[11C]DTBZ-PET correlates of levodopa responses in asymmetric Parkinson’s disease

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Summary
Levodopa effectively improves motor symptoms of Parkinson’s disease. However, the beneficial effects of levodopa often erode over time with the emergence of response fluctuations. Although these response changes have been recognized from the early levodopa era, their mechanisms remain poorly understood. We investigated the role of dopamine (DA) terminal loss in the development of motor fluctuations by employing PET with [11C](±)-dihydrotetrabenazine ([11C]DTBZ) as an in vivo marker for DA nerve terminals. Levodopa response was characterized by analysing the time–response curve to a single dose of levodopa with a finger-tapping test. PET scans were performed in 11 patients with asymmetric Parkinson’s disease (age: 61.12 ± 7.97 years; duration of Parkinson’s disease: 10.55 ± 4.53 years; mean ± SD). Each patient performed finger-tapping tests for up to 5 h after taking a therapeutic dose of levodopa. Results showed significantly lower [11C]DTBZ binding potential (BP; Bmax/Kd) and baseline tapping rates on the more affected putamen and corresponding body side, respectively, than on the other (P = 0.003 for the former, P = 0.013 for the latter). Among the variables describing the time–response curve, the duration and early decay time were significantly shorter on the more affected side (P = 0.051 and P = 0.021, respectively). Latency to the onset and latency to 50% Emax (the magnitude of the levodopa response) were significantly longer on the more-affected side (P = 0.013 and P = 0.004, respectively). Emax was not significantly different between the two sides. The asymmetry (difference from the more affected to less affected side) of [11C]DTBZ BP in the putamen showed a highly significant correlation with the corresponding asymmetry of the estimated EC50 (levodopa concentration producing 50% of the maximal response; P = 0.022; r = −0.727), a marginally significant correlation with that of latency to the onset (P = 0.065; r = −0.583) and no significant correlation with that of the magnitude, duration or early decay time. This pattern of changes in levodopa response from the less affected to more affected side was similar to that from stable to fluctuating responders except for the latency to onset. These findings suggest a pathogenetic role for DA terminal loss in the development of motor fluctuations. However, the absence of a significant correlation between the early decay of levodopa response and DA terminal density suggests that DA terminal loss alone cannot account for the development of motor fluctuations. Therefore, our study suggests that both levodopa treatment and DA terminal loss contribute to the pathogenesis of motor fluctuations.

Keywords: Parkinson’s disease; PET; motor fluctuations; levodopa; dihydrotetrabenazine

Abbreviations: BP = binding potential; DA = dopamine; [11C]DTBZ = [11C](±)-dihydrotetrabenazine; Emax = magnitude of levodopa response; EC50 = levodopa concentration producing 50% of the maximal response; ROI = region of interest; T1/2eq = equilibration half-life

Introduction
Parkinson’s disease is a common neurodegenerative disorder, presenting primarily with motor deficits associated with dopamine (DA) loss in the striatum (Bernheimer et al., 1973). Unlike patients with other neurodegenerative disorders, patients with Parkinson’s disease enjoy a remarkable improvement of motor disability by exogenous DA supplementation with levodopa. However, levodopa response may change over time, leading to motor fluctuations, dyskinesia or
Thirdly, pharmacological studies suggest that response motor fluctuations earlier (Ahlskog and Muenter, 2001). Duration of disease before starting levodopa therapy develops suggest that Parkinson’s disease patients with longer therapy are functions of time. A recent review of the literature both severity of Parkinson’s disease and duration of levodopa changes to levodopa leading to motor fluctuations, because of the interaction between presynaptic and postsynaptic factors (Gerfen et al., 1990). The localization of pathophysiological mechanisms of motor fluctuations without in vivo biological markers representing presynaptic and postsynaptic factors is therefore not straightforward.

A finger-tapping test is a sensitive and reproducible method to obtain the time–response curve of levodopa, and has been used frequently for pharmacodynamic modelling of levodopa response (Contin et al., 1992, 1993). Levodopa kinetic–dynamic studies have shown that changes in levodopa response causing motor fluctuations can be characterized by changes in variables describing the time–response curve of levodopa, such as the levodopa concentration producing 50% of the maximal response (EC50), the steepness or sigmoidality of the time–response curve (Hill coefficient) and the equilibration half-life (T1/2eq) (Nutt and Holford, 1996). In our study, we investigated the role of DA terminal loss in the response changes to levodopa by (i) using the finger-tapping test to obtain a time–response curve of levodopa; (ii) employing PET with [11C](+)dihydrotetrabenazine ([11C]DTBZ) as an in vivo biological marker for DA nerve terminals (more specifically, DA synaptic vesicles) in the putamen; and, finally, (iii) comparing these variables on the more affected side with those on the contralateral, less affected side in patients with asymmetric Parkinson’s disease. Here we report direct evidence that changes in levodopa response are associated with both DA terminal loss and levodopa treatment.

**Subjects and methods**

**Subjects**

We selected 11 patients with asymmetric parkinsonian signs who met the criteria for definite Parkinson’s disease (Calne et al., 1992) for this study from patients in the Movement Disorders Clinic at the University of British Columbia. Patients with moderate to severe dyskinesia were excluded as dyskinesia may interfere with tapping performance. All patients had been on stable antiparkinson medication for at least 3 months before testing. All patients were taking levodopa/carbidopa (controlled release, standard or a combination), and some patients were also on dopaminergic agonists. Table 1 summarizes the characteristics of the patients.

### Table 1 Characteristics of patients with Parkinson’s disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.12 ± 7.97*</td>
</tr>
<tr>
<td>Hoehn–Yahr stage in OFF state</td>
<td>2.36 ± 0.64</td>
</tr>
<tr>
<td>UPDRS in OFF state</td>
<td>36.45 ± 11.63</td>
</tr>
<tr>
<td>Duration of symptoms (years)</td>
<td>10.55 ± 4.53</td>
</tr>
<tr>
<td>Duration of treatment (years)</td>
<td>8.43 ± 3.50</td>
</tr>
<tr>
<td>First morning dose of levodopa (mg)</td>
<td>209.09 ± 83.12</td>
</tr>
<tr>
<td>Test dose of levodopa (mg)</td>
<td>263.64 ± 67.42</td>
</tr>
</tbody>
</table>

*Mean ± SD.

UPDRS = Unified Parkinson’s Disease Rating Scale.

Both. Clinical data show that ~50% of patients develop these motor complications after 5 years of levodopa therapy (Marsden and Parkes, 1977; Ahlskog and Muentener, 2001). These duration-dependent complications, particularly motor fluctuations, are a major disabling factor in patients with advanced Parkinson’s disease. Response changes during the course of levodopa therapy seem to follow a consistent pattern: mild and long-lasting response in the early stage, followed by greater response with shorter duration resulting in waxing and waning between levodopa doses (‘wearing-off’), and eventually, abrupt changes in response as if turned on and off by a switch (hence, ‘on–off’) (Duvoisin, 1989). Although these phenomena have been recognized since the early levodopa era (Barbeau, 1971; Claveria et al., 1973), their pathogenetic mechanisms have remained poorly understood. ‘Wearing-off’ was attributed to the deficiency of DA storage function caused by a gradual loss of presynaptic DA terminals in the striatum (Chase et al., 1989). Other authors emphasize postsynaptic factors as a significant player in the pathogenesis of response changes to levodopa (Chase and Oh, 2000).

Studies of mechanisms of response changes to levodopa causing motor fluctuations have been hampered by a number of factors. First, it is difficult to characterize and quantify the severity of motor fluctuations. In most cross-sectional studies, levodopa response was compared between groups, e.g. stable and fluctuating responders, which were divided based on the duration of ‘ON’ time (Fabbrini et al., 1987, 1988). However, the duration of ‘ON’ time is also influenced by drug dose (Nutt and Woodward, 1986), the therapeutic level of which is highly variable among individuals. Secondly, longitudinal studies have shown that changes in levodopa response are greater with longer duration of treatment (de Jong et al., 1987). However, it is difficult to distinguish the effects of disease severity from those of levodopa therapy on response changes to levodopa leading to motor fluctuations, because both severity of Parkinson’s disease and duration of levodopa therapy are functions of time. A recent review of the literature suggests that Parkinson’s disease patients with longer duration of disease before starting levodopa therapy develop motor fluctuations earlier (Ahlskog and Muentener, 2001).

Thirdly, pharmacological studies suggest that response changes to levodopa are derived from central mechanisms, particularly postsynaptic factors (Fabbrini et al., 1987, 1988; Mouradian et al., 1988; Colosimo et al., 1996; Verhagen Metman et al., 1997). However, evidence from those studies does not preclude the causative role of presynaptic factors in response changes to levodopa because of the interaction between presynaptic and postsynaptic factors (Gerfen et al., 1990). The localization of pathophysiological mechanisms of motor fluctuations without in vivo biological markers representing presynaptic and postsynaptic factors is therefore not straightforward.

Clinical assessment and finger-tapping tests

We used the Core Assessment Program for Intracerebral Transplantation for definitions of OFF state (Langston et al., 1990). The localization of pathophysiological mechanisms of motor fluctuations without in vivo biological markers representing presynaptic and postsynaptic factors is therefore not straightforward.
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For the clinical assessment in the OFF state, patients were examined between 08.00 and 09.00 h following ≥12 h withdrawal of antiparkinson drugs [18 h for controlled release levodopa/carbidopa (Sinemet CR)]. Patients were assessed using the Unified Parkinson’s Disease Rating Scale, subset III (maximum score = 108). The test dose of standard Sinemet for each patient was the same as the clinically effective morning dose they were all taking. If an adequate response (defined as 20% increase in tapping rate on the more affected side) was not obtained, then the test was repeated using a 50% higher test dose. Patients were asked to tap a cell counter alternately with the index and middle fingers for three trials of 10 s each. Tapping rates were obtained separately for each side. Four such sequences of three trials each were carried out at 15 min intervals to obtain baseline tapping rates before the administration of levodopa. Following a clinically effective dose of levodopa, tapping rates were again obtained every 15 min for up to 5 h until tapping rates reached at least lower than 50% of the maximum tapping rate.

**PET studies and image analysis**

PET scans were performed using $[^{11}C]$DTBZ in 3D mode with an ECAT 953B/31 tomograph (CTI/Siemens, Knoxville, TN) (Spinks et al., 1992). $[^{11}C]$DTBZ binds to vesicular monoamine transporter type 2 (VMAT2) on the synaptic vesicles in monoaminergic nerve terminals. Expression of VMAT2 in the striatum predicts integrity of the nigrostriatal projection (Vander Borght et al., 1995a). However, the expression of VMAT2 per DA nerve terminal seems to be resistant to regulatory changes following DA terminal loss (Lee et al., 2000) or pharmacological treatment (Vander Borght et al., 1995b). Patients stopped all antiparkinson medications at least 12–15 h before each assessment, or 18 h for Sinemet CR, DA agonists and catechol-o-methyltransferase inhibitors. Patients fasted overnight and had a standard low-protein breakfast on the morning of the scan. Patients were positioned supine in the gantry with the head centred in the field of view. A thermoplastic mask was moulded to the patient’s head to minimize movement. A transmission scan with $^{68}$Ge rods was obtained for attenuation correction before the injection of $[^{11}C]$DTBZ. Using a Harvard infusion pump, $[^{11}C]$DTBZ (237 ± 36 MBq in 10 ml of saline) was injected intravenously over 60 s. The PET protocol included 4 × 1 min, 3 × 2 min, 8 × 5 min and 1 × 10 min sequential emission scans starting at tracer injection, for a total acquisition time of 60 min. Data processing and reconstruction are described in detail elsewhere (Sossi et al., 1998).

The PET image was analysed as previously (Vingerhoets et al., 1994). In brief, all PET scans for each patient were analysed by using the same protocol with the same set of regions of interest (ROIs). The ROIs were placed on the summed images from the last 30 min of scanning in the five adjacent planes (i.e. a total axial thickness of 16.9 mm) where the striatum was best seen. One circular ROI of 61.2 mm$^2$ (diameter 8.8 mm) was positioned by inspection on each caudate nucleus and adjusted to maximize the average ROI radioactivity. Three ROIs with the same size and shape were placed without overlap along the rostrocaudal axis of the putamen on each side. Three background circular ROIs of 296 mm$^2$ were placed on the temporo-occipital lobe on each side. These ROIs were then replicated on each of the acquired time frames to obtain a time–activity curve for each ROI. The $[^{11}C]$DTBZ data were analysed using a tissue input graphical method (Logan et al., 1996). The radioactivity time course of the occipital cortex region was used as input function to obtain the distribution volume ratio. Values of the kinetic rate constant $K_2^*$ required by this approach had been evaluated previously by conventional compartmental analysis to be 0.073 for $[^{11}C]$DTBZ (Chan et al., 1999). The binding potential (BP; $B_{\text{max}}/K_d$) was obtained from the distribution volume ratio by subtracting 1.

**Data analysis and statistics**

The onset of levodopa response was defined as a 10% increase in average baseline tapping rate. The magnitude of the levodopa response ($E_{\text{max}}$) was defined as the difference between the maximal tapping rate and the mean baseline tapping rate. Rising time was the interval from the onset of levodopa response to $E_{\text{max}}$. Peak response time was the latency from drug administration to $E_{\text{max}}$. Early decay time was the interval from $E_{\text{max}}$ to subsequent 50% of $E_{\text{max}}$. The duration of levodopa response was the sum of the rising time and the early decay time. Variables describing the time–response curve and $[^{11}C]$DTBZ BP were compared between the two sides using Wilcoxon’s signed rank test. Asymmetry of $[^{11}C]$DTBZ BP was obtained by subtracting the value of the more affected putamen from the value of the less affected putamen. Asymmetry of variables describing the time–response curve between the two sides was obtained by subtracting the value on the side contralateral to the more affected putamen from the value on the side contralateral to the less affected putamen. Spearman rank correlations were used to determine the association between the asymmetry of variables describing the time–response curve and the corresponding asymmetry of $[^{11}C]$DTBZ BP, and 95% confidence intervals (CIs) were derived. Statistical significance was set at $P \leq 0.05$.

**Results**

Mean $[^{11}C]$DTBZ BP was 0.296 ± 0.093 (mean ± SD, $B_{\text{max}}/K_d$) on the more affected putamen, and 0.359 ± 0.127 on the less affected putamen ($P = 0.003$ between the two sides). Baseline tapping rates on the contralateral side to each putamen were significantly different ($P = 0.013$): 26.67 ± 6.02 for the more affected putamen, and 30.86 ± 7.99 for the less affected putamen. The asymmetry of baseline tapping rates (difference between the more affected and less affected side) showed a marginally significant correlation with the corresponding asymmetry of $[^{11}C]$DTBZ BP ($P = 0.050; r = 0.618$, 1992).
95% CI = 0.029±0.888), suggesting that lower baseline tapping rates on the more affected side were associated with lower [11C]DTBZ BP in the more affected putamen.

The time–response curve on the more affected side was not always in parallel to that on the less affected side. Moreover, bilateral comparisons of the time–response curves did not show a consistent pattern as the side-to-side differences between individuals (Fig. 1). The onset of levodopa response was delayed on the more affected side in eight cases, and was about the same between the two sides in the remaining three cases. The mean latency to onset was significantly longer on the more affected side than on the less affected side (P=0.013, Fig. 2). However, statistical significance was not attained in the correlation analysis between the asymmetry of latency to the onset and the corresponding asymmetry of [11C]DTBZ BP in the putamen (P=0.065; r=−0.583, 95% CI=−0.876 to 0.026). The rising time (i.e. interval from the onset to the maximal response) was not significantly different between the two sides (Fig. 2). There was a significant negative correlation between the asymmetry of latency to the onset and the asymmetry of rising time (P=0.017; r=−0.752, 95% CI=−0.932 to −0.277), indicating that delayed onset of levodopa response was followed by a steeper rising phase.

Mean latency to the peak response was longer on the more affected side than on the less affected side (152.73±32.04 min for the former, 135.00±29.24 min for the latter; P=0.041 between the two sides). In contrast to the rising time, the mean value of the early decay time (i.e. interval from the peak response to subsequent 50% E_{max}) was significantly shorter on the more affected side (P=0.021, Fig. 2). The asymmetry of early decay time did not show significant correlation with the corresponding asymmetry of [11C]DTBZ BP in the putamen, nor with the asymmetry of the other time-related variables (i.e. the onset, the latency to 50% E_{max} or the rising time).

At the end of the observation period (279.55±42.04 min...
after levodopa intake), levodopa response did not return to the onset level (i.e. 10% above baseline tapping rate) on the less affected side in two cases, on the more affected side in one case, and on both sides in one case. Therefore, the duration was estimated from the onset of levodopa response to 50% $E_{\text{max}}$ in the decay phase. The side-to-side difference in duration was marginally significant ($P = 0.05$; 164.46 ± 43.88 min on the more affected side, 193.30 ± 44.39 min on the less affected side; Fig. 2). No significant correlation was observed between the asymmetry of duration and the corresponding asymmetry of $[^{11}\text{C}]$DTBZ BP in the putamen ($P = 0.565$).

The $E_{\text{max}}$ was highly variable, amounting to 36.95 ± 13.06% (range: 20.9–57.5%) of baseline tapping rate on the more affected side, and to 33.87 ± 14.68% (range: 18.2–60.0%) of baseline tapping rate on the less affected side ($P = 0.109$ between the two sides). There was no significant correlation between the asymmetry of $E_{\text{max}}$ and the corresponding asymmetry of $[^{11}\text{C}]$DTBZ BP in the putamen, indicating that the density of synaptic vesicles in DA nerve terminals was not a main determinant of the $E_{\text{max}}$.

The asymmetry of $EC_{50}$ (difference between the $EC_{50}$ of the more affected and the less affected side) was inferred by the asymmetry of latency to 50% $E_{\text{max}}$ on the rising phase. Latency to 50% $E_{\text{max}}$ on the rising phase was consistently longer on the more affected side than on the less affected side (69.07 ± 21.85 min for the former, 47.93 ± 25.79 min for the latter; $P = 0.004$ between the two sides). There was also a significant correlation between the estimated asymmetry of $EC_{50}$ and the corresponding asymmetry of $[^{11}\text{C}]$DTBZ BP in the putamen ($P = 0.022$; $r = -0.727$, 95% CI = −0.924 to −0.225).

Discussion

There are two important findings in this study. First, bilateral comparisons of the time–response curves in asymmetric Parkinson’s disease showed delayed onset, shorter duration and similar magnitude on the more affected side compared with the less affected side. This pattern of changes in the levodopa response on the more affected side is similar, but not exactly identical, to that from stable to fluctuating responders, or that over time in longitudinal observations. Secondly, the asymmetry (defined as the difference between the more affected and the less affected side) of parameters describing the time–response curve showed a varying degree of correlation with the asymmetry of $[^{11}\text{C}]$DTBZ BP in the putamen: highly significant with the latency to 50% $E_{\text{max}}$, marginally significant with latency to the onset of response, and not significant with the magnitude or duration of levodopa response. For the correlation analysis between the parameters describing the time–response curve and $[^{11}\text{C}]$DTBZ BP in the putamen, we used the asymmetry of each measure as our variable. It was based on the premise that if there was a correlation between a parameter of the time–response curve and $[^{11}\text{C}]$DTBZ BP, then the asymmetry of this parameter would probably correlate with the corresponding asymmetry of $[^{11}\text{C}]$DTBZ BP.

Central to motor fluctuations is the shortening of the levodopa response, especially of the decay time (Fabbrini et al., 1987; Contin et al., 1990, 1997; Colosimo et al., 1996). Thus, findings of significantly shorter levodopa response, particularly the decay time, on the more affected side are similar to those in motor fluctuations as observed in cross-sectional or longitudinal studies. Significantly shorter decay time on the more affected side indicates that DA terminal density plays a role in determining the decay time. However, the absence of a significant correlation between the asymmetry of decay time and the corresponding asymmetry of $[^{11}\text{C}]$DTBZ BP suggests that the decay time cannot be accounted for solely by DA terminal density; more specifically, by the density of DA synaptic vesicles. These observations are in keeping with our earlier studies: one showed that Parkinson’s disease patients with motor fluctuation had lower F-dopa $K_{i}$ values than those with stable response, but that this alone could not account for fluctuating response (de la Fuente-Fernandez et al., 2000). Another demonstrated evidence for the mismatch between striatal DA levels and motor response, but it showed that Parkinson’s disease patients with increased turnover of striatal DA went on to develop motor response fluctuations (de la Fuente-Fernandez et al., 2001). We did not observe significant side-to-side differences in the rising time. However, a highly significant negative correlation between the asymmetry of rising time and that of latency to the onset of levodopa response indicates a tendency—the more delayed the onset of levodopa response, the steeper the rising phase. These changes may reflect greater sigmoidality of the time–response curve on the more affected side (Nutt and Holford, 1996), similar to the changes of the time–response curve from stable to fluctuating responders.

Our study consistently showed that the onset of levodopa response was more delayed on the more affected side. A previous study in asymmetric Parkinson’s disease, where levodopa was given by intravenous infusion for 60 min, reported that the latency to the onset of levodopa response was shorter on the more affected side than on the less affected side (Rodriguez et al., 1994). However, similar studies using intravenous levodopa showed conflicting results depending on the infusion time (Fabbrini et al., 1988; Gancher et al., 1988), indicating that intravenous infusion of levodopa may produce different pharmacokinetic profiles (Contin et al., 1990), hence limiting the extrapolation of data from those studies to ours. Another study in asymmetric Parkinson’s disease showed no difference in the onset and wearing off of levodopa response after a single oral dose (Kempster et al., 1989). However, these findings may be confounded by a selection bias because ‘patients with more advanced disease and well developed motor fluctuations’ were selected for the study (Kempster and Lees, 1994). As shown in Fig. 1, our data suggest multiple mechanisms for response changes to levodopa. Therefore, we believe that the delayed onset of
levodopa response on the more affected side is a true biological phenomenon.

Our finding of the significant delay in the onset of levodopa response on the more affected side is not only at variance with previous observations in cross-sectional studies in which fluctuating responders showed earlier onset of levodopa response than stable responders (Contin et al., 1990; Colosimo et al., 1996), but is also not consistent with longitudinal observations in which the onset of levodopa response did not change over time (Hughes et al., 1994). Changes in levodopa response leading to motor fluctuations can be explained by changes in variables describing the concentration–response relationship: rise of EC₅₀ (the drug concentration at 50% of Eₘ₉₉), increase in the steepness or sigmoidality of the time–response curve (Hill coefficient) and shortening of the T₁/₂ₑₒ (Nutt and Holford, 1996). As predicted, longitudinal studies showed the rise of EC₅₀ and the shortening of T₁/₂ₑₒ over time in patients with Parkinson’s disease (Contin et al., 1997). According to this levodopa kinetic–dynamic model, the rise of EC₅₀ shifts the time–response curve downwards, whereas the shortening of T₁/₂ₑₒ shifts the time–response curve to the left. Both these changes result in shortening of the duration of levodopa response. However, the rise of EC₅₀ and shortening of T₁/₂ₑₒ would change the onset of levodopa response differently: the onset would be more delayed by the former, and would be earlier by the latter. We estimated the asymmetry (i.e. difference between the more affected and the less affected side) of EC₅₀ from the asymmetry of latency to 50% Eₘ₉₉. EC₅₀ on the more (or less) affected side is the plasma drug concentration corresponding to 50% Eₘ₉₉ on the more (or less) affected side. Since the more affected and less affected sides share the same peripheral pharmacokinetics of levodopa, the asymmetry of latency to 50% Eₘ₉₉ would be the same as the asymmetry of latency to EC₅₀. If plasma drug concentration is a linear function of time near EC₅₀, the asymmetry of EC₅₀ should be proportional to the asymmetry of latency to EC₅₀ and, hence, to the asymmetry of latency to 50% Eₘ₉₉. Thus, our findings of longer latency to 50% Eₘ₉₉ on the more affected side would reflect a higher EC₅₀ on the same side and, hence, would account for the delayed onset of levodopa response as predicted by the kinetic–dynamic model (Nutt and Holford, 1996).

This observation is at variance with observations in cross-sectional studies, in which fluctuating responders had higher measured EC₅₀ than stable responders, and yet had an earlier (Contin et al., 1993; Colosimo et al., 1996; Harder and Baas, 1998) or similar onset (Contin et al., 1990) of levodopa response compared with stable responders. It is also not consistent with longitudinal observations where measured EC₅₀ became higher but the onset of levodopa response did not change significantly over time (Hughes et al., 1994). These discrepancies may be derived from the fact that both disease severity and levodopa treatment vary in longitudinal or cross-sectional studies, whereas disease severity, but not levodopa treatment, varies for side-to-side comparisons in asymmetric Parkinson’s disease. Therefore, the discrepancy of the onset of levodopa response between our study and previous longitudinal or cross-sectional studies is explained if the onset of levodopa response is determined by both levodopa treatment and disease severity: in particular, the onset of levodopa response becomes earlier with longer duration of treatment, and delayed with greater disease severity. This view is consistent with our findings of marginal significance in the correlation between the asymmetry of latency to the onset and the corresponding asymmetry of [¹¹C]DTBZ BP in the putamen.

In summary, the changes of levodopa response from the less affected side to the more affected side in asymmetric Parkinson’s disease showed the same characteristics of response changes associated with the development of motor fluctuations. These observations indicate that the severity of motor fluctuations is greater on the more affected side than on the less affected side, providing direct evidence for a role for DA terminal loss in the pathogenesis of motor fluctuations. However, the absence of a significant correlation between the early decay of levodopa response and DA terminal density suggests that DA terminal loss alone cannot account for the development of motor fluctuations. Furthermore, the discrepancy in the onset of levodopa response between our data and data in previous longitudinal or cross-sectional studies provides indirect evidence for the role of levodopa treatment in the pathogenesis of motor fluctuations. Therefore, we conclude that both levodopa treatment and DA terminal loss contribute to the development of motor fluctuations as in the case of levodopa-induced dyskinesias.

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