Serotonin-to-dopamine transporter ratios in Parkinson disease
Relevance for dyskinesias

ABSTRACT

Objective: To investigate whether a serotonin-to-dopamine terminal ratio is related to the appearance of dyskinesias in patients with Parkinson disease (PD).

Methods: Twenty-eight patients with idiopathic PD (17 with levodopa-induced dyskinesias [LIDs], 11 without dyskinesias) and 12 age-matched healthy controls were studied with PET and 5[11C]-3-amino-4-(2-dimethylaminomethylphenyl-sulfanyl)-benzonitrile ([11C-DASB]) and with SPECT and [123I]N-w-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ([123I]-ioflupane), which are in vivo specific markers of the serotonin and dopamine transporters’ availability, respectively. We have employed a simplified reference tissue model for the quantification of [11C-DASB], whereas a semiquantification approach was used for [123I]-ioflupane data. We calculated [11C-DASB] binding to [123I]-ioflupane uptake ratios for the caudate and the putamen.

Results: Patients with PD showed striatal decreases in [11C-DASB] binding potential (p < 0.01) and in [123I]-ioflupane mean uptake (p < 0.001) compared to controls. The mean [11C-DASB] binding to [123I]-ioflupane uptake ratio in the putamen was 0.779 (increased by 75.8% of the controls’ mean) for the nondyskinetic group and 0.901 (increased by 103.4% of the controls’ mean) for the patients with dyskinesias. There was a statistically significant difference (p < 0.001) in [11C-DASB] binding to [123I]-ioflupane uptake ratio in the putamen between the group of patients with and without dyskinesias. Higher [11C-DASB] to [123I]-ioflupane binding ratios correlated with longer disease duration for the 28 patients with PD (r = 0.52; p < 0.01).

Conclusions: Serotonin-to-dopamine transporter binding ratio increases as PD progresses and patients experience LIDs. Our findings suggest that, when the dopaminergic innervation in the striatum is critically low, the serotonergic system plays an important role in development of LIDs. 

GLOSSARY

AIMS = Abnormal Involuntary Movement Scale; BP = binding potential; [11C-DASB] = 5[11C]-3-amino-4-(2-dimethylaminomethylphenyl-sulfanyl)-benzonitrile; DAT = dopamine transporter; HAM-D = Hamilton Depression Rating Scale; [123I]-ioflupane = [123I]N-w-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane; LID = L-dopa-induced dyskinesia; MMSE = Mini-Mental State Examination; PD = Parkinson disease; ROI = region of interest; SERT = serotonin transporter; UPDRS = Unified Parkinson’s Disease Rating Scale; VDR = volume of distribution ratio.

Studies in the animal model of Parkinson disease (PD) as well as in humans have indicated that degeneration of dopaminergic presynaptic terminals in the striatum is critical in the development of L-dopa-induced dyskinesias (LIDs). Due to the progressive degeneration, striatal dopaminergic terminals lose their dopamine storage capacity and the ability to maintain a stable dopamine release rate in the synapse.

Serotonergic terminals have been found capable of converting exogenous levodopa into dopamine, store it in synaptic vesicles, and release it in an activity-dependent manner. The above studies propose that serotonergic terminals in the degenerating striatum are responsible for mishandling exogenous levodopa and exacerbating dyskinesia in the animal model and PD. Accordingly, the presence of dyskinesia could be a reflection of serotonergic over...
dopaminergic terminals’ activity. Nonetheless, the above mechanisms have not been fully understood in humans.

Dopamine transporter (DAT) and serotonin transporter (SERT) are densely located in the presynaptic terminals in the striatum. The SPECT tracer [123]I-N-w-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ([123]I-ioflupane) and the PET ligand 5[11C]-3-amino-4-(2-dimethylaminomethylphenylsulfanyl)benzonitrile ([11C-DASB]) are in vivo specific markers of DAT and SERT availabilities. This study intended to assess the interaction of dopaminergic and serotonergic presynaptic mechanisms in the development of LIDs. We hypothesized that a SERT-to-DAT ratio in the striatum is related to the occurrence of LIDs and employed the above imaging techniques with [11C-DASB] and [123]I-ioflupane to assess this ratio.

METHODS Standard protocol approvals, registrations, and patient consents. All participants provided their written consent in accordance with the Declaration of Helsinki. This study was reviewed and approved by the West London Research Ethics Committee, the Imperial College Joint Research Compliance Office, and the Administration of Radioactive Substances Advisory Committee, UK.

Participants. Patients with PD were recruited from our Movement Disorders Clinic at the Imperial College Healthcare NHS Trust, London, UK. Patients with PD fulfilled the UK Brain Bank Criteria for idiopathic PD. At screening, patients with PD were on levodopa treatment for at least 2 years. Patients with a history of dementia or depression were excluded from this study. Clinical data were acquired by detailed medical history including medication history cross-checked with patients’ medical notes and clinical letters to their general practitioners. Patients with PD were assessed in an outpatient clinical setting for their motor and nonmotor symptoms including the Unified Parkinson’s Disease Rating Scale (UPDRS) and the modified Hoehn & Yahr staging scale.

All participants were assessed for depression using the Hamilton Depression Rating Scale (HAM-D) and for cognitive impairment using the Mini-Mental State Examination (MMSE). None of the patients with PD had a history of depression and HAM-D scores above 7 were an exclusion criterion. Patients with PD with cognitive impairment were excluded from this study; an MMSE score below 26 was an exclusion criterion.

Thirty-six patients with idiopathic PD were screened for enrollment in the study, 6 of whom failed one of the exclusion criteria, and 2 declined participation in the study. Twenty-eight patients with idiopathic PD were included in the study. Seventeen patients experienced LIDs and 11 did not experience LIDs.

Clinical evaluation. Presence of LIDs was then assessed on separate days within 1 hour after the patients had taken their usual levodopa dose (range of single dose: 100–200 mg). LIDs were scored using the Abnormal Involuntary Movement Scale (AIMS) every 15 minutes for the next 120 minutes.

The LEDTotal, LEDl dopa, and LEDDag doses were calculated in milligrams for each individual following the formulas described in table e-1 on the Neurology Web site at Neurology.org. DDON was defined as the time from the date of the PD diagnosis at the movement disorders clinic and DDON as the time since each individual first experienced a PD motor symptom. At the time of diagnosis, all patients with PD were classified as stage 1 on the modified Hoehn & Yahr staging scale. We also calculated the time from diagnosis to initiation of dopaminergic medication per individual. None of the patients with PD was treated with any drugs that directly act on the serotonergic system.

We also included 12 healthy controls who undertook the same imaging procedures as described below (table 1).

Scanning procedures. All participants had brain SPECT imaging with [123]I-ioflupane and brain PET imaging with [11C-DASB]. All participants also had a 1.5 T1-weighted MRI scan for coregistration to the PET imaging data.

Patients with PD were asked to withdraw from medication 18 hours prior to any procedure involving ionizing radiation and this was defined as the “off” dopaminergic medication state. All patients with PD were assessed for motor symptoms with the UPDRS part III scale in “off” dopaminergic medication state.

All imaging were performed at the Hammersmith and Chartham Cross Hospitals of Imperial College in London.

[11C-DASB] PET scan images were obtained with an EXACT HR+ scanner (Siemens; Munich, Germany) and details on the PET and MRI scanners have been described previously. Briefly, patients with PD underwent a low-dose CT brain scan prior to the administration of the [11C-DASB] PET tracer to measure tissue attenuation of radiation. A mean activity dose of 450 MBq was administered to each individual undertaking a [11C-DASB] PET scan. PET images were obtained for 90 minutes starting after IV bolus injection of the PET tracer.

For the administration of [123]I-ioflupane, thyroid gland blockade was performed by administering potassium iodide tablets 60 mg twice daily for 3 consecutive days, starting 24 hours prior to the SPECT scan day, in accordance with the clinical protocol of our nuclear medicine department. All [123]I-ioflupane SPECT scan images were obtained with a Symbia T SPECT-CT scanner (Siemens). A mean activity dose of 185 MBq was administered to each individual undergoing a [123]I-ioflupane SPECT scan. SPECT images were obtained 180 minutes after IV bolus injection of [123]I-ioflupane for approximately 45 minutes.

[11C-DASB] PET imaging data analysis. We have employed a simplified reference tissue model using the cerebellum as the reference tissue for the quantification of [11C-DASB]. Following reconstruction of the dynamic PET image volume, a summed image volume was created from the entire dynamic dataset using an in-house software package. A template of high-contrast regions of interest (ROIs) was defined directly on the summed image and these ROIs were then applied to the dynamic dataset. Any movement detected was corrected using a frame-by-frame realignment procedure. Individual participant MRIs were coregistered to the summed PET volume using the SPM2 software package (Wellcome Department of Cognitive Neuroscience, Institute of Neurology) implemented in Matlab 6.5 (MathWorks; Natick, MA). Following coregistration, the definition of ROIs was performed on the coregistered MRI using Analyze medical imaging software (version 8.1; Mayo Foundation; Rochester, NY). ROIs were standardized for volume throughout and were manually defined for caudate and putamen. Volume of distribution ratios (VDRs) were computed.
The specific SERT binding as reflected by $^{11}$C-DASB relative to the nondisplaceable tracer in tissue was calculated as the binding potential (BP) of the specifically bound PET tracer for both hemispheres.

The specific DAT binding as reflected by $^{11}$C-DASB BP to $^{123}$I-ioflupane uptake for the caudate and the putamen comprising the average caudate and average putamen uptake values for each individual. SERT-to-DAT ratios were calculated as described previously in patients with PD who received neural transplantation.\textsuperscript{12}

**RESULTS Clinical findings.** The demographics and clinical characteristics of patients with PD and healthy controls are summarized in table 1.

**Imaging data.** The mean uptake of $^{123}$I-ioflupane, $^{11}$C-DASB BP, and the SERT-to-DAT ratios are listed in table 2. Representative $^{11}$C-DASB PET images are shown in figure 1.

**TABLE 1 Demographics and clinical characteristics of patients with PD and healthy controls**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy controls</th>
<th>PD all</th>
<th>Non-LID</th>
<th>LID</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>12</td>
<td>28</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Sex, M:F</td>
<td>7:5</td>
<td>19:9</td>
<td>10:1</td>
<td>9:8</td>
</tr>
<tr>
<td>Age at the time of the scan, y</td>
<td>64.41 ± 8.64</td>
<td>64.87 ± 8.21</td>
<td>69.32 ± 4.67</td>
<td>61.69 ± 8.89*</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.7 ± 0.67</td>
<td>28.28 ± 1.22</td>
<td>28 ± 1.26</td>
<td>28.44 ± 1.20</td>
</tr>
<tr>
<td>HAM-D</td>
<td>1.8 ± 1.62</td>
<td>4.28 ± 1.25</td>
<td>4.27 ± 0.65</td>
<td>4.28 ± 1.53</td>
</tr>
<tr>
<td>Disease duration from diagnosis, y</td>
<td>—</td>
<td>7.89 ± 5.01</td>
<td>5.82 ± 4.88</td>
<td>9.56 ± 5.48*</td>
</tr>
<tr>
<td>Disease duration from onset, y</td>
<td>—</td>
<td>9.79 ± 4.99</td>
<td>7.82 ± 3.66</td>
<td>11.07 ± 5.41*</td>
</tr>
<tr>
<td>H&amp;Y &quot;off&quot;</td>
<td>—</td>
<td>2.34 ± 0.57</td>
<td>2.27 ± 0.47</td>
<td>2.39 ± 0.63</td>
</tr>
<tr>
<td>UPDRS-III &quot;off&quot;</td>
<td>—</td>
<td>27.59 ± 8.32</td>
<td>26.7 ± 7.25</td>
<td>28.11 ± 9.07</td>
</tr>
<tr>
<td>UPDRS total &quot;off&quot;</td>
<td>—</td>
<td>45.03 ± 10.89</td>
<td>40.55 ± 10.30</td>
<td>47.78 ± 10.59</td>
</tr>
<tr>
<td>Tremor dominant/akinetic-rigid/mixed</td>
<td>—</td>
<td>2:15:11</td>
<td>2:5:4</td>
<td>0:10:7</td>
</tr>
<tr>
<td>AIMS</td>
<td>—</td>
<td>—</td>
<td>0</td>
<td>8.06 ± 4.26</td>
</tr>
<tr>
<td>Duration on dopaminergic medication, y</td>
<td>—</td>
<td>6.69 ± 4.68</td>
<td>4.41 ± 2.07</td>
<td>8.40 ± 5.07*</td>
</tr>
<tr>
<td>Time from diagnosis to initiation of DA medication, y</td>
<td>—</td>
<td>—</td>
<td>1.45 ± 1.05</td>
<td>1.03 ± 1.27</td>
</tr>
<tr>
<td>Time from PD onset to initiation of DA medication, y</td>
<td>—</td>
<td>—</td>
<td>3.42 ± 2.66</td>
<td>2.55 ± 1.60</td>
</tr>
<tr>
<td>Daily LED\textsubscript{total} mg</td>
<td>—</td>
<td>—</td>
<td>537.59 ± 199.87</td>
<td>826.59 ± 350.70*</td>
</tr>
<tr>
<td>Daily LED\textsubscript{dopa} mg</td>
<td>—</td>
<td>—</td>
<td>376.68 ± 167.68</td>
<td>650.82 ± 369.69</td>
</tr>
<tr>
<td>Daily LED\textsubscript{dop} mg</td>
<td>—</td>
<td>—</td>
<td>160.91 ± 193.87</td>
<td>175.76 ± 207.02</td>
</tr>
</tbody>
</table>

Abbreviations: AIMS = Abnormal Involuntary Movement Scale; DA = dopamine; H&Y = modified Hoehn & Yahr staging scale in "off" medication state; HAM-D = Hamilton Depression Rating Scale; LID = l-dopa-induced dyskinesia; MMSE = Mini-Mental State Examination; PD = Parkinson disease; UPDRS = Unified Parkinson’s Disease Rating Scale.

Data represent mean ± 1 SD.

* $p<0.05$ between the non-LID and the LID groups.

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and 123I-ioflupane SPECT images at the level of dorsal basal ganglia in 2 patients with PD with and without LIDs are shown in figure e-1.

Patients with PD showed reduced 11C-DASB BP (p < 0.01) in the putamen compared to healthy controls (34%). Patients with PD without LIDs showed 37% loss, while the patients with PD with LIDs showed 31% loss relative to the mean value of the healthy controls (between-group comparison for the putamen; p = 0.19) (figure 1A). No differences were found for the caudate (between-group comparison for the putamen; p = 0.23) (figure e-2).

Patients with PD showed reduced 123I-ioflupane uptake values (p < 0.001) compared to healthy controls in the caudate and the putamen. Patients with PD without LIDs showed 51% loss, while patients with LIDs showed 62% loss relative to healthy controls (between-group difference for the putamen; p = 0.13) (figure 1B). No differences were found for the caudate (between-group comparison for the putamen; p = 0.16) (figure e-3).

Healthy controls had a mean 11C-DASB BP to 123I-ioflupane uptake ratio in the putamen of 0.443. All patients with PD had increased 11C-DASB BP to 123I-ioflupane uptake ratio in the putamen compared to healthy controls (p < 0.001). In particular, patients with PD with LIDs had a mean 11C-DASB BP to 123I-ioflupane uptake ratio in the putamen of 0.901 (increased by 103.4% compared to healthy controls), while in the group of patients without LIDs, the mean ratio was 0.779 (increased by 75.8%, relative to healthy controls) with a significant between-group difference (p < 0.001) (figure 1D).

No significant differences were found in the caudate for the 11C-DASB BP to 123I-ioflupane uptake ratios (figure 1C).

There was a statistically significant correlation between putaminal 11C-DASB BP to 123I-ioflupane uptake ratios and disease duration from diagnosis for all patients with PD (r = 0.52; p < 0.01) (figure 2).

No correlation was found between putaminal 123I-ioflupane uptake values and either age, UPDRS, AIMS scores, the mean LEDTotal, the mean LEDLdopa, or the times from diagnosis to initiation of dopaminergic medication. No correlation was found between putaminal 123I-ioflupane uptake values and either age, UPDRS, AIMS scores, the mean LEDTotal, the mean LEDLdopa, or the times from diagnosis to initiation of dopaminergic medication.

**DISCUSSION** We found a statistically significant correlation between the putaminal SERT-to-DAT ratio and the disease duration in patients with PD. Our findings indicate that as PD progresses, the putaminal SERT-to-DAT ratio, as reflected by the 11C-DASB BP to 123I-ioflupane uptake ratio, becomes higher, thus potentially implicating an important role for the development of LIDs. We have shown that the density of DAT in the putamen of patients with PD with LIDs declines more than the SERT density compared to patients without LIDs. These data indicate that as disease

### Table 2

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>Healthy controls</th>
<th>PD all</th>
<th>Non-LID</th>
<th>LID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate</td>
<td>1.31 ± 0.06</td>
<td>0.58 ± 0.20&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.62 ± 0.22</td>
<td>0.56 ± 0.18</td>
</tr>
<tr>
<td>Putamen</td>
<td>1.36 ± 0.11</td>
<td>0.90 ± 0.25&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.86 ± 0.24</td>
<td>0.94 ± 0.22</td>
</tr>
<tr>
<td>Caudate</td>
<td>3.42 ± 0.44</td>
<td>1.98 ± 0.52&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.10 ± 0.49</td>
<td>1.90 ± 0.53</td>
</tr>
<tr>
<td>Putamen</td>
<td>3.07 ± 0.28</td>
<td>1.26 ± 0.42&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.51 ± 0.40</td>
<td>1.15 ± 0.33</td>
</tr>
</tbody>
</table>

Abbreviations: 11C-DASB = [11C]-(4-carboxy2-1-(3-iodophenyl)-6-methyl-3,4-dihydro-2H-1-benzopyran-2-y]lation; DAT = dopamine transporter; 123I-ioflupane = [123I]-(4-iodophenyl)-N-(2-carboxy-3-(4-dimethylaminomethylphenyl)-benzonitrile; LID = L-dopa-induced dyskinesia; PD = Parkinson disease; SERT = serotonin transporter.

<sup>a</sup>p < 0.01 between the PD and healthy controls group.

<sup>b</sup>p < 0.05 between the PD and healthy controls group.

<sup>c</sup>p < 0.001 between the non-LID and LID groups.
As PD progresses, reductions in striatal DAT density have been proposed to support presynaptic mechanisms as responsible for the development of LIDs due to the subsequent loss of dopamine storage capacity. hotspot-ly Patients with advanced PD lose their ability to maintain a stable rate of dopamine release in the striatum. Thus, the dopamine release is fairly dependent on the levodopa delivery rate into the synapse.

PET studies with $^{11}$C-raclopride, which reflects postsynaptic dopamine D2 receptor distribution, are able to estimate in vivo the dopamine release in the striatum. hotspot-Tedroff et al. hotspot-have shown that the same dose of exogenous levodopa can induce higher levels of synaptic dopamine in advanced PD in comparison to early disease. Furthermore, standard levodopa doses can cause high swings in synaptic dopamine increases in PD with LIDs, the magnitude of which correlated with higher dyskinesia scores. hotspot-Wide fluctuations in the synaptic concentration of dopamine in patients with motor fluctuations have been also shown to precede clinically apparent LIDs and were linked with longer disease duration and a younger age at onset.

Figure 2 Correlation of serotonin transporter (SERT)–to–dopamine transporter (DAT) binding ratios and disease duration in 28 patients with Parkinson disease (PD)
Alongside these dopaminergic mechanisms, serotonergic terminals in the striatum have been shown to be also involved in the development of LIDs.

In experimental animals, the chemical blockade of serotonin neurons as well as selective lesions in the serotonin terminals led to a dramatic reduction of the induced involuntary movements without counteracting levodopa’s main effects.10,12,26,27 In addition, serotonin receptor agonists have been shown to have antidyskinetic effects in both rodent and nonhuman primate models of dyskinesias.12,28

In humans, a recent clinical and PET imaging study from our group showed that buspirone, a 5-HT1a partial agonist, when administered acutely prior to levodopa in patients with PD with LIDs, is able to normalize levodopa-derived levels of synaptic dopamine and to alleviate dyskinesias.12 Similarly, a recent phase I/IIa clinical trial in patients with PD confirmed antidyskinetic effects of the 5-HT1a/5-HT1b partial agonist eltoprazine following the promising results of the same drug in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated macaques.12

Taken together, these studies suggest that the development of LIDs is dependent on compromised dopaminergic function and on aberrant serotonergic function in the striatum.

A recent imaging study estimated midbrain-SERT to striatal-DAT binding ratio in early-stage, drug-naive patients with PD. The authors showed that imbalanced ratios do not predict the development of LIDs in early stages of the disease, but hypothesized that imbalance ratios may occur at later stages of PD.30

Our study suggests that the putaminal SERT-to-DAT terminals ratio is a good index to quantify in vivo the serotonergic over dopaminergic terminals’ activity. Using PET and SPECT imaging, we have shown that the presence of LIDs is related to an imbalanced serotonergic-over-dopaminergic terminals density ratio in the putamen. Our results indicate that while the striatum becomes critically depleted of the dopaminergic terminals with the progression of the disease, the serotonergic terminals remain reasonably preserved to uptake levodopa and release dopamine. Hence, the serotonergic terminals in the striatum may start to contribute to the development of dyskinesias once the dopaminergic innervation becomes critically low.

Previous studies looking for clinical risk factors in LIDs have shown that the occurrence of LIDs is linked with younger age at onset of PD,31–35 as well as with longer disease duration.32,34 The LIDs and non-LIDs groups of our PD cohort were clinically different (so that reached statistical significance) for sex, age, disease duration, the duration on dopaminergic medication, and LEDTotal. We performed separate analysis corrected for sex and found similar but less significant results compared to our whole cohort (male and female). Our dyskinetic patients with PD had longer disease duration, had a younger age at onset, and were treated with higher daily levodopa doses. This may reflect that the 2 groups represent 2 different factions within our studied population, which may have had an influence on the SERT-to-DAT terminals ratio. Nonetheless, we did not find any correlation between the SERT-to-DAT binding ratios and the age at onset or the duration of dopaminergic medication. Hence, we propose that sex, age, and duration of dopaminergic medication may have not affected the outcome of our findings in this cohort and that disease duration may indeed be a good index to reflect the serotonergic over dopaminergic terminals’ changes that occur in the striatum during PD progression.

Serotonin-to-dopamine transporter binding ratio increases as PD progresses and patients experience dyskinesias. Our findings support the hypothesis that the serotonergic terminals are involved in the occurrence of LIDs, once the dopaminergic innervation in the striatum is critically low. There may be a threshold during the progression of the disease that dyskinesias occur; nonetheless, this study makes it difficult to address this point. Future longitudinal studies with SERT and DAT imaging in a larger number of patients may be able to address this point by studying the time from initiation of dopaminergic medication to the first time dyskinesias are observed in relation to serotonergic terminals’ activity. Future clinical trials with highly selective 5-HT1A/B drugs as antidyskinetic agents could also provide robust support to the above findings.

AUTHOR CONTRIBUTIONS
P.P. and M.P. conceptualized the experimental design of the study. A.A.R., M.P., D.T., and P.P. organized the study. A.A.R. acquired the data. A.A.R. analyzed the clinical data. A.A.R. and D.T. analyzed the imaging data. A.A.R. and M.P. conducted the statistical analysis. A.A.R. wrote the first draft of the manuscript and interpreted the findings. A.A.R. and P.P. were responsible for the clinical supervision of the patients. All authors gave input and revised the manuscript.

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