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>1.2 (0.4)</td>
<td>1.0 (0.5)</td>
<td>12.9</td>
<td>.56 .85</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>1.2 (0.4)</td>
<td>1.2 (0.6)</td>
<td>−6.1</td>
<td>.56 .86</td>
</tr>
<tr>
<td>Amygdala</td>
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<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>0.5 (0.1)</td>
<td>0.5 (0.2)</td>
<td>−22.0</td>
<td>.92 .35</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>0.5 (0.1)</td>
<td>0.5 (0.2)</td>
<td>−25.2</td>
<td>.92 .52</td>
</tr>
<tr>
<td>Hippocampus</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>0.2 (0.1)</td>
<td>0.3 (0.1)</td>
<td>−28.5</td>
<td>.79 .69</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>0.2 (0.1)</td>
<td>0.3 (0.1)</td>
<td>−28.5</td>
<td>.79 .77</td>
</tr>
<tr>
<td>Raphe</td>
<td>1.0 (0.2)</td>
<td>1.3 (0.4)</td>
<td>−22.1</td>
<td>.40 .13</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>1.2 (0.2)</td>
<td>1.4 (0.4)</td>
<td>−16.6</td>
<td>.04 .76</td>
</tr>
<tr>
<td>Locus coeruleus</td>
<td>1.0 (0.2)</td>
<td>1.2 (0.4)</td>
<td>−23.5</td>
<td>.29 .10</td>
</tr>
</tbody>
</table>

Abbreviations: HC, healthy control; PD, Parkinson disease; SUR, specific uptake ratio.

### Abbreviations

a Significantly different from HC, P < .001.
b Significantly different from mild PD, P < .01.
c Significantly different from mild PD, P < .05.
d Significantly different from HC, P < .01.
e Significantly different from mild PD, P < .001.
f Significantly different from HC, P < .05.
LC (norepinephrine system), were well demonstrated in the HC group. The striatum contained the highest VMAT2 level, with the lowest ones in both the cortex and cerebellum (approximately 1% of the striatal concentration).^{30,38,39}

For the characteristic of F-F-DTBZ imaging in patients with PD (Figure 1), the nigrostriatal binding showed a gradual reduction with the disease progression. Regional integrity of VMAT2 was mostly affected in the PPs among all patients with PD, followed by the APu, caudate, and SN. This result was in line with the postmortem results indicating that the apoptosis of dopaminergic neurons in the lateral ventral tier of the SN projecting to the putamen was most severe. The degeneration of dopaminergic pathways was worse in the dopaminergic axonal terminals of the striatum than that in the cell bodies of the SN.\(^{36,40-42}\) Previous in vivo PET and postmortem studies had proven that VMAT2/dopamine level in the PPs had 70% to 80% reduction in patients with PD with the initial manifestation of symptoms.\(^{16,25,28,43-45}\) We also observed the same tendency of decline in F-F-DTBZ binding for mild PD (70.0% decline in the bilateral PPs). Moreover, the VMAT2 availability in the striatum showed a significant difference between HC individuals and patients with mild PD (Figure 1), indicating that F-F-DTBZ imaging might be a sensitive tool for early detection of dopaminergic degeneration in PD. Furthermore, the striatal SURs correlated with disease severity. The decline of F-F-DTBZ binding was highest for advanced PD and lowest for mild PD. These observations are in agreement with postmortem studies, with the greatest decrease of dopaminergic innervations in the PPs for more advanced PD.\(^{39,42,46,47}\) A similar trend was also found in a previous ¹¹C-DTBZ study of patients with PD of early and moderate stages.\(^{25}\) There was no significant difference between SURs in moderate and advanced PD in the contralateral PPu region (Table 2). This may be owing to the reduction of radioactivity in this region reaching its lower limit earlier than other striatal regions in patients with moderate to advanced PD.

One of the important F-F-DTBZ imaging features of patients with PD was the asymmetric loss of dopaminergic innervations, with an obvious decline in the contralateral striatum (Figure 1; Table 2; eAppendices 1 and 2 and the asymmetry index\(^{7}\) in eTable 2 in Supplement). These asymmetries were consistent with previous studies using ¹¹C-DTBZ and \(^{99m}\)Tc-labeled tropane derivative.\(^{25,48}\)

The significant deficit of F-F-DTBZ uptake in patients with PD was mainly located in the nigrostriatum from both regional and voxelwise analysis. In the NAc, significant SUR reduction only appeared in the contralateral side for both moderate and advanced PD. However, there was no significant loss of F-F-DTBZ uptake among the 3 PD stages in the serotonin and norepinephrine systems including the raphe, hippocampus, and amygdala. These findings were consistent with the literature that the dopaminergic neuron damage in PD primarily starts from nigrostriatal, then mesocortical, pathways and finally affects the mesolimbic system in the advanced stage.\(^{3}\) A previous ¹¹C-DTBZ study also reported a similar result, with no statistical difference of the VMAT2 activity between patients with PD and age-matched control participants in the raphe that has major serotonergic innervations.\(^{49}\)

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**Figure 2. Bilateral Posterior Putamen [¹⁸F]9-fluoropropyl-(+)-dihydrotetrazenemazine Specific Uptake Ratio vs Modified Hoehn-Yahr Stage, Disease Duration, and Unified Parkinson Disease Rating Scale III Score**

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Relationship of Image Quantification to Clinical Measures

Biomarkers for the early detection of pathology changes prior to the clinical symptoms would be important for development of disease modification and for treatment planning. In previous imaging studies of dopamine systems, the loss of dopamine innervations—as measured by $^{99m}$Tc-labeled tropane derivative, iodine I 123–labeled 2β-carbomethoxy-3β-(4-iodophenyl)tropane, 123I-labeled N-(3-fluoropropyl)-2beta-carbomethoxy-3beta-(4-iodophenyl)nortropane, $[^{18}F]$fluorodopa, $[^{11}C]$-DTBZ, and $[^{18}F]$-DTBZ—was correlated with the clinical severity particularly the motor scores of UPDRS. The results in this study were in agreement with those in the literature and showed significantly exponential correlation between striatal $[^{18}F]$-DTBZ binding and clinical characteristics of PD including mH-Y stage, duration of disease, UPDRS III, and subscores of UPDRS. Moreover, the $[^{18}F]$-DTBZ binding of the SN also exponentially related to the UPDRS scores (except rigidity). These findings suggested that SUR level in the SN can provide supplementary information for evaluating the severity of motor symptoms in patients with PD.

The SURs of $[^{18}F]$-DTBZ in the PPu, the motor part of nigrostriatal projections, displayed good correlation to disease stage and might be a good marker to represent the motor disability and to monitor the effects of therapy for rescuing nigral dopamine neurons in the early disease stage.

As disease progressed, the increase of PI/GD scores was highest, followed by akinesia and rigidity scores (Table 1). These findings suggested that axial signs may make the greatest impact on the clinical deterioration of PD. Thus, the high correlation of SURs to clinical measurements in this study displayed potential and important application of $[^{18}F]$-DTBZ imaging for clinical PD severity evaluations in moderate and severe stages. In addition to the motor functions, nonmotor complications, including cognitive and mood changes, might also play important roles in disease progression of PD. Future work should include correlation of cognitive and mood performances to the VMAT2 distributions using $[^{18}F]$-DTBZ imaging.
The SURs of the raphe, amygdala, hippocampus, and LC exhibited an increasing trend with disease severity (Table 2). In particular, SURs of the LC in moderate and advanced stages showed significant differences compared with HC individuals. Similar results could also be observed in Figure 1. One possible reason is that the VMAT2 in these regions were relatively preserved in PD, whereas uptake in the occipital lobe might decrease as disease progressed owing to occipital hypoperfusion in the advanced stage of disease. Therefore, using the occipital lobe as a reference region, the SURs in the raphe, amygdala, hippocampus, and LC might be overestimated in the moderate and advanced stages. In PD, the severe reduction of VMAT2 density in the nigrostriatal system makes the effect of occipital hypoperfusion on the quantification of striatal regions too minimal to be neglected. Therefore, we suggest that the quantification of VMAT2 availability in extrastriatal regions should be more cautious when using the occipital lobe as a reference region in diseases with occipital hypoperfusion or atrophy.

Other limitations of the present study were the small sample size in each mH-Y stage and use of cross-sectional data. A large number of patients with PD for every mH-Y stage and longitudinal studies for further validation are warranted.

Conclusions

In PD, 18F-DTBZ PET imaging could potentially provide a stronger power for detecting dysfunction of the dopaminergic system. In addition, SURs of 18F-DTBZ reveal good correlation to clinical severity of PD. Thus, 18F-DTBZ imaging is a potential biomarker for monitoring dopaminergic degeneration and may likely be useful for assessing the disease progression of PD.


