Motor-Symptom Laterality Affects Acquisition in Parkinson’s Disease: A Cognitive and Functional Magnetic Resonance Imaging Study

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ABSTRACT: Background and Objectives: Asymmetric onset of motor symptoms in PD can affect cognitive function. We examined whether motor-symptom laterality could affect feedback-based associative learning and explored its underlying neural mechanism by functional magnetic resonance imaging in PD patients.

Methods: We recruited 63 early-stage medication-naive PD patients (29 left-onset medication-naive patients, 34 right-onset medication-naive patients) and 38 matched normal controls. Subjects completed an acquired equivalence task (including acquisition, retention, and generalization) and resting-state functional magnetic resonance imaging scans. Learning accuracy and response time in each phase of the task were recorded for behavioral measures. Regional homogeneity was used to analyze resting-state functional magnetic resonance imaging data, with regional homogeneity lateralization to evaluate hemispheric functional asymmetry in the striatum.

Results: Left-onset patients made significantly more errors in acquisition (feedback-based associative learning) than right-onset patients and normal controls, whereas right-onset patients performed as well as normal controls. There was no significant difference among these three groups in the accuracy of either retention or generalization phase. The three groups did not show significant differences in response time. In the left-onset group, there was an inverse relationship between acquisition errors and regional homogeneity in the right dorsal rostral putamen. There were no significant regional homogeneity changes in either the left or the right dorsal rostral putamen in right-onset patients when compared to controls.

Conclusions: Motor-symptom laterality could affect feedback-based associative learning in PD, with left-onset medication-naive patients being selectively impaired. Dysfunction in the right dorsal rostral putamen may underlie the observed deficit in associative learning in patients with left-sided onset.

Key Words: Parkinson’s disease; hemispheric asymmetry; dopamine; association learning; resting-state functional MRI

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Drs. Huang and Tan contributed equally to this work.

Dr. Huang, Dr. Tan and Dr. Chen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Parkinson’s disease (PD) is the second-most common neurodegenerative disorder, characterized by resting tremor, rigidity, bradykinesia, and postural instability. Onset and progression of motor symptoms in PD are usually asymmetric, reflecting asymmetric contralateral dopamine depletion in the basal ganglia. Relationships between cognitive performance and symptom asymmetry have been revealed that left-onset PD patients performed worse on cognitive measures, such as spatial attention and tasks of orientation and mental imagery, than right-onset PD patients. Cognitive processes that are closely related with dopamine, such as cognitive flexibility and motivation, showed different deficits between right-onset and left-onset PD patients. For example, left-onset PD patients with greater loss of dopamine in the right hemisphere had impaired cognitive flexibility.

Feedback-based associative learning, which involves learning through corrective feedback provided on each trial, has been correlated with striatal dopamine release and function of the basal ganglia. Previous studies have reported that feedback-based associative learning was impaired in PD patients. However, the impairment in feedback-based learning in PD is not a universal finding, and many factors could contribute to this variability. Wilkinson and colleagues did not find a selective impairment in PD in probabilistic feedback-based learning, but reported that there was a significant correlation between disease severity and the impairment in feedback-based learning. It has also been reported that off-medication PD patients learned stimulus-response associations equally well compared to healthy controls, but learning was impaired by dopaminergic medication. Thus, in the underlying disease process, disease severity and dopaminergic medication might be all involved in modulating feedback-based learning. However, it is still not clear how dopamine asymmetry affects feedback-based associative learning in PD patients.

To control and minimize the effects of medication involvement and disease severity, we recruited early-stage medication-naive right-handed PD patients including left-onset medication-naive patients (L-naive) and right-onset medication-naive patients (R-naive). We used a computer-based cognitive task of learning and generalization based on the acquired equivalence paradigm to test the effects of dopamine asymmetry on feedback-based associative learning. The Acquired Equivalence Task, which includes tests of acquisition, retention, and generalization, was repetitively used to evaluate feedback-based associative learning in patients with PD and other neurodegenerative disorders. In the acquisition phase, learning through trial-by-trial feedback learning was shown to correlate with striatal function, whereas generalization without feedback was shown to correlate with hippocampal and medial temporal lobe (MTL) functionality. Although striatal involvement in associative learning has been consistently reported in previous task-based functional magnetic resonance imaging (fMRI) studies, such as caudate nucleus, amygdala, and ventral striatum, the specific loci are not always the same. Thus, which subdivision of the basal ganglia is associated with feedback-based associative learning remains unclear, and resting-state fMRI (rs-fMRI) data were collected to explore the underlying neural mechanism of feedback-based learning.

In the present study, we examined whether motor-symptom laterality could affect feedback-based associative learning and explored its underlying neural mechanism using rs-fMRI in PD patients.

Subjects and Methods

Subjects

We recruited 63 right-handed, early-stage (H & Y scores between 1 and 2), medication-naive PD patients and 38 right-handed normal controls (NCs) during 2012-2015. Subjects in the PD and NC groups were matched for age, sex, education, and general cognitive status. According to motor-symptom laterality, PD patients were divided into L-naive (N = 29) and R-naive (N = 34) subgroups. All participants were nondemented (Mini–Mental State Examination (MMSE) ≥ 24) and scored less than 15 on the Beck Depression Inventory II (BDI-II). Participants were also screened for history of cerebral trauma, cerebrovascular diseases, head surgery, severe sleep disorders, hyperthyroidism, insulin-dependent diabetes, psychiatric or neurological disorders, abuse of alcohol, tobacco use, use of hormonal contraceptives, anticholinergic drugs, or antidepressants. For subjects with PD, only patients with unilateral side of onset and asymmetrical motor symptoms were involved and diagnosis was confirmed by two movement disorder specialists according to the UK Brain Bank criteria for the diagnosis of PD. Side of onset was determined by medical history and physical examination. Severity of motor symptoms was evaluated by UPDRS-III. Motor asymmetry index (MAI) was calculated as (right side symptoms – left side symptoms) / (right side symptoms + left side symptoms).

Standard Protocol Approvals, Registrations, and Patient Consents

We received approval from the Ethics Committee of Ruijin Hospital affiliated with Shanghai Jiao Tong University School of Medicine (Shanghai, China). We obtained written informed consents from all patients and controls before their participation in the study.
Behavioral Data Acquisition and Evaluation

We used an Apple MacBook to run the Acquired Equivalence Task. This task is composed of two phases: acquisition and transfer. In the acquisition phase, participants acquire associations of colored faces and fish through trial-by-trial feedback-based learning. Following this acquisition, the transfer phase includes two types of trials: tests of previously learned associations (retention) and tests of new associations (generalization). Mean number of incorrect choices and mean response time in each phase were recorded for behavioral measures. For the detailed procedure, please refer to eMethod 1 and eTable 1 in the Supporting Information.

MRI Data Acquisition and Processing

An MRI scan was performed after the acquired equivalence test with an interval of 8.6 ± 1.5 days. A subgroup of 70 subjects (23 L-naive, 25 R-naive, and 22 NCs) participated in rs-fMRI on a 3.0 Tesla GE Medical System (GE Healthcare, Little Chalfont, UK) scanner based on subjects’ willingness. During the scan, subjects were asked to remain motionless and awake with their eyes closed. For each participant, 210 functional images were collected using echo planar imaging T2*-weighted sequence (repetition time [TR] = 2,000 ms; echo time [TE] = 30 ms; flip angle = 90 degrees; 33/35/37 slices; matrix = 64 × 64; voxel size = 3.75 × 3.75 × 4 mm3). Then, the high-resolution, three-dimensional, T1-weighted structural images (TR = 5.78 ms; TE = 1.77 ms; flip angle = 12 degrees; 196 slices; matrix = 256 × 256; voxel size = 1 × 1 × 1 mm3) were acquired for registration and normalization of the functional images.

After exclusion because of vascular diseases (1 L-naive, 2 R-naive, and 3 NCs) and obvious head motion (2 L-naive and 2 R-naive, with the translation and rotation head motion parameters larger than 2 mm or 2 degrees), MRI data from 60 subjects (20 L-naive, 21 R-naive, and 19 NCs) qualified for analysis. MRI data were processed with Data Processing Assistant for Resting-State fMRI programs. Regional homogeneity (ReHo), as a commonly used method to analyze rs-fMRI data, was used with the rs-fMRI Data Analysis Toolkit (REST; http://www.restfmri.net) by calculating the Kendall's coefficient of concordance of the time series of a given voxel with its 26 nearest neighboring voxels. With the assumption that PD patients with unilateral onset of motor symptoms had asymmetric functional impairments in the brain, the ReHo lateralization index was used to evaluate hemisphere asymmetry in neural activity as previously reported. Striatum subregions, including the putamen, caudate, and pallidum, were chosen as regions of interest (ROIs). For detailed methods, please refer to eMethod 2 in the Supporting Information.

Statistical Analysis

Normality of clinical and demographic data distribution was checked by the Kolmogorov–Smirnov test. One-way analysis of variance (ANOVA) was used to compare the normally distributed continuous variables (age), and the chi-square test was used to analyze categorical variables (sex). The continuous variables that were not normally distributed (education, disease duration, H & Y, BDI-II, MMSE, UPDRS-III score, and MAI) were analyzed by the Kruskal–Wallis test. Mix-model ANOVAs, with group as between-subject factor and phase as within-subject factor, were used to analyze the behavioral data. Post-hoc analysis was done using Tukey’s honest significant difference test. In the correlational analysis, Spearman’s rho was calculated. The alpha level was set at 0.05. All P values less than the alpha level were considered statistically significant. SPSS software (version 17.0; IBM Corp., Chicago, IL) was used for statistical analysis.

For the fMRI data analysis, comparison of the hemispheric asymmetry among groups was performed using one-way analysis of covariance (ANCOVA). Age, sex, the mean frame-wise displacement corresponding to the temporal derivative of the head motion parameters, and mean gray matter volume of ROI were used as nuisance covariates. Post-hoc analysis was performed within the significant regions. To control for family-wise error rates, Monte Carlo simulations were performed (3dClustSim; 10,000 iterations) using all brain voxels within the half-striatum ROI. The cluster threshold for a corrected alpha level of P = 0.05 was 27 voxels for ANCOVA and seven voxels for post-hoc t test, respectively.

### TABLE 1. Clinical and demographic characteristics of medication-naive PD patients and normal controls

<table>
<thead>
<tr>
<th></th>
<th>L-Naive (n = 29)</th>
<th>R-Naive (n = 34)</th>
<th>NC (n = 38)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.3 (8.6)</td>
<td>59.6 (9.2)</td>
<td>56.4 (8.5)</td>
<td>0.580</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>16/13</td>
<td>19/15</td>
<td>14/24</td>
<td>0.190</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.6 (3.4)</td>
<td>12.9 (3.3)</td>
<td>12.6 (2.6)</td>
<td>0.288</td>
</tr>
<tr>
<td>Disease duration</td>
<td>2.7 (2.2)</td>
<td>2.2 (1.4)</td>
<td>—</td>
<td>0.799</td>
</tr>
<tr>
<td>UPDRS-III</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>1.9 (1.9)</td>
<td>1.6 (1.7)</td>
<td>—</td>
<td>0.545</td>
</tr>
<tr>
<td>Rigidity</td>
<td>3.6 (2.2)</td>
<td>3.9 (1.6)</td>
<td>—</td>
<td>0.203</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>5.0 (3.6)</td>
<td>4.1 (2.0)</td>
<td>—</td>
<td>0.204</td>
</tr>
<tr>
<td>Left-side symptoms</td>
<td>9.2 (4.0)</td>
<td>9.6 (1.2)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Right-side symptoms</td>
<td>0.8 (2.7)</td>
<td>8.4 (2.8)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Dominant-side symptoms</td>
<td>9.2 (4.0)</td>
<td>8.4 (2.8)</td>
<td>—</td>
<td>0.565</td>
</tr>
<tr>
<td>Non-dominant-side symptoms</td>
<td>0.8 (2.7)</td>
<td>0.6 (1.2)</td>
<td>—</td>
<td>0.415</td>
</tr>
<tr>
<td>Total score</td>
<td>14.9 (8.5)</td>
<td>13.2 (5.6)</td>
<td>—</td>
<td>0.391</td>
</tr>
<tr>
<td>MAI</td>
<td>—0.9 (0.2)</td>
<td>0.9 (0.2)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>H &amp; Y score</td>
<td>1.2 (0.3)</td>
<td>1.4 (0.4)</td>
<td>—</td>
<td>0.104</td>
</tr>
<tr>
<td>BDI-II</td>
<td>5.2 (3.0)</td>
<td>5.6 (3.3)</td>
<td>5.0 (2.7)</td>
<td>0.740</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.8 (10.1)</td>
<td>28.7 (1.4)</td>
<td>29.0 (1.2)</td>
<td>0.363</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation). MAI = (right side symptoms – left side symptoms) / (right side symptoms + left side symptoms).
TABLE 2. Differences in the asymmetry of ReHo in the striatum

<table>
<thead>
<tr>
<th>Brain Regions</th>
<th>Voxels</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>F/T Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCOVA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsal rostral putamen</td>
<td>27</td>
<td>−24</td>
<td>12</td>
<td>−3</td>
<td>5.229 (F)</td>
</tr>
<tr>
<td>L-naive &gt; NC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsal rostral putamen</td>
<td>22</td>
<td>−24</td>
<td>12</td>
<td>−3</td>
<td>2.811 (T)</td>
</tr>
<tr>
<td>L-naive &gt; R-naive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsal rostral putamen</td>
<td>7</td>
<td>−12</td>
<td>12</td>
<td>−9</td>
<td>3.141 (T)</td>
</tr>
</tbody>
</table>

Max, Montreal Neurological Institute.

Results

Clinical and Demographic Characteristics of Subjects

The clinical and demographic characteristics of subjects are presented in Table 1. All the groups were matched for age, sex, education, MMSE, and BDI-II \( (P \geq 0.190) \). There were no significant differences in disease duration, H & Y score, and UPDRS-III scores (including tremor, rigidity, bradykinesia subscores, and total scores) between the L-naive and R-naive PD groups \( (P \geq 0.104) \). MAI was calculated as (right side symptoms – left side symptoms) / (right side symptoms + left side symptoms). Mean values of MAI for L-naive and R-naive groups were −0.9 (0.2) versus 0.9 (0.2) respectively, indicating that motor-symptom asymmetry was also matched. In addition, subjects participating in the MRI examination were also matched across the three groups (see eTable 2 in the Supporting Information).

Behavioral Performance

Acquisition Was Impaired in L-Naive but Normal in R-Naive Patients

Mix-model ANOVAs showed that both group \( (F_{2, 294} = 7.228; \ P = 0.001) \) and phase \( (F_{2, 294} = 52.680; \ P < 0.001) \) had significant effects on accuracy. The interaction between group and phase was at a trend-level \( (F_{4, 294} = 2.127; \ P = 0.077) \). Figure 1A indicated that the group effect is primarily driven by the acquisition phase. Post-hoc analysis showed that accuracy was significantly different among L-naive, R-naive, and NCs. L-naive patients made significantly more errors than R-naive patients \( (P = 0.003) \) and NCs \( (P = 0.002) \), whereas R-naive patients performed as well as NCs \( (P = 0.996; \) Fig. 1A). There were no significant differences between groups in retention or generalization phase, indicating that retrieval function and generalization were preserved in both L-naive and R-naive patients \( (P = 0.201 \) vs. generalization, \( P = 0.331; \) Fig. 1A). Thus, L-naive patients, rather than R-naive patients, were selectively impaired in feedback-based associative learning, indicating a potential effect of asymmetric dopamine depletion on associative learning.

Phase had a significant effect on the response time \( (F_{2, 294} = 12.564; \ P < 0.001) \). However, there was neither an effect of group \( (F_{2, 294} = 0.733; \ P = 0.481) \) nor an interaction between group and phase \( (F_{4, 294} = 0.782; \ P = 0.538; \) Fig. 1B).

fMRI Results

Dorsal Rostral Putamen Was Impaired in the Right Side in L-Naive but Intact in R-Naive Patients

One-way ANCOVA analysis showed that L-naive, R-naive, and NC groups were significantly different in ReHo lateralization in the dorsal rostral putamen (voxel level: \( P < 0.05) \); cluster size: > 27 voxels; corresponding to cluster-level corrected: \( P < 0.05) \); Fig. 2A; Table 2). Post-hoc analysis showed that L-naive patients had higher ReHo lateralization in the dorsal rostral putamen compared to the NC group \( (F_{2, 294} = 0.331; \) Fig. 2B; Table 2) and R-naive group \( (F_{2, 294} = 0.201; \) Table 2; voxel level: \( P < 0.05) \); cluster size: > 7 voxels; corresponding to cluster-level corrected: \( P < 0.05) \). Further graphing using a scatter plot in Figure 2D indicated that higher
ReHo lateralization in L-naive patients was attributed to decreased ReHo activity in the right side of the dorsal rostral putamen. There was no significant difference between the left and the right dorsal rostral putamen in R-naive patients, suggesting that neural function of the left dorsal rostral putamen in R-naive patients was relatively preserved in early-stage PD. Our results showed that the right dorsal rostral putamen of L-naive patients had reduced neural activity compared with the left dorsal rostral putamen in R-naive patients, indicating that the right side of dorsal rostral putamen might be more sensitive to dopamine depletion than the left side.

Dorsal Rostral Putamen Was Correlated With Feedback-Based Associative Learning

Correlational analysis in the L-naive group showed that the mean number of errors in acquisition was inversely correlated with ReHo activity of the right dorsal rostral putamen ($r = -0.535; P = 0.015$; Fig. 2E). This suggests that reduced activity in the right dorsal rostral putamen might be associated with poor feedback-based associative learning in L-naive patients. In addition, poor performance in acquisition was also inversely correlated with ReHo activity of the left dorsal rostral putamen in L-naive patients ($r = -0.479; P = 0.033$; Fig. 2E). However, there was no significant ReHo activity change in the left dorsal rostral putamen of L-naive patients. Thus, this inverse correlation between acquisition and ReHo activity of the left dorsal rostral putamen has no clinical significance in those early-stage L-naive PD patients.

Because only 60 cases (20 L-naïve, 21 R-naïve, and 19 NCs) underwent rs-fMRI examination based on subjects’ willingness, performance in the acquired equivalence task was also analyzed in these 60 cases. Results were consistent with the earlier results from all 101 subjects (see eResult 1 and eFigure 1 in the Supporting Information). Our results showed that the dorsal rostral putamen activity might be specifically implicated in acquisition learning.

Function of the Dorsal Rostral Putamen Did Not Correlate With the Severity of Motor Symptoms

In order to test whether the dorsal rostral putamen was associated with motor function, correlation analysis was done between UPDRS-III scores and ReHo activity in the dorsal rostral putamen in L-naive patients. No significant correlation was found between UPDRS-III score and neural activity of either the right or the left dorsal rostral putamen (right $r = -0.141$, $P = 0.554$ vs. left $r = -0.092$, $P = 0.701$; Fig. 3). In addition, neither the right nor the left dorsal rostral putamen was significantly associated with left-side motor symptom scores in L-naive patients (right $r = -0.067$, $P = 0.779$ vs. left $r = -0.046$, $P = 0.848$; see eFigure 2 in the Supporting Information), suggesting that activity of the dorsal rostral putamen did not correspond consistently with motor-symptom severity.

Discussion

The present study confirms previous reports regarding impaired acquisition and normal generalization in PD. The novel finding in our study in medication-naïve PD
patients indicated that impaired acquisition was only detected in L-naive patients, whereas R-naive patients learned equally well as healthy controls. Results from rs-fMRI results indicated that there was a correlation between the impairment in acquisition and the activity in the dorsal rostral putamen, but not with motor-symptom severity. Dysfunction of the right dorsal rostral putamen was associated with acquisition deficit in L-naive patients, which confirms the earlier reports that the dorsal rostral putamen is mainly involved in cognitive function rather than in motor function.31-33

**Dorsal Rostral Putamen Resting-State Activity Correlated With Performance in Acquisition Not Motor Symptom Severity in PD**

In the present study, impairment in acquisition was inversely correlated with ReHo activity in the right dorsal rostral putamen, identifying that the dorsal rostral putamen could be an important region involved in feedback-based associative learning. The hypothesis of ReHo measurement postulates that significant brain activities would more likely occur in clusters rather than in a single voxel. ReHo measures the functional coherence of a given voxel with its nearest neighbors and can be used to evaluate resting-state brain activities.25 Wu and colleagues reported that ReHo, which was negatively correlated with UPDRS, decreased in extensive motor-function–related brain regions, including the putamen, thalamus, and supplementary motor area, etc., in off-medication PD patients compared to NCs. Administration of levodopa relatively normalized ReHo.34 Thus, changes in ReHo can happen secondary to dopamine deficiency and can be related to the motor symptom severity of the disease. In the present study, decreased ReHo in the dorsal rostral putamen, which might also be secondary to dopamine deficiency, was associated with the impairment in acquisition learning, but not with motor-symptom severity. Decreased ReHo reflects asynchronous neural activity of the dorsal rostral putamen and might lead to impaired performance in associative learning.

The putamen was classically regarded as a motor-related structure. However, recent studies have revealed that the putamen’s subdivisions were involved in comprehensive connectivity with motor, cognitive, and emotional function.35-37 For example, caudal putamen exhibited coactivation with primary sensorimotor cortex, caudal supplementary motor cortices, and anterior cerebellum, demonstrating its role in motor function.31,38 The rostral putamen had connectivity with dorsolateral prefrontal cortex (DLPFC), rostral anterior cingulate cortex, and posterior parietal cortex, suggesting its participation in higher-level cognitive functions.31,32 Moreover, the rostral putamen combined with most of the head of the caudate, referred to as associative striatum,31 played a dominant role in instrumental learning.33,39 The dorsal striatum was involved in both motor function and associative cognition and has been implicated in maintaining information about reward outcomes and consequences.40,41 Our results were consistent with previous studies, but more specifically, the dorsal rostral putamen was identified as the region closely related to feedback-based associative learning.

In our study, no correlation was found between the dorsal rostral putamen and severity of motor symptoms, which further substantiated that the dorsal rostral putamen was mainly associated with cognitive function rather than motor function. ReHo in both sides of the putamen was associated with acquisition errors in L-naive, but not in R-naive, patients. However, in the scatter plot of Figure 2D, there was no significant ReHo activity change in the left dorsal rostral putamen of L-naive patients. Thus, this inverse correlation between acquisition errors and ReHo activity of the left dorsal rostral putamen does not have much clinical significance in those early-stage L-naive PD patients. But we believe, with the disease progression, ReHo activity of the left dorsal rostral putamen will decrease and finally lead to associative learning impairment in R-naive patients. This suggests a greater role for the dorsal rostral putamen in associative learning in left-onset, rather than right-onset, patients and may have implications for understanding of disease progression in relation to motor-symptom laterality.

**Right and Left Dorsal Rostral Putamen Might Function Differently Following Dopaminergic Denervation**

ReHo activity of the right dorsal rostral putamen was inversely correlated with the mean number of errors in acquisition in L-naive. R-naive, with intact function of the dorsal rostral putamen, performed equally well to NCs in acquisition. The possible reason for different acquisition performance between...
L-naive and R-naive could be that the left and the right dorsal rostral putamen might function differently following dopaminergic denervation. Generally speaking, L-naive had more dopaminergic neuronal loss in the right substantia nigra (SN), resulting in more severely reduced dopamine release in the right striatum. The reverse was true in R-naive patients. Based on the fact that L-naive and R-naive patients were well matched in UPDRS-III scores in our study, we assumed that the degree of dopaminergic denervation contralateral to the onset side should be similar in the two groups. However, our fMRI results showed reduced neural activity in the right dorsal rostral putamen in L-naive patients, whereas the activity of the left dorsal rostral putamen in R-naive was similar to that of controls. This indicates that the right and left dorsal rostral putamen might function differently after PD-related dopaminergic loss. The right dorsal rostral putamen might be more sensitive to dopamine depletion and finally led to impaired feedback-dependent associative learning function.

There is no pathological or anatomical evidence to explain why the right and left dorsal rostral putamen function differently following dopaminergic denervation. However, recent studies reported asymmetric dopamine signaling in the striatal and frontal regions caused by genetic variants of dopamine transporter and dopamine D2 receptor and left-right asymmetric dopamine D2/3 receptor availability in the dorsal putamen in healthy population. Asymmetric dopamine receptor availability and asymmetric dopamine signaling might contribute to asymmetric functional changes to dopamine depletion between the right and left dorsal rostral putamen. Asymmetric or uneven function between the left and right striatum has been evidenced from 18F-dopa PET scan, where Tower of London scores correlated with activity in the right caudate nucleus. On the other hand, activity in the left putamen was related to verbal working memory task. A task-related fMRI study of healthy subjects observed activity in the right striatum and right inferior prefrontal cortices during earlier phases of probability learning. A study by Postuma and colleagues provided stronger evidence for asymmetric function of the putamen by analyzing the functional connectivity between the cortex and striatum in a meta-analysis of 126 published functional neuroimaging studies. The right and left putamen coactivated in conjunction with different brain regions with different laterality. Briefly, the left putamen showed a large ipsilateral coactivation essentially with the entire primary motor and somatosensory cortex, whereas the right putamen showed a peak coactivation with the right DLPC. These functional connectivity pictures delineated by the above study fully illustrated asymmetric function of the right and left putamen. Therefore, the left and right dorsal rostral putamen might coactivate with different regions and function unevenly and differently in feedback-based associative learning. Early-stage R-naive patients would be spared in acquisition as long as the right dorsal rostral putamen was not affected. But with the progression of the disease, deficits in acquisition of learning will appear because both sides of the dorsal rostral putamen will be affected.

Our results also showed that both retrieval and generalization function were normal in PD. It has been reported that PD might exhibit impaired retrieval function, which could benefit substantially from cueing. Normal retrieval function in our study might be attributed to the fact that these early-stage PD patients had relatively normal executive function at that point, or because the faces shown on the computer screen acted as efficient cueing to help patients recall what they had learned. Normal generalization in our study indicated that in the early stage of PD, asymmetric dopamine depletion did not affect MTL function and patients had normal cognitive flexibility to use learned knowledge in a new context, which is consistent with the previous studies.

**Limitations and Conclusions**

Although the relationship between asymmetric motor symptoms and laterality of dopaminergic depletion is well founded, there are a considerable proportion of PD patients who have ipsilateral or bilateral deficits of dopaminergic function. Erro and colleagues analyzed a data set of 46 [123I] FP-CIT scans of PD patients and reported a prevalence of 4.3% of scans with predominant ipsilateral dopaminergic deficit. The limitation in this study is that severity of motor symptoms, instead of neuroimaging, was used as the indicator for the extent of relative dopamine depletion between the hemispheres. In a study by Kaasinen, MAI and dopamine transporter binding asymmetry index showed good accord with each other in both right-handed and left-handed PD patients, which provided evidence that the MAI could be used as an indicator for asymmetry evaluation. Future studies should apply neuroimaging to directly measure dopaminergic asymmetry and analyze its associations with associative learning.

In conclusion, our study showed that motor-symptom laterality could affect feedback-based associative learning in L-naive PD patients. We conjecture that dysfunction of the right dorsal rostral putamen in L-naive, but not in R-naive, patients might be a rationale to explain why L-naive patients performed worse than R-naive patients in acquisition. Left and right dorsal rostral putamen might function differently or respond differently to dopamine depletion, which needs further exploration.
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Supporting Data

Additional Supporting Information may be found in the online version of this article.