

Left hemispheric predominance of nigrostriatal dysfunction in Parkinson's disease

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The aim of this study was to investigate the distribution and the degree of asymmetric putaminal dopamine transporter availability in right-handed patients with Parkinson's disease and its association with the severity of lateralized motor signs. Asymmetry of motor symptoms was defined by the difference between right- and left-sided scores for lateralized items assessed by the Unified Parkinson's Disease Rating Scale Motor Score in a series of 68 patients with Parkinson's disease (disease duration 2.1 ± 1.5 years; Unified Parkinson's Disease Rating Scale Motor Score 22.7 ± 9). Putaminal dopamine transporter availability was measured with the radioligand [^{123}I]- β -carboxymethoxy-3- β -(4-iodophenyl) tropine ([^{123}I]- β -CIT) and single photon emission computed tomography. We found that in the right-handed Parkinson's disease cohort, the number of patients who had lower dopamine transporter uptake in the left posterior putamen was significantly greater compared with those with lower uptake in the right posterior putamen (Parkinson's disease-left group, $n = 49$; Parkinson's disease-right group, $n = 19$; $P < 0.001$). In addition, one-way analysis of variance revealed significant reductions of mean total putaminal [^{123}I]- β -CIT binding of the Parkinson's disease-right patients compared with Parkinson's disease-left patients ($P < 0.05$). The preponderance of reduced left putaminal dopamine transporter availability strengthens clinical observations of a greater proportion of right-handed patients with Parkinson's disease with predominantly right-sided motor signs and argues against a randomly distributed asymmetric vulnerability of substantia nigra dopaminergic neurons. The coexistence of a subgroup of right-handed patients with Parkinson's disease with more severe and predominant ipsilateral putaminal dopamine transporter decline suggests that asymmetry of dopaminergic denervation and motor dysfunction in Parkinson's disease cannot be fully explained by hemispheric dominance alone, but that other factors must be involved.

Keywords: Parkinson's disease; laterality; dopamine transporter; SPECT

Abbreviations: [^{123}I]- β -CIT = [^{123}I]-2- β -carboxymethoxy-3- β -(4-iodophenyl) tropine; B_{max} = maximum receptor concentration; BP_{ND} = binding potential; PD-LEFT = patients with Parkinson's Disease with lower [^{123}I]- β -CIT BP_{ND} values in their left putamen; PD-RIGHT = patients with Parkinson's Disease with lower [^{123}I]- β -CIT BP_{ND} values in their right putamen; SPECT = single photon emission computed tomography; UPDRS = Unified Parkinson's Disease Rating Scale; V_{ND} = radioligand distribution volume of non-displaceable compartment; V_{T} = radioligand distribution volume of total ligand uptake in tissue

Introduction

Unilateral onset and persisting asymmetry of the cardinal motor features are diagnostic hallmarks of Parkinson's disease, differentiating it from similar but distinct parkinsonian disorders (Gibb and Lees, 1988; Hughes *et al.*, 1992). The mechanisms underlying asymmetric expression of motor symptoms in Parkinson's disease are unknown. Several recent studies have found that in right-handed patients with Parkinson's disease, a greater proportion of subjects had more severe motor impairments on the right compared with the left side raising the issue that handedness and hemispheric dominance might somehow be involved (Uitti *et al.*, 2005; Haaxma *et al.*, 2010; Barrett *et al.*, 2011). However, exactly why a neurodegenerative disorder, most likely caused by genetic and environmental factors or combinations thereof, should affect the right and left nigrostriatal systems in an asymmetric fashion remains enigmatic (Melamed and Poewe, 2012). Most series relating laterality of symptoms to handedness or other factors have to some degree suffered from a potential of recall bias by patients as to where their symptoms first appeared, due to the fact that Parkinson's disease motor features affecting the dominant hand would be noted at a lower threshold compared with the non-dominant side. Asymmetry of striatal dopaminergic terminal function, a correlate of the lateralized severity of motor symptoms in Parkinson's disease can be measured with single photon emission computed tomography (SPECT) using the dopamine transporter radioligand [¹²³I]-2β-carbomethoxy-3β-(4-iodophenyl) tropine ([¹²³I]β-CIT; Innis *et al.*, 1993; Seibyl *et al.*, 1995; Marek *et al.*, 1996). To further test whether dopaminergic degeneration affects the left and right striatum randomly, we analysed

dopaminergic terminal function of each side of the caudate and posterior putamen in a large cohort of right-handed patients with Parkinson's disease using dopamine transporter SPECT to minimize observer or patient bias in assessing asymmetry. The asymmetry of putaminal dopamine transporter loss in patients with Parkinson's disease was correlated with the dichotomized Unified Parkinson's Disease Rating Scale (UPDRS) motor asymmetry score. In addition, predictors were calculated for lateralized putaminal dopamine transporter signal decline.

Materials and methods

The study population was selected from a cohort of consecutive patients with Parkinson's disease diagnosed according to the UK Parkinson's Disease Society Brain Bank clinical criteria with a disease onset beyond 50 years of age and a pathological putaminal dopamine transporter signal determined by [¹²³I]β-CIT SPECT, identified retrospectively from our movement disorders outpatients clinic records (Gibb and Lees, 1988). The complete dataset included gender, age at symptom onset, the motor score of the UPDRS part III in ON-drug state, side of initial motor symptom and handedness (Table 1). To determine the patient's predominately affected side, an asymmetry index was calculated as the absolute value of the right- minus left-sided scores from the UPDRS motor score comprising items 20–26 (UPDRS motor asymmetry index). A UPDRS motor asymmetry index of at least two points difference was used as the threshold for defining clinical asymmetry (Uitti *et al.*, 2005; Barrett *et al.*, 2011). In the final data analysis, only patients whose initial side of motor disability documented by the neurologist matched that revealed by the UPDRS motor asymmetry index were included. Handedness was determined at routine visits and for the purpose of this study retrospectively by

Table 1 Demographic and clinical characteristics of patients with Parkinson's disease and control subjects

	PD-LEFT patients [n = 49* (72%)]	PD-RIGHT patients [n = 19 (28%)]	Healthy subjects (n = 13)
Gender, female/male	19/30	6/13	5/8
Age at DAT SPECT (years)	62.2 ± 7.4	63.9 ± 6.3	62.2 ± 8.4
Disease duration until DAT SPECT (years)	2.2 ± 1.5	2 ± 1.5	
UPDRS motor score	20 ± 7.1	30.2 ± 9.9**	
Time period between DAT SPECT and UPDRS (years)	0.8 ± 1.2	1 ± 1.3	
UPDRS asymmetry subscore ^a	7.2 ± 3.4	6 ± 3.3	
Right-side	41 (83.7)	2 (10.5)	
Left-side	8 (16.3)	17 (89.5)	
Medication status at DAT SPECT ^b			
Levodopa equivalent dosage (mg/day)	382 ± 298	538 ± 352	
Levodopa alone	n = 12	n = 9	
Dopamine agonists alone	n = 9	n = 3	
Levodopa and dopamine agonists	n = 3	n = 2	
Monoamine oxidase inhibitor	n = 3	None	
Amantadine	n = 2	None	
Not medicated	n = 20	n = 5	

Values are expressed as mean (±1 SD) or n (%).

*P < 0.001 and **P < 0.01, between Parkinson's disease groups.

a Measured by the UPDRS asymmetry index including items: 20, 21, 22, 23 and 25.

b Doses of 100 mg of levodopa are regarded as equivalent to 5 mg of Ropinirole = 1 mg of Pramipexol, Pergolide or Rasagiline = 3.3 mg of Rotigotine = 100 mg of Amantadine. Levodopa dose was multiplied by 0.33 when treated with entacapone and added to the levodopa dose. Controlled release levodopa formulations were multiplied by 0.75.

DAT = dopamine transporter.

telephone inquiries using the Edinburgh Handedness Inventory (Oldfield, 1971). Cerebral MRI or CT was available for all cases to exclude alternative causes of parkinsonism. All patients had been followed clinically for at least 2 years, had a good response to levodopa or dopamine agonists, and none had developed clinical features suggestive of atypical parkinsonism. [¹²³I]β-CIT SPECT studies were performed at the Department of Nuclear Medicine at Innsbruck Medical University. None of the patients were taking selective serotonin reuptake inhibitors for a period of at least 14 days before dopamine transporter SPECT. Dopaminergic medication at the day of dopamine transporter SPECT is listed in Table 1. Following dopamine transporter SPECT as outlined below, patients with Parkinson's disease were divided into two groups according to the side of the lower posterior putaminal [¹²³I]β-CIT binding potential (BP_{ND}) and the asymmetry index of the posterior putamen both exceeding the 95% confidence interval (CI) obtained from the healthy control group. From the entire dataset, three subjects had symmetric putaminal [¹²³I]β-CIT uptake and one subject showed symmetric distribution of lateralized motor impairment, leaving a total of 68 patients with Parkinson's disease to be analysed. The PD-LEFT group comprised patients with Parkinson's disease with lower [¹²³I]β-CIT BP_{ND} values in their left putamen and the PD-RIGHT group comprised patients with Parkinson's disease with lower [¹²³I]β-CIT BP_{ND} values in their right putamen. In addition [¹²³I]β-CIT SPECT findings for Parkinson's disease were also compared with a group of 13 age-matched and right-handed, healthy control subjects (five females and eight males). The [¹²³I]β-CIT SPECT study of normal volunteers was approved by the Ethics Committee of the Medical University of Innsbruck.

Radiopharmaceutical preparation

[¹²³I]β-CIT was obtained from the Austrian Research Centre, Seibersdorf. Radiolabelling, safety and dosimetry have been described previously (Kuikka *et al.*, 1994). Radiochemical purity was >95% and specific activity between 37 and 55 MBq/nmol.

Scanning protocol

After blocking thyroid uptake with 600 mg sodium perchlorate orally 30 min before tracer application, patients received a bolus dose of 148–185 MBq [¹²³I]β-CIT intravenously. The patient's head was positioned in a head holder by means of a crossed laser beam system. Data acquisition started 18 h post tracer application and lasted 42 min and 40 s (Laruelle *et al.*, 1994). All scans were performed with a dual-detector scintillation camera ADAC, Vertex Plus (EPIC detector system, VXHR collimator) with a spatial resolution of 12 mm full-width at half-maximum in the transaxial plane. The camera heads were equipped with low-energy collimators. For each scan, a total of 64 projections (80 s per frame) were collected in a step-and-shoot mode. The image data were reconstructed by standard filtered back projection using a Gaussian weighted ramp filter (cut-off frequency 0.38, order 20) and attenuation was corrected using Chang's first-order method (attenuation coefficient $\mu = 0.12 \text{ cm}^{-1}$; Chang, 1978).

Data analysis

The reversible binding characteristics and the stability of regional [¹²³I]β-CIT uptake 18 h post application allowed the estimation of the binding potential that was calculated according to the equilibrium model introduced by Laruelle *et al.* (1994).

[¹²³I]β-CIT BP_{ND} was estimated as the ratio of specifically bound radioligand to that of the non-displaceable ligand in the occipital cortex. The parameter BP_{ND} was shown under equilibrium conditions to be proportional to B_{max} , the maximum receptor concentration and can be computed for every voxel by the formula (De Keyser *et al.*, 1989):

$$\text{BP}_{\text{ND}} = \frac{V_T(\text{counts per minute/voxel}) - V_{\text{ND}}(\text{counts per minute/voxel})}{V_{\text{ND}}(\text{counts per minute/voxel})}$$

where V_{ND} is the distribution volume of non-displaceable compartment relative to total concentration of ligand in plasma and V_T the distribution volume of total ligand uptake in tissue relative to total concentration of the ligand in plasma (Innis *et al.*, 2007). To calculate V_{ND} , a region of interest comprising the occipital cortex was extracted and transformed onto the [¹²³I]β-CIT image as outlined in the next section (Rorden and Brett, 2000).

Calculation of regions of interest

Calculation of parametric BP_{ND} and estimation of region of interest mean BP_{ND} values were conducted using Statistical Parametric Mapping 8 (Wellcome Department of Cognitive Neurology, London; Friston *et al.*, 1995) implemented in Matlab 7.8 (Mathworks Inc.). Reconstructed [¹²³I]β-CIT images were normalized onto a [¹²³I]β-CIT template image in MNI (Montreal Neurological Institute) space as previously described (Scherfler *et al.*, 2005). To calculate V_{ND} , a mask of the occipital cortex as defined by the broadman brain template provided with the software package MRIcro 1.37 was extracted and transformed onto the individual [¹²³I]β-CIT image by inverting the deformation fields obtained when normalizing images onto the [¹²³I]β-CIT template image (Ashburner *et al.*, 2000). To accurately localize the caudate and posterior putamen and to keep partial volume effects and spill-over effects at a minimum, two circular regions with a diameter of 10 mm comprising three consecutive slices (thickness 2 mm) were outlined on the T₁-weighted MRI template in MNI space provided with Statistical Parametric Mapping and transposed onto the [¹²³I]β-CIT template image (Fig. 1).

The percentage of dopamine transporter asymmetry for the caudate and posterior putamen was calculated according to the formula: $|[(a - b)/(a + b)] \times 2 \times 100|$, where a and b represent the two different sides of either the caudate or posterior putamen (Zijlmans *et al.*, 2007). Additionally, the ratio between the caudate and putaminal dopamine transporter SPECT signal was measured on each side. Data processing was performed on a Dell Studio XPS 435 T workstation.

Statistical analysis

The binomial test was used to test for the distribution of lateralized putaminal dopamine transporter availability and lateralized UPDRS motor score asymmetry values. One-way ANOVA and *post hoc* least significance difference were applied for clinical data, mean caudate and putamen region of interest values, the caudate and putamen [¹²³I]β-CIT asymmetry indices and the caudate to putamen ratio. Two-tailed paired Student's *t*-tests were employed for comparison of [¹²³I]β-CIT uptake measures between the left and right striatum within each group. The dichotomized UPDRS motor score asymmetry, and the dichotomized putaminal dopamine transporter asymmetry were subjected to a binary logistic regression analysis.

To identify predictors for left or right lateralized reduction of putaminal dopamine transporter availability, multinomial logistic regression analysis was performed, including 'group' as the dependent variable (PD-RIGHT 0, PD-LEFT 1) and gender (male 1, female 0), age at disease onset, disease duration, UPDRS motor score and percentage

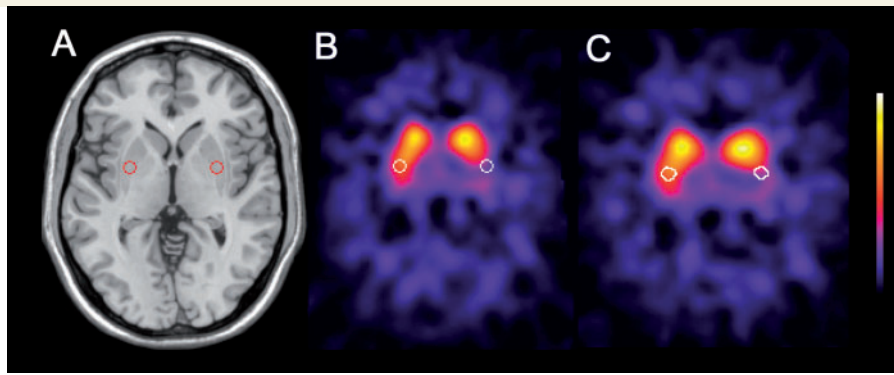


Figure 1 Two circular regions of interest outlined on the putamen of a T₁-weighted MRI in MNI space (A) and rendered onto a [¹²³I]β-CIT SPECT image of a patient with Parkinson's disease (B) previously normalized into MNI space. The putaminal region of interest was transformed onto the individual [¹²³I]β-CIT image by inverting the deformation fields obtained when normalizing the individual image to MNI space (C).

of posterior putamen asymmetry as covariates. Data were tabulated and analysed using a commercial software package (SPSS for Windows 17.0 for windows, SPSS Inc.).

Results

Overall left, right and mean caudate and putaminal [¹²³I]β-CIT BP_{ND} values were significantly decreased and asymmetry indices were significantly increased in patient groups compared with the normal control group ($P < 0.001$). Of the total of 68 right-handed patients with Parkinson's disease, 49 subjects had lower dopamine transporter uptake in the left versus the right posterior putamen (PD-LEFT), while 19 subjects had more marked reduction of dopamine transporter ligand binding in the right posterior putamen (PD-RIGHT, $P < 0.001$, Fig. 2). Gender, age of onset, disease duration as well as the time period between the clinical assessment through the UPDRS motor scale and dopamine transporter imaging were not significantly different between PD-LEFT and PD-RIGHT patients (Table 1). However, PD-RIGHT patients showed significantly greater motor impairment when compared with the PD-LEFT group (UPDRS motor score 30.2 ± 9.9 versus 20 ± 7.1 , $P < 0.01$). In addition, one-way ANOVA revealed significant reductions of mean total putaminal [¹²³I]β-CIT BP_{ND} of the PD-RIGHT cohort compared with the PD-LEFT group ($P < 0.05$; Table 2), whereas no significant difference was apparent when comparing mean caudate [¹²³I]β-CIT BP_{ND} of the PD-LEFT versus the PD-RIGHT cohort. Furthermore, the posterior putaminal asymmetry index was significantly increased in the PD-LEFT compared with the PD-RIGHT group ($P < 0.01$).

The caudate-to-putamen ratio of [¹²³I]β-CIT BP_{ND} of the left side was significantly increased in the PD-LEFT and PD-RIGHT cohort compared with control subjects (PD-LEFT, $P < 0.01$; PD-RIGHT, $P < 0.01$). On the right side a significant increase of the caudate-to-putamen ratio was evident for the PD-RIGHT versus the control group ($P < 0.01$), whereas for the PD-LEFT group only a trend of $P = 0.074$ was detected.

The dichotomized UPDRS motor score asymmetry and the dichotomized putaminal dopamine transporter asymmetry index was significantly correlated ($r^2 = 0.6$; $P < 0.001$). Multinomial

logistic regression analysis revealed that higher UPDRS motor score and lower dopamine transporter asymmetry index were predictors of right lateralized predominant [¹²³I]β-CIT BP_{ND} decreases and vice versa ($r^2 = 0.52$; $P < 0.001$).

Discussion

In Parkinson's disease, the neurodegenerative process affects the dopaminergic innervation of both striata in an asymmetric fashion leading to lateralized onset of motor symptoms with persisting asymmetry as the disease progresses (Marek *et al.*, 1996). The present dopamine transporter-SPECT study is the first to analyse the distribution and severity of lateralized putaminal dopamine transporter binding in a large group of right-handed patients with Parkinson's disease. In a significantly higher proportion of patients, dopamine transporter binding was more severely reduced in the left compared with the right posterior putamen. This appears consistent with recent studies showing greater proportions of right-handed patients with Parkinson's disease presenting with greater motor impairment of their right compared with their left-sided limbs (Uitti *et al.*, 2005; Haaxma *et al.*, 2010; Barrett *et al.*, 2011). The cause of predominant left-sided striatal dopaminergic dysfunction in right-handed patients with Parkinson's disease is not clear and hypotheses of inherently lower dopamine levels in the left compared with the right nigrostriatal pathway and/or a selective vulnerability of nigro-striatal dopamine projections towards pathogenetic mechanisms underlying Parkinson's disease have been raised (Djaldetti *et al.*, 2006; Melamend and Poewe, 2012). The only report on post-mortem studies of brains not affected by a neurodegenerative disease identified by the authors has, however, reported higher dopamine levels in the left compared with the right striatum and globus pallidus (Glick *et al.*, 1982). In line with this finding, we and others have found slightly higher concentrations of [¹⁸F]-DOPA and [¹²³I]β-CIT tracer binding in the left compared with the right striatum at the group level of right-handed healthy subjects, arguing against reduced nigrostriatal innervation or terminal function in the left striatum as a determinant of earlier and more significant impact of Parkinson's

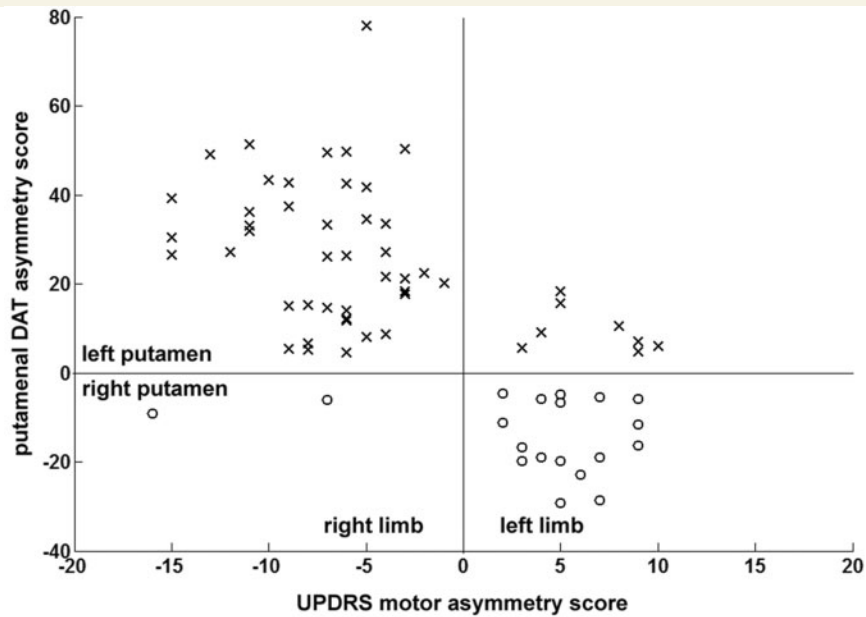


Figure 2 Crosses represent patients with Parkinson's disease with lower [^{123}I]β-CIT BP_{ND} values in their left putamen (PD-LEFT group) and circles represent patients with Parkinson's disease with lower [^{123}I]β-CIT BP_{ND} values in their right putamen (PD-RIGHT group). DAT = dopamine transporter.

Table 2 Mean regional [^{123}I]β-CIT BP_{ND} in patients with Parkinson's disease and control subjects

	PD-LEFT patients (n = 49 ^{†††})	PD-RIGHT patients (n = 19)	Healthy subjects (n = 13)
Left caudate	7.2 ± 1.9 ^{***}	7.5 ± 1.5 ^{***}	12.1 ± 2.1
Right caudate	7.4 ± 1.9 ^{***}	6.6 ± 1.5 ^{***}	12 ± 1.9
Left posterior putamen	3.9 ± 1.32 ^{**}	4 ± 0.9 ^{***}	9.3 ± 1.6
Right posterior putamen	5 ± 1.4 ^{***}	3.6 ± 0.8 ^{***,†††}	9.1 ± 1.4
Mean caudate	7.3 ± 1.8 ^{***}	7 ± 1.6 ^{***}	12 ± 2
Mean posterior putamen	4.5 ± 1.2 ^{***}	3.8 ± 0.9 ^{***,†}	9.2 ± 1.5
Asymmetry index of caudate	13.6 ± 8.8 ^{***}	15.1 ± 9.1 ^{***}	3.6 ± 2.2
Asymmetry index of posterior putamen	25.2 ± 16.5 ^{***,††}	13.8 ± 8.1 [*]	3.1 ± 2.2
Ratio of caudate/posterior putamen left	2 ± 0.8 ^{**}	1.9 ± 0.5 ^{**}	1.3 ± 0.1
Ratio of caudate/posterior putamen right	1.6 ± 0.6 ^{†,‡}	1.9 ± 0.6 ^{**}	1.3 ± 0.1

Values represent the means (±1 SD).

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ versus normal controls.

[†] $P < 0.05$, ^{††} $P < 0.01$, ^{†††} $P < 0.001$ between Parkinson's disease groups.

[‡] $P < 0.001$ intragroup difference.

disease pathology and thereby right-sided predominance of motor asymmetry in patients with established Parkinson's disease (Table 2; Wagner *et al.*, 1983; De la Fuente *et al.*, 2000; van Dyck *et al.*, 2002).

Another hypothesis suggests that handedness might increase the susceptibility towards Parkinson's disease pathology via asymmetric activation levels of basal ganglia motor circuits with higher baseline activity in the left nigrostriatal system (Melamed and Poewe, 2012). A meta-analysis investigating the association of motor dominance in Parkinson's disease and handedness included 4405 patients with asymmetric Parkinson's disease and revealed 59.5% of right-handed patients with right-dominant and 59.2%

of left-handed patients with left-dominant motor symptoms (van der Hoorn *et al.*, 2011). Although the authors reported a significant correlation between handedness and symptom dominance, there were still a considerable proportion of right-handers with predominantly left-sided Parkinson's disease signs and vice versa, questioning the role of handedness as the key causative factor for asymmetric presentation of motor signs in Parkinson's disease. In addition to 68 right-handed patients with Parkinson's disease, we identified four left-handed patients with Parkinson's disease as defined by the Edinburgh inventory of handedness. These patients also consistently showed a left-striatal predominant reduction of the dopamine transporter signal, arguing against a major effect of

handedness upon selective unilateral striatal dopamine transporter vulnerability. However, four cases are clearly insufficient to draw any firm conclusions, and further studies in larger samples of left-handed patients are needed to test the effects of handedness on the side of predominant nigro-striatal dysfunction.

One potential weakness of studies documenting more severe motor impairments of the dominant hand lies in the fact of greater subject awareness of subtle motor deficits of the dominant compared with the non-dominant hand. By measuring putaminal dopamine transporter asymmetry with SPECT, the present study was not affected by such confounders. The proportion of patients with Parkinson's disease with left predominant putaminal dopamine transporter decline was even higher than reported in previous clinical observation studies consistent with the hypothesis that motor dominance of the left hemisphere is associated with increased vulnerability of the left dopaminergic nigro-striatal projections of right-handed patients with Parkinson's disease. However, there was still a considerable number of right-handed patients with Parkinson's disease left with lower dopamine transporter binding of their right putamen. This clearly argues against hemispheric dominance as the only factor determining asymmetric nigrostriatal dysfunction in Parkinson's disease. In contrast to right-handed patients with Parkinson's disease with lower dopamine transporter binding in the left putamen, those patients with Parkinson's disease had more advanced disease course documented by significantly higher UPDRS motor scores and corresponding lower putaminal dopamine transporter availability despite similar age and disease duration. Although reasons for this difference remain unclear, there is a possibility that patients with Parkinson's disease with initial and predominant dysfunction of the right nigrostriatal system might have longer latencies between onset of neurodegeneration and subjective awareness of motor deficits in the non-dominant hand or limb. Thereby, neurodegeneration might have progressed more by the time they come to medical attention. Consistent with this hypothesis is our finding that a higher degree of motor disability was identified as a predictor of right lateralized dopamine transporter signal decline in right-handed patients with Parkinson's disease in this cross-sectional study design. This finding must, however, be interpreted with caution, as regression analysis including the ordinal assessment of motor impairment was affected by pharmacotherapy and the interval of ~1 year between dopamine transporter imaging and UPDRS rating. Nevertheless, our results of greater severity of right putaminal dopamine transporter-binding loss and contralateral motor dysfunction call for future studies of potential differences in the clinical course and rates of progression between Parkinson's disease patient groups with right versus left predominance of motor signs followed from their initial drug-naïve stage of the disease.

Dopaminergic medication could also have altered the striatal dopamine transporter signal, although the effects of dopaminergic therapy on dopamine transporter binding are controversial (Ahlskog *et al.*, 1999; Guttman *et al.*, 2001; Ravina *et al.*, 2005). In our sample of 49 right-handed patients with Parkinson's disease with left predominant putaminal dopamine transporter decline, we retrospectively identified subgroups of DOPA naïve patients ($n = 20$); patients treated with levodopa

alone ($n = 12$) and patients solely treated with dopamine-agonists ($n = 9$) at the time of dopamine transporter-SPECT assessment. Analysis of variance of the caudate and posterior putaminal dopamine transporter signal as well as posterior putamen asymmetry indices and caudate to putamen ratios revealed no significant differences among the dopaminergic naïve and medicated subgroups. Although this analysis was not powered to detect potentially mild signal alterations arising from pharmacotherapy, marked drug effects can be ruled out. In addition, any such effects should affect both striata and are unlikely to account for the asymmetries observed in this study.

Two patients with Parkinson's disease with lower dopamine transporter availability in the right putamen and eight patients with Parkinson's disease with lower dopamine transporter availability in the left putamen had more severe motor symptoms on the ipsilateral side (Fig. 2). Interestingly, all of them revealed scores within the lower third of the maximum putaminal dopamine transporter asymmetry score and six of them had marked rest tremor, which has been reported not to correlate with the severity of putaminal dopamine transporter signal decline (Seibyl *et al.*, 1995; Isaias *et al.*, 2007).

Other reasons for the mismatch between asymmetries of putaminal dopamine transporter signal decline and lateralized motor symptoms in patients with mild striatal dopamine transporter asymmetry scores might be due to the equivalent affinities of [123 I]β-CIT to both the dopamine transporter and serotonin transporter. Using selective serotonin transporter ligands and PET, the putaminal serotonin transporter availability was repeatedly shown to be reduced in patients with Parkinson's disease (Kerenyi *et al.*, 2003; Strecker *et al.*, 2011). Nevertheless, *in vivo* and *in vitro* receptor ligand occupancy studies strongly suggested that due to the different binding kinetics of [123 I]β-CIT to serotonin transporter rich brain areas and the striatum, the delayed state of binding equilibrium allows for almost exclusive quantification of striatal dopamine transporter binding. However, mild signal alterations potentially arising from serotonin transporter binding in the putamen cannot be entirely excluded (Staley *et al.*, 1994; Pirker *et al.*, 1995). It remains to be shown if the distribution of reduced striatal serotonin transporter availability follows that of dopamine transporter in right-handed patients with Parkinson's disease.

Conclusion

Dopamine transporter-SPECT of right-handed patients with Parkinson's disease revealed a significantly higher proportion of patients with left predominant putaminal dopamine transporter decline and hence clearly argues against a randomly distributed asymmetric vulnerability of monoaminergic nerve terminals in the putamen. The coexistence of a subgroup of right-handed patients with Parkinson's disease with more severe and predominant ipsilateral putaminal dopamine transporter decline suggests that hemispheric asymmetry of neurodegeneration and motor dysfunction in Parkinson's disease cannot be fully explained by hemispheric dominance alone. Further studies into the right-left hemispheric asymmetry of the functional organization of basal ganglia motor circuits are needed to better understand the

mechanisms underlying asymmetric motor features in Parkinson's disease.

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