Presynaptic and Postsynaptic Dopaminergic Binding Densities in the Nigrostriatal and Mesocortical Systems in Early Parkinson’s Disease: A Double-Tracer Positron Emission Tomography Study

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To investigate changes in the relation between presynaptic and postsynaptic dopaminergic functions in vivo in both nigrostriatal and mesocortical systems in Parkinson’s disease (PD), 10 drug-naive early PD patients were studied twice using positron emission tomography with [11C]CFT (dopamine transporter probe) followed by [11C]SCH 23390 (D1 receptor probe). Regional binding potentials \( k_3/k_4 \) of [11C]CFT and [11C]SCH 23390 in the striatum (nigrostriatal system) and the orbitofrontal cortex (mesocortical system) were estimated by compartment analyses. Levels of [11C]CFT \( k_3/k_4 \) in the two projection areas were shown to be significantly lower in PD, whereas [11C]SCH 23390 levels remained unchanged. Regression analysis showed that estimates of CFT \( k_3/k_4 \) were positively correlated with those of SCH 23390 \( k_3/k_4 \) in the striatum in normal control, whereas the two binding estimates were less positively correlated in the caudate and inversely correlated in the putamen in PD. No significant correlation was observed in the orbitofrontal cortex in both groups. These results indicated that dopamine transporters and D1 receptors change in parallel in the normal striatal synapses, but the association becomes asymmetrical because of reduction in presynaptic and relative elevation in postsynaptic markers in PD. Alterations in synaptic parallel regulation in the nigrostriatal system might reflect early pathophysiology in the parkinsonian brain.


Loss of nigral dopamine neurons and the corresponding loss of dopamine-containing nerve terminals in the striatum are well-known pathological evidences in Parkinson’s disease (PD).1,2 These histopathological findings support in vivo studies with positron emission tomography (PET), using several dopamine transporter (DAT) markers such as [11C]nomifensine,3 [18F]dopa,4 [11C]WIN 35,428,5 [11C]dihydrotetrabenazine.6 The decline of these presynaptic tracers’ uptake is thought to be caused by either exaggerated aging-related cell attrition7 or pathological processes8 in the nigrostriatal system in PD. In contrast to this reduction of presynaptic functions in the PD striatum, the striatal dopaminergic D1 and D2 receptor concentrations are reported to be the same as or larger than those of age-matched normal controls.9–11

It is speculated that the difference in tracer binding in the dopaminergic presynaptic and postsynaptic binding sites in PD resulted from alterations in functional integrities in the synapse, such as the presence of postsynaptic denervation supersensitivity. One previous PET study with double tracers ([18F]dopa and [11C]raclopride) in drug-naive PD patients examined at 2-month intervals showed an asymmetric change in the two markers in the striatum, but did not detect any positive correlation between the two binding levels in the putamen in normal subjects.12 In another PET study with [11C]methylphenidate and [11C]raclopride

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examined at intervals, however, a parallel change of presynaptic and postsynaptic dopamine markers in the striatum was reported in normal aging.\textsuperscript{13} Thus, it remains unclear whether the presynaptic and postsynaptic dopamine markers should change in parallel or uncouple with each other in the same patients with drug-naive PD. Presence of altered patterns in the association between presynaptic and postsynaptic markers would imply functional derangement, which may feature early pathophysiological change in PD brain. In addition to the alteration in this nigrostriatal system, the mesocortical dopaminergic system that arises in the ventral mesencephalic tegmentum (A10)\textsuperscript{14} was reported to be affected in PD.\textsuperscript{15-17}

The aim of the present PET study was to investigate in vivo alterations in the presynaptic and postsynaptic binding sites in the two dopaminergic projection systems by quantitatively measuring DATs by using 2-\textit{b-[\textsuperscript{11}C]carbomethoxy-3\textit{b}-(4-fluorophenyl)tropone (\textsuperscript{[11}C]CFT), and D1 receptors by using \textsuperscript{13}C]SCH 23390 (\textsuperscript{[11}C]SCH) in patients with drug-naive PD at an early stage.

Subjects and Methods

Subjects and Patients

Nine normal subjects (5 men and 4 women; mean age, 51.2 ± 13.8 years [± SD]) and 10 age-matched drug-naive PD patients (7 men and 3 women; mean age, 59.4 ± 6.7 years), rated at stage 1–2 on the Hoehn and Yahr scale, were studied. Clinical assessment of each PD patient was performed with the Unified Parkinson’s Disease Rating Scale and the Mini-Mental State Examination and the Wechsler Adult Intelligence Scale-revised (Table 1). Magnetic resonance imaging (MRI) study showed no brain morphological abnormalities in all participants. L-Dopa treatment for all PD patients (7 men and 3 women; mean age, 59.4 ± 6.7 years) was set parallel to the AC-PC line, determined by MRI, 18\textsuperscript{°} to 90\textsuperscript{°}. The in-plane spatial resolution was 2.7 mm and the resolution in the axial plane was 5.5 mm full width at half maximum with an 80-mm axial field of view.\textsuperscript{19} The gantry was set parallel to the AC-PC line, determined by MRI,\textsuperscript{18} and a 20-minute transmission scan for attenuation correction was performed with a \textsuperscript{68}Ge/\textsuperscript{68}Ga source.

PET Procedure and Blood Analysis

We used a high-resolution brain PET scanner (SHR2400; Hamamatsu Photonics KK, Hamamatsu, Japan) with five detector rings yielding nine slice images simultaneously. The gantry of this tomograph could be tilted from −20\textsuperscript{°} to +90\textsuperscript{°}. The in-plane spatial resolution was 2.7 mm and the resolution in the axial plane was 5.5 mm full width at half maximum with an 80-mm axial field of view.\textsuperscript{19} The gantry was set parallel to the AC-PC line, determined by MRI,\textsuperscript{18} and a 20-minute transmission scan for attenuation correction was performed with a \textsuperscript{68}Ge/\textsuperscript{68}Ga source.

For \textsuperscript{[11}C]CFT study, serial scans (time frames: 4 × 30 seconds, 20 × 60 seconds, 14 × 300 seconds) and periodical arterial blood sampling were performed for 90 minutes after a slow bolus injection (taking 1 minute) of a 450-MBq dose of \textsuperscript{[11}C]CFT. To determine radioactive metabolites, additional arterial blood samples were drawn at 1, 5, 20, 30, and 45 minutes after \textsuperscript{[11}C]CFT injection and analyzed by using thin-layer chromatography and a storage phosphor screen bioimaging analyzer (BAS-1500; Fuji Film, Tokyo, Japan). The free metabolite-corrected plasma activities were fitted to a sum of three exponentials by the nonlinear least-squares method with the nonweighted Gauss–Newton algorithm.

The \textsuperscript{[11}C]SCH study was performed after a time interval of 3 hours to allow for decay of radioactivity. Each partici-

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>DD</th>
<th>H&amp;Y</th>
<th>MMSE</th>
<th>AIS-R (v/p/t)</th>
<th>UPDRS (me/act/mo)</th>
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<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>M</td>
<td>0.4</td>
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<td>25</td>
<td>125/111/119</td>
<td>2/3/14</td>
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<td>2</td>
<td>47</td>
<td>M</td>
<td>0.5</td>
<td>2</td>
<td>29</td>
<td>97/98/97</td>
<td>2/4/20</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>M</td>
<td>0.4</td>
<td>2</td>
<td>26</td>
<td>92/86/87</td>
<td>2/6/15</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>M</td>
<td>0.8</td>
<td>2</td>
<td>26</td>
<td>90/82/84</td>
<td>2/9/19</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>M</td>
<td>1.8</td>
<td>2</td>
<td>27</td>
<td>92/87/89</td>
<td>2/15/21</td>
</tr>
<tr>
<td>6</td>
<td>53</td>
<td>M</td>
<td>0.5</td>
<td>1</td>
<td>30</td>
<td>116/110/112</td>
<td>1/6/12</td>
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<tr>
<td>7</td>
<td>49</td>
<td>M</td>
<td>0.8</td>
<td>1</td>
<td>30</td>
<td>109/101/104</td>
<td>1/8/16</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>F</td>
<td>1.2</td>
<td>2</td>
<td>27</td>
<td>96/91/94</td>
<td>2/6/20</td>
</tr>
<tr>
<td>9</td>
<td>62</td>
<td>F</td>
<td>1.2</td>
<td>2</td>
<td>24</td>
<td>84/78/80</td>
<td>10/10/21</td>
</tr>
<tr>
<td>10</td>
<td>64</td>
<td>F</td>
<td>1.5</td>
<td>2</td>
<td>27</td>
<td>99/86/93</td>
<td>7/11/26</td>
</tr>
</tbody>
</table>

DD = disease duration (yr); H&Y = modified Hoehn & Yahr disability score (1–5); MMSE = Mini-Mental State Examination (max = 30); WAIS-R = Wechsler Adult Intelligence Scale-revised (v = verbal IQ; p = performance IQ; t = total IQ); UPDRS = Unified Parkinson’s Disease Rating Scale (me = mentation, behavior, and mood; act = activities of daily living; mo = motor examination).
pant, with the head fixated at the same position as in the \([^{11}C]CFT\) measurement, underwent dynamic PET scans (4 × 30 seconds, 20 × 60 seconds, 4 × 300 seconds) for 60 minutes after venous injection of a 400-MBq dose of \([^{11}C]SCH\). Simultaneously, after tracer injection, periodic arterial blood was sampled in the same way as in the \([^{11}C]CFT\) study, and four additional arterial samples were drawn for analysis of the percentage of unchanged ligand in plasma.

**Image Data Analysis**

In the ROI setting, irregular ROIs (64 ~ 800 mm\(^2\)) were drawn bilaterally over the caudate, putamen, orbitofrontal cortex, and cerebellum (Fig 1) on the MR images and transferred onto the corresponding CFT-PET and SCH-PET images, using image-processing software (Dr View; Asahi Kasei Co, Tokyo, Japan) on a SUN workstation (Hypersparc ss-20; SUN Microsystems, CA).\(^{21}\) To investigate the partial volume effects on the PET results, a volumetric study of each brain structure was performed by using the multiform area product (identical to ROI on the PET images) drawn on the MR images and the slice thickness. Each volume was calculated by multiplying the area product by the slice thickness. The border of the orbitofrontal cortex was determined in the prefrontal region from the rectus gyrus to the bottom of the genu of the corpus callosum.\(^{22,23}\) The borders for the caudate and putamen were outlined on all planes on which these structures appeared.\(^{24}\)

In the \([^{11}C]CFT\) study, based on the three-compartment model, data were analyzed by fitting artery and tissue time–activity curves (TACs) for blood–brain barrier transport rates (\(K_1\)), the free plus nonspecific distribution volume (\(K_1/k_2\)), and the binding and dissociation rate constants (\(k_3\) and \(k_4\), respectively).\(^{25,26}\) The distribution volume, \(K_1/k_2\), was first fitted to the cerebellum, which was assumed to be an appropriate region for estimation of nonspecific binding because it contains negligible concentrations of dopamine and dopamine receptors.\(^{27}\) The TACs were corrected for the presence of the vascular compartment, which was fixed to a value of 3.5% of brain volume.\(^{26}\) On the assumption that the ratio \(K_1/k_2\) in the cerebellum was the same in other parts of the brain including the striatum, the rate constants \(K_1\), \(k_3\), and \(k_4\) in the concerned brain regions were measured by fitting the metabolite-corrected plasma time–radioactivity curves of \([^{11}C]CFT\) and cerebral blood volume-corrected brain TACs, using a nonlinear least-squares algorithm. The \(k_3/k_4\) ratio equivalent to \(B_{max}/k_d\) (binding potential)\(^{28}\) was the final estimate for evaluating DAT (presynaptic) activity in the present study.

In the \([^{11}C]SCH\) study, data analysis was based on Logan graphical analysis suitable for a reversibly bound tracer.\(^{29}\) With metabolite-corrected plasma input function and two- and three-compartment models in which the cerebellar radioactivity was regarded as an estimate of the unbound radioligand in the target tissues, \(B_{max}/k_d\) was estimated...
by using the following equation and the nonlinear least-squares fitting method: \( B_{\text{max}}/k_d = (\text{target tissue } V_d)/(\text{cerebellum } V_d) - 1^{29,30} \); where each \( V_d \) (distribution volume for \([^{11}\text{C}]\text{SCH} \) in each region) was obtained by the Logan graphical method. Because ROIs on the \([^{11}\text{C}]\text{SCH} \) images were, principally, identical in size and location to those on the \([^{11}\text{C}]\text{CFT} \) images, \([^{11}\text{C}]\text{SCH} \) binding potentials (postsynaptic activity) in each region could be compared directly with one \([^{11}\text{C}]\text{CFT} \) (presynaptic activity) in the corresponding region.

**Statistics**

Age-related reduction was reported in DAT \(^{31}\) and D1 receptors\(^{20}\) in normal subjects. In the present study, however, age-related correction for PET results was not considered because there was no significant difference in age between PD and normal control subjects \((p > 0.05, \chi^2 \text{ test})\). Two-way analysis of variance (ANOVA), with a post hoc Scheffé's \( F \) test for correcting multiple comparisons, was first performed to assess levels of binding potentials (for both \([^{11}\text{C}]\text{CFT} \) and \([^{11}\text{C}]\text{SCH} \)), with respect to one intersubject factor (PD and normal) and intrasubject factor (striatal region consisting of the caudate and putamen, and extrastriatal region consisting of the orbitofrontal cortex), for evaluating the level of binding reduction in the extrastriatal region because of a lower dopamine binding site. Next, because there was no significant interaction in two-way ANOVA between the locations (striatal or extrastriatal regions and types of group), all estimates were assessed by one-way ANOVA, in either region separately, with correction for multiple comparisons. Because post hoc multiple comparisons were performed in these analyses, statistical significance was set as \( p < 0.05 \). Statistical analysis for volume was performed by using one-way ANOVA with post hoc Scheffé's \( F \) test. In addition, simple linear regression analysis was performed to analyze the relationship between \([^{11}\text{C}]\text{CFT} \) and \([^{11}\text{C}]\text{SCH} \) binding levels in each region in PD and normal groups. The level of significance was \( p < 0.05 \).

**Results**

*The Levels of \([^{11}\text{C}]\text{CFT} \) and \([^{11}\text{C}]\text{SCH} \) Binding*

The tissue TACs of \([^{11}\text{C}]\text{CFT} \) and \([^{11}\text{C}]\text{SCH} \) are shown in Figure 2. In the \([^{11}\text{C}]\text{CFT} \) study, after administration of \([^{11}\text{C}]\text{CFT} \), radioactivity accumulated gradually in the striatum (putamen), and also to a lesser extent in the orbitofrontal cortex in normal subjects (see Fig 2A), whereas putaminal and orbitofrontal radioactivities decreased with time in PD patients (see Fig 2B). TAC patterns of the cerebellum looked alike between the two groups. This was confirmed by the result that the distribution volume, \( K_1/k_2 \), in the cerebellum was almost the same between the two groups (Table 2). In contrast, in the \([^{11}\text{C}]\text{SCH} \) study, there were no marked differences, in the patterns of TACs in all regions examined after \([^{11}\text{C}]\text{SCH} \) administration,
between normal (see Fig 2C) and PD groups (see Fig 2D). In normal controls, tracer accumulation patterns of the orbitofrontal TACs were consistently higher than those of the occipital TACs obtained from ROIs on the visual cortex (not shown) in [11C]CFT and [11C]SCH studies, suggesting that the occipital cortex was less specific to the dopaminergic system than the orbitofrontal cortex.

One-way ANOVA showed that the levels of $B_{max}/k_4$ ($k_3/k_4$) for [11C]CFT were significantly lower in all parts of the striatum ($p < 0.01$) and the orbitofrontal cortex ($p = 0.0445$) in the PD group than those in normal group. The magnitude of $k_3/k_4$ in the PD group was more reduced in the striatal region contralateral to the clinically affected side (see Table 2). On the contrary, no significant difference was observed in the $k_3/k_4$ levels of [11C]SCH between the normal and PD groups in any regions. There was no significant difference in volumes of all structures involved, between the PD group and normal group (Table 3).

**Table 2. Levels of Binding Potential and Distribution Volume for [11C]CFT and [11C]SCH 23390 in Both Groups**

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Group</th>
<th>Cerebellum (Bilateral) $K_r/k_s$</th>
<th>Caudate</th>
<th>Putamen</th>
<th>Orbitofrontal (Bilateral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFT</td>
<td>Normal</td>
<td>7.84 ± 1.30</td>
<td>4.07 ± 0.73</td>
<td>4.09 ± 0.60</td>
<td>4.17 ± 0.49</td>
</tr>
<tr>
<td></td>
<td>Parkinson</td>
<td>7.98 ± 0.85</td>
<td>2.22 ± 0.45</td>
<td>1.86 ± 0.65</td>
<td>1.13 ± 0.51</td>
</tr>
<tr>
<td>SCH 23390</td>
<td>Normal</td>
<td>1.21 ± 0.13</td>
<td>1.16 ± 0.10</td>
<td>1.29 ± 0.11</td>
<td>1.28 ± 0.12</td>
</tr>
<tr>
<td></td>
<td>Parkinson</td>
<td>1.17 ± 0.11</td>
<td>1.13 ± 0.16</td>
<td>1.23 ± 0.18</td>
<td>1.20 ± 0.10</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD values.

$^a p < 0.01$, $^b p = 0.0445$, vs. normal group.

CFT = 2-β-carboxymethoxy-3β-(4-fluorophenyl)tropane.

**Correlation Between Age and [11C]CFT or [11C]SCH Binding**

Levels of [11C]CFT and [11C]SCH binding were negatively correlated with age in the striatum (Fig 3A) and the orbitofrontal cortex (see Fig 3B) in the normal group. However, the PD group, with the narrow age range (mostly in their 60s), failed to show such a negative correlation between age and the binding levels (not shown).

**Discussion**

To the best of our knowledge, the present dopaminergic PET study, with double ligands applied to the same subject on the same day, is the first to attempt to clarify the in vivo relationship between dopaminergic presynaptic and postsynaptic functions in the nigrostriatal and the mesocortical systems in PD. Our results showed that the presynaptic binding site densities in both the nigrostriatal and mesocortical dopaminergic systems were reduced in PD. Reduction in the nigrostriatal presynaptic binding (75% reduction in the putamen) was in agreement with results of the first report on the dopamine terminal functions in PD, using [18F]dopa and PET, and another PET study, with [11C]WIN 35,428 identical to [11C]CFT, showing 78% binding reduction in the putamen in medicated...
PD patients at Hoehn and Yahr stage 2. We speculated that presynaptic terminal losses or down-regulation of DAT in the residual terminals might be responsible for the reduction in [11C]CFT binding in early PD.

Concurrent reduction in [11C]CFT binding in the orbitofrontal cortex of early PD was of interest. The orbitofrontal cortex is part of the limbic association cortex, connecting to both the ventral tegmental area and the dorsal tier of the substantia nigra compacta. Postmortem studies showed neuronal loss by 40% to 60% in the ventral tegmental area, along with depletion of dopamine levels in the PD frontal cortex. This neuronal loss was similar to our result showing a 52% reduction in the \( k_3/k_4 \) level in the orbitofrontal cortex of PD patients. Thus, this observation suggested that approximately half of the mesocortical dopaminergic neurons were also affected in their lifetime at Hoehn and Yahr stage 2. One caveat for assessment on the presynaptic mesocortical system was relatively low concentrations of [11C]CFT in the area. A recent PET study with [18F]dopa (another presynaptic marker), showing that the level of [18F]dopa uptake in the medial prefrontal cortex in younger normal controls ranged from 0.1 to 1.0, with an average of 0.54, supported our data, similarly ranging from 0.05 to 0.6, with an average of 0.25, in the orbitofrontal cortex (not shown). However, involvement of other monoaminergic systems cannot be neglected because the frontal cortex is not quite dopamine specific.

In contrast to this presynaptic availability reduction in the nigrostriatal and mesocortical systems, the postsynaptic D1 receptor availability was not changed in the present study (eg, Fig 5). This unchanged D1 receptor availability was consistent with the results from other studies with SCH in vitro and in vivo. A recent PET study with [11C]SCH in PD patients indicated that the level of putamen D1 receptor binding decreased with the extent of exposure to L-dopa treatment, whereas elevation in the putamen D2 binding seen in untreated PD patients returned to normal after exposure to L-dopa. Because PD patients in our study were selected as drug-naïve patients with de novo parkinsonism, our results on receptor binding were likely to reflect primary receptor availability.
binding are not subject to criticism on drug interference as a confounding effect. The prefrontal D1 binding in schizophrenic patients was reported to be significantly lower and correlated with the severity of negative emotional symptoms.\(^{40}\) Therefore, PD patients showing mental abnormality would have shown a greater reduction in the orbitofrontal \(^{[11}C\)SCH binding. In the present study, there was a slight reduction in the orbitofrontal D1 receptor binding in PD patients, two of whom had a moderately severe Unified Parkinson’s Disease Rating Scale mentation score (see Table 1). That there was no difference in the volume of the orbitofrontal cortex, between the PD and normal groups, confirmed that the PET results reflected in vivo pathophysiological change, not partial volume effects.

Direct comparison of the dopaminergic presynaptic marker with the postsynaptic marker disclosed that presynaptic \(^{[11}C\)CFT binding was positively correlated with postsynaptic \(^{[11}C\)SCH binding in the striatum of normal control subjects (see Fig 4A). This positive correlation in normal subjects with a larger age range was in agreement with results from the previous PET study, with \(^{[11}C\)methylphenidate and \(^{[11}C\)raclopride, indicating synaptic functional changes with age.\(^{13}\) Thus, the present tight positive correlation between these two bindings might be, in part, caused by regulatory changes in the synapse with age. This hypothesis is supported by one biochemical study showing that the reduction in DAT correlated with the decrease in DAT gene expression with age.\(^{41}\) Although it should be clarified, one reason for the loss of this positive correlation in the orbitofrontal cortex in normal subjects (see Fig 4C) may be that the orbitofrontal cortex is lacking in a restricted geometry of such higher density of connectivity\(^{42}\) because the orbitofrontal area has weak dopaminergic innervation compared with the striatum.

In PD patients, a negative correlation between presynaptic and postsynaptic markers in the putamen, and a lack of positive correlation in the caudate, were found in the present study (see Fig 4B). This inverse correlation may give credibility to the idea that the postsynaptic dopaminergic neurons are relatively up-regulated, in compensation for presynaptic neuronal degeneration in the nigrostriatal system in early PD. One explanation for the incomplete inverse shift in the caudate might be the in vitro observation showing that there is a relative sparing of dopamine in the caudate nucleus of the postmortem PD brain.\(^{2,43}\) Another possibility is that the more than 50% of DAT reduction in the caudate may be in partial compensation for a less severe terminal loss. In the PD orbitofrontal cortex, there was no significant CFT/SCH correlation, but the pattern of plots was in a more positive correlative manner compared with the pattern seen in the normal group (see Fig 4C). Biochemical studies showed that levels of dopamine, noradrenaline, and serotonin in the frontal cortex were lower, with a predominance of serotonergic depression in patients with PD\(^{17,44}\); although in the neuromuscular junction, an electrophysiological study with cell recordings showed that there was a putative synaptic elimination cascade, which may cause each muscle fiber to undergo a transition from polyneural to single innervation.\(^{45}\) In view of these studies, and although it has yet to be clarified, it may be extrapolated that a decrease in innervation of the

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**Fig 5.** Positron emission tomographic (PET) images superimposed on magnetic resonance imaging scans for 2-\(\beta\)-\(^{[11}C\)carbomethoxy-3\(\beta\)-(4-fluorophenyl)tropane (\(^{[11}C\)CFT) uptake (top row) and \(^{[11}C\)SCH 23390 uptake (bottom row), which were accumulated 60 to 90 minutes after tracer injection and normalized to the cerebellar count, for a normal subject and a Parkinson’s disease (PD) patient with Hoehn and Yahr stage 2. PET images of PD showed marked reduction in \(^{[11}C\)CFT uptake without any decrease in \(^{[11}C\)SCH 23390 accumulation in the putamen. The color bar indicates the normalized count from 0 to 90 Bq/ml.
monoaminergic projection systems (predominantly the serotonergic system\textsuperscript{17}) in the frontal cortex may help the otherwise irrelevant presynaptic and postsynaptic dopaminergic association in the orbitofrontal cortex to become in a parallel-change fashion in early PD. Further studies, using a larger cohort of drug-naive PD patients with or without mental abnormality, are needed to clarify this issue.

Clinically, these putative striatal postsynaptic up-regulation and the mesocortical presynaptic and postsynaptic parallel-shift phenomena in PD suggest that a minimal dose of L-dopa along with other antiparkinsonian drugs such as D1 agonist are appropriate for treating the disease at an early stage.\textsuperscript{46} A combination of tomographic imaging and dopaminergic agonist (apomorphine) injection was reported to be of diagnostic value in identifying PD.\textsuperscript{47} But, considering pharmacological invasiveness and adverse effects, a double-tracer study without any drug administration is more advantageous for evaluating presynaptic and postsynaptic functions in the PD dopaminergic system and for designing a therapeutic protocol.

In conclusion, reductions in the presynaptic dopaminergic function in both nigrostriatal and mesocortical systems, along with a disruption of parallel functional changes in the synapse in the putamen, might be related to in vivo pathophysiology of early PD.

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