

Motor-symptom Laterality Affects Acquisition in Parkinson's disease: a Cognitive and fMRI study

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1 **Title Page**2 **Motor-symptom Laterality Affects Acquisition in Parkinson's disease: a**3 **Cognitive and fMRI study**

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60 **Abstract**

61 **Objective:** Asymmetric onset of motor symptoms in PD can affect cognitive function.

62 We examined whether motor-symptom laterality could affect feedback-based
63 associative learning and explored its underlying neural mechanism by fMRI in PD
64 patients.

65
66 **Methods:** We recruited 63 early-stage medication-naïve PD patients (29 left-onset
67 medication-naïve patients, 34 right-onset medication-naïve patients) and 38 matched
68 normal controls. Subjects completed an acquired equivalence task (including
69 acquisition, retention and generalization) and resting-state fMRI scans. Learning
70 accuracy and response time in each phase of the task was recorded for behavioral
71 measures. Regional homogeneity was used to analyze resting-state fMRI data, with
72 regional homogeneity lateralization to evaluate hemispheric functional asymmetry in
73 the striatum.

74
75 **Results:** Left-onset patients made significantly more errors in acquisition
76 (feedback-based associative learning) than right-onset patients and normal controls,
77 while right-onset patients performed as well as normal controls. There was no
78 significant difference among these three groups in the accuracy of either retention or
79 generalization phase. The three groups did not show significant differences in response
80 time. In the left-onset group, there was an inverse relationship between acquisition

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4 81 errors and regional homogeneity in the right dorsal rostral putamen. There were no
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6 82 significant regional homogeneity changes in either the left or the right dorsal rostral
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9 83 putamen in right-onset patients when compared to controls.
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14 85 **Conclusions:** Motor-symptom laterality could affect feedback-based associative
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17 86 learning in PD, with left-onset medication-naïve patients being selectively impaired.
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19 87 Dysfunction in the right dorsal rostral putamen may underlie the observed deficit in
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22 88 associative learning in patients with left-sided onset.
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For Peer Review

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103 Introduction

104 Parkinson's disease (PD) is the second most common neurodegenerative disorder,
105 characterized by resting tremor, rigidity, bradykinesia and postural instability. The
106 onset and progression of motor symptoms in PD are usually asymmetric, reflecting
107 asymmetric contralateral dopamine depletion in the basal ganglia.¹⁻⁴ Relationships
108 between cognitive performance and symptom asymmetry have been revealed that
109 left-onset PD patients performed worse on cognitive measures, such as spatial attention
110 and tasks of orientation and mental imagery, than right-onset PD patients.⁵⁻⁷ Cognitive
111 processes that are closely related with dopamine, such as cognitive flexibility and
112 motivation, showed different deficits between right-onset and left-onset PD patients.⁸
113 For example, left-onset PD patients with greater loss of dopamine in the right
114 hemisphere had impaired cognitive flexibility.^{5, 8}

115 Feedback-based associative learning, which involves learning through corrective
116 feedback provided on each trial, has been correlated to striatal dopamine release⁹ and
117 the function of the basal ganglia.^{10, 11} Previous studies have reported that
118 feedback-based associative learning was impaired in PD patients.^{12, 13} However, the
119 impairment in feedback-based learning in PD is not a universal finding, and many
120 factors could contribute to this variability. Wilkinson L et al. did not find a selective
121 impairment in PD in probabilistic feedback-based learning, but reported that there was
122 a significant correlation between disease severity and the impairment in
123 feedback-based learning.¹⁴ It has also been reported that off-medication PD patients

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4 124 learned stimulus-response associations equally well compared to healthy controls but
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6 125 learning was impaired by dopaminergic medication.¹³ Thus, in the underlying disease
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9 126 process, disease severity and dopaminergic medication might be all involved in
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11 127 modulating feedback-based learning. However, it is still not clear how the dopamine
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14 128 asymmetry affects feedback-based associative learning in PD patients.

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17 129 To control and minimize the effects of medication involvement and disease
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19 130 severity, we recruited early-stage medication-naïve right-handed PD patients including
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22 131 Left-onset medication-naïve patients (L-naïve) and Right-onset medication-naïve
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25 132 patients (R-naïve). We used a computer-based cognitive task of learning and
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28 133 generalization based on the acquired equivalence paradigm to test the effects of
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31 134 dopamine asymmetry on feedback-based associative learning. The acquired
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35 135 equivalence task, which includes tests of acquisition, retention and generalization, was
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38 136 repetitively used to evaluate feedback-based associative learning in patients with PD
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41 137 and other neurodegenerative disorders.^{10, 11} In the acquisition phase, learning through
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44 138 trial-by-trial feedback learning was shown to correlate to striatal function, while
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47 139 generalization without feedback was shown to correlate with hippocampal and medial
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50 140 temporal lobe (MTL) functionality.^{10, 11} Although striatal involvement in associative
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53 141 learning has been consistently reported in the previous task-based fMRI studies, such as
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56 142 caudate nucleus, amygdala and ventral striatum, the specific loci are not always the
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59 143 same.¹⁵⁻¹⁷ Thus, which subdivision of the basal ganglia is associated with
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144 feedback-based associative learning remains unclear, and resting-state fMRI (rs-fMRI)

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4 145 data were collected to explore the underlying neural mechanism of feedback-based
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6 146 learning.

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9 147 In the present study, we examined whether motor-symptom laterality could affect
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11 148 feedback-based associative learning and explored its underlying neural mechanism
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14 149 using rs-fMRI in PD patients.

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18 19 151 **Subjects and Methods**

20 152 **Subjects.** We recruited 63 right-handed, early stage (H-Y scores between 1 and 2),
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22 153 medication-naïve PD patients and 38 right-handed normal controls (NC) during
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25 154 2012-2015. Subjects in the PD and NC groups were matched for age, gender, education
26
27 155 and general cognitive status.¹⁸ According to the motor-symptom laterality, PD patients
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30 156 were divided into L-naïve (N = 29) and R-naïve (N = 34) subgroups. All participants
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32 157 were non-demented (Mini Mental State Examination, MMSE \geq 24) and scored less
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35 158 than 15 on the Beck Depression Inventory II (BDI-II).^{19, 20} Participants were also
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38 159 screened for history of cerebral trauma, cerebrovascular diseases, head surgery, severe
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41 160 sleep disorders, hyperthyroidism, insulin-dependent diabetes, psychiatric or
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44 161 neurological disorders, abuse of alcohol, tobacco use, use of hormonal contraceptives,
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47 162 anticholinergic drugs, or antidepressants. For subjects with PD, only patients with
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50 163 unilateral side of onset and asymmetrical motor symptoms were involved and diagnosis
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53 164 was confirmed by two movement disorder specialists according to the UK Brain Bank
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56 165 criteria for the diagnosis of PD.²¹ The side of onset was determined by medical history
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4 166 and physical examination. The severity of motor symptoms was evaluated by Unified
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6 167 Parkinson's Disease Rating Scale III (UPDRS-III).²² Motor asymmetry index (MAI)
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9 168 was calculated as (right side symptoms - left side symptoms) / (right side symptoms +
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12 169 left side symptoms).

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17 171 **Standard protocol approvals, registrations, and patient consents.** We received
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19 172 approval from the Ethics Committee of Ruijin Hospital affiliated with Shanghai Jiao
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21 173 Tong University School of Medicine. We obtained written informed consents from all
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24 174 patients and controls prior to their participation in the study.
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30 176 **Behavioral data acquisition and evaluation.** We used an Apple MacBook to run the
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32 177 Acquired Equivalence Task.¹¹ This task is composed of two phases: acquisition and
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35 178 transfer. In the acquisition phase, participants acquire associations of colored faces and
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38 179 fish through trial-by-trial feedback-based learning. Following this acquisition, the
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41 180 transfer phase includes two types of trials: tests of previously learned associations
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43 181 (retention) and tests of new associations that are presented without feedback
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46 182 (generalization). The mean number of incorrect choices and the mean response time in
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49 183 each phase was recorded for behavioral measures. For detailed procedure, please refer
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51 184 to eMethod 1 and eTable 1 in the Supplement.

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56 186 **MRI data acquisition and processing.** MRI scan was performed after the acquired
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4 187 equivalence test with an interval of 8.6 ± 1.5 days. A subgroup of 70 subjects (23
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6 188 L-naïve, 25 R-naïve and 22 NC) participated in resting-state fMRI on a 3.0 T GE
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9 189 Medical System scanner based on the subjects' willingness. During the scan, the
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12 190 subjects were asked to remain motionless and awake with their eyes closed. For each
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14 191 participant, 210 functional images were collected using echo planar imaging
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17 192 T2*-weighted sequence (repetition time = 2000 ms, echo time = 30 ms, flip angle = 90
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19 193 °, 33/35/37 slices, matrix = 64×64 , voxel size = $3.75 \times 3.75 \times 4 \text{ mm}^3$). Then the
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22 194 high-resolution, three-dimensional T1-weighted structural images (repetition time =
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24 195 5.78 ms, echo time = 1.77 ms, flip angle = 12° , 196 slices, matrix = 256×256 , voxel
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27 196 size = $1 \times 1 \times 1 \text{ mm}^3$) were acquired for registration and normalization of the functional
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30 197 images.

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33 198 After exclusion due to vascular diseases (1 L-naïve, 2 R-naïve and 3 NC) and
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35 199 obvious head motion (2 L-naïve and 2 R-naïve, with the translation and rotation head
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38 200 motion parameters larger than 2 mm or 2°), MRI data from 60 subjects (20 L-naïve, 21
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41 201 R-naïve, and 19 NC) qualified for analysis. MRI data were processed with Data
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43 202 Processing Assistant for Resting-State fMRI (DPARSF) programs.²³ Regional
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46 203 homogeneity (ReHo), as a commonly used method to analyze rs-fMRI data, was used
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49 204 with the rs-fMRI Data Analysis Toolkit (REST, <http://www.restfmri.net>) by calculating
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52 205 the Kendall's coefficient of concordance (KCC) of the time series of a given voxel with
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54 206 its 26 nearest neighboring voxels.^{24, 25} With the assumption that PD patients with
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57 207 unilateral onset of motor symptoms had asymmetric functional impairments in the
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4 208 brain, ReHo lateralization index was used to evaluate hemisphere asymmetry in neural
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6 209 activity as previously reported.^{26,27} Striatum subregions including the putamen, caudate
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9 210 and pallidum were chosen as regions of interest (ROIs). For detailed methods, please
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11 211 refer to eMethod 2 in the Supplement.
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18 213 **Statistical analysis.** The normality of clinical and demographic data distribution was
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20 214 checked by the Kolmogorov-Smirnov test. One-way ANOVA was used to compare the
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22 215 normally distributed continuous variables (age), and the chi-square test was employed
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24 216 to analyze categorical variables (gender). The continuous variables that were not
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27 217 normally distributed (education, disease duration, H-Y, BDI-II, MMSE, UPDRS-III
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29 218 score, MAI) were analyzed by Kruskal-Wallis test. Mix-model ANOVAs with group as
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31 219 between-subject factor and phase as within-subject factor were used to analyze the
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33 220 behavioral data. Post-hoc analysis was done using Tukey HSD test. In the correlational
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35 221 analysis, Spearman rho was calculated. The alpha level was set at 0.05. All P values less
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37 222 than the alpha level were considered statistically significant. SPSS version 17.0 (IBM,
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39 223 Chicago, IL, USA) was used for statistical analysis.
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46 224 For the fMRI data analysis, comparison of the hemispheric asymmetry among
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48 225 groups was performed using one-way ANCOVA. Age, gender, the mean frame-wise
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50 226 displacement (FD) corresponding to the temporal derivative of the head motion
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52 227 parameters, and mean gray matter (GM) volume of ROI were used as nuisance
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55 228 covariates.^{28, 29} Post-hoc analysis was performed within the significant regions. To
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4 229 control for family-wise error rates, Monte Carlo simulations were performed
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6 230 (3dClustSim; 10,000 iterations) using all brain voxels within the half-striatum ROI.³⁰
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9 231 The cluster threshold for a corrected alpha level of $P = 0.05$ was 27 voxels for
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11 232 ANCOVA and 7 voxels for post-hoc t-test, respectively.
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17 234 **Results**

19 235 **Clinical and demographic characteristics of subjects**

22 236 The clinical and demographic characteristics of subjects are presented in Table 1. All
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24 237 the groups were matched for age, gender, education, MMSE, and BDI-II ($P \geq 0.190$).
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27 238 There were no significant differences in disease duration, H-Y score, and UPDRS-III
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30 239 scores (including tremor, rigidity, bradykinesia sub-scores and total scores) between the
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32 240 L-naïve and R-naïve PD groups ($P \geq 0.104$). MAI was calculated as (right side
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35 241 symptoms - left side symptoms) / (right side symptoms + left side symptoms). The
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38 242 mean value of MAI for L-naïve and R-naïve groups were -0.9 (0.2) vs. 0.9 (0.2)
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41 243 respectively, indicating that motor-symptom asymmetry was also matched. In addition,
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43 244 subjects participating in the MRI examination were also matched across the three
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46 245 groups (see eTable 2 in the Supplement).
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51 247 **Behavioral performance**

53 248 **Acquisition was impaired in L-naïve but normal in R-naïve patients**

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56 249 Mix-model ANOVAs showed that both group [$F(2, 294) = 7.228, P = 0.001$] and phase
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4 250 [F (2, 294) = 52.680, P < 0.001] had significant effects on accuracy. The interaction
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6 251 between group and phase was at a trend-level [F (4, 294) = 2.127, P = 0.077]. Fig.1A
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8 252 indicated that the group effect is primarily driven by the acquisition phase. Post-hoc
9
10 253 analysis showed that accuracy was significantly different among L-naïve, R-naïve and
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12 254 NC. L-naïve patients made significantly more errors than R-naïve patients (P = 0.003)
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14 255 and NC (P = 0.002), while R-naïve patients performed as well as NC (P = 0.996) (Fig.
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16 256 1A). There were no significant differences between groups in retention or
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18 257 generalization phase, indicating that retrieval function and generalization were
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20 258 preserved in both L-naïve and R-naïve patients (retention, P = 0.201 vs. generalization,
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22 259 P = 0.331) (Fig. 1A). Thus, L-naïve patients, rather than R-naïve patients, were
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24 260 selectively impaired in feedback-based associative learning, indicating a potential
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26 261 effect of asymmetric dopamine depletion on associative learning.

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28 262 Phase had significant effect on the response time [F (2, 294) = 12.564, P < 0.001].
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30 263 However, there was neither an effect of group [F (2, 294) = 0.733, P = 0.481] nor an
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32 264 interaction between group and phase [F (4, 294) = 0.782, P = 0.538] (Fig. 1B).
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44 266 **Functional MRI results**

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47 267 **Dorsal rostral putamen was impaired in the right side in L-naïve but intact in**

48 268 **R-naïve patients**

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51 269 One-way ANCOVA analysis showed that L-naïve, R-naïve and NC groups were
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53 270 significantly different in ReHo lateralization in the dorsal rostral putamen (voxel level
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4 271 $P < 0.05$, cluster size > 27 voxels, corresponding to cluster-level corrected $P < 0.05$)
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6 272 (Fig. 2A and Table 2). Post-hoc analysis showed that L-naïve patients had higher ReHo
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8 273 lateralization in the dorsal rostral putamen compared with NC group (Fig. 2B and Table
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10 274 2) and R-naïve group (Fig. 2C and Table 2) (voxel level $P < 0.05$, cluster size > 7
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12 275 voxels, corresponding to cluster-level corrected $P < 0.05$). Further graphing using a
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14 276 scatterplot in Fig. 2D indicated that higher ReHo lateralization in L-naïve patients was
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16 277 due to decreased ReHo activity in the right side of the dorsal rostral putamen. There
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18 278 was no significant difference between the left and the right dorsal rostral putamen in
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20 279 R-naïve patients, suggesting neural function of the left dorsal rostral putamen in
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22 280 R-naïve patients was relatively preserved in early stage PD. Our results showed that the
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24 281 right dorsal rostral putamen of L-naïve patients had reduced neural activity compared
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26 282 with the left dorsal rostral putamen in R-naïve patients, indicating that the right side of
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28 283 dorsal rostral putamen might be more sensitive to dopamine depletion than the left side.
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285 **Dorsal rostral putamen was correlated with feedback-based associative learning**

286 Correlational analysis in the L-naïve group showed that the mean number of errors in
287 acquisition was inversely correlated with ReHo activity of the right dorsal rostral
288 putamen ($r = -0.535$, $P = 0.015$) (Fig. 2E). This suggests that reduced activity in the
289 right dorsal rostral putamen might be associated with poor feedback-based associative
290 learning in L-naïve patients. In addition, poor performance in acquisition was also
291 inversely correlated with ReHo activity of the left dorsal rostral putamen in L-naïve

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4 292 patients ($r = -0.479$, $P = 0.033$) (Fig. 2E). However, there was no significant ReHo
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6 293 activity change in the left dorsal rostral putamen of L-naïve patients. Thus, this inverse
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9 294 correlation between acquisition and ReHo activity of the left dorsal rostral putamen has
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11 295 no clinical significance in those early-stage L-naïve PD patients.

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14 296 Since only 60 cases (20 L-naïve, 21 R-naïve and 19 NC) underwent resting-state
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16 297 fMRI examination based on subjects' willingness, performance in the acquired
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18 298 equivalence task was also analyzed in these 60 cases. Results were consistent with the
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20 299 earlier results from all 101 subjects (See eResult 1 and eFigure 1 in the Supplement).
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24 300 Our results showed that the dorsal rostral putamen activity might be specifically
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26 301 implicated in acquisition learning.
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33 303 **Function of the dorsal rostral putamen did not correlate with the severity of**
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35 304 **motor symptoms**

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38 305 In order to test whether the dorsal rostral putamen was associated with motor function,
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40 306 correlation analysis was done between UPDRS-III scores and ReHo activity in the
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42 307 dorsal rostral putamen in L-naïve patients. No significant correlation was found
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44 308 between UPDRS-III score and neural activity of either the right or the left dorsal rostral
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46 309 putamen (right $r = -0.141$, $P = 0.554$ vs. left $r = -0.092$, $P = 0.701$) (Fig. 3). In addition,
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48 310 neither the right nor the left dorsal rostral putamen was significantly associated with
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50 311 left-side motor symptom scores in L-naïve patients (right $r = -0.067$, $P = 0.779$ vs. left r
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52 312 $= -0.046$, $P = 0.848$) (see eFigure 2 in the Supplement), suggesting that activity of the
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4 313 dorsal rostral putamen did not correspond consistently with motor-symptom severity.
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9 315 **Discussion**

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11 316 The present study confirms previous reports regarding impaired acquisition and normal
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14 317 generalization in PD. The novel finding in our study in medication-naïve PD patients
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17 318 indicated that impaired acquisition was only detected in L-naïve patients, while
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20 319 R-naïve patients learned equally well as healthy controls. Results from rs-fMRI results
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22 320 indicated that there was a correlation between the impairment in acquisition and the
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25 321 activity in the dorsal rostral putamen, but not with motor-symptom severity.
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27 322 Dysfunction of the right dorsal rostral putamen was associated with acquisition deficit
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30 323 in L-naïve patients, which confirms the earlier reports that the dorsal rostral putamen is
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32 324 mainly involved in cognitive function rather than in motor function.³¹⁻³³
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38 326 **Dorsal rostral putamen resting-state activity correlated with performance in**
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40 327 **acquisition not motor symptom severity in Parkinson's disease**

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43 328 In the present study, the impairment in acquisition was inversely correlated with ReHo
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46 329 activity in the right dorsal rostral putamen, identifying that the dorsal rostral putamen
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49 330 could be an important region involved in feedback-based associative learning. The
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51 331 hypothesis of ReHo measurement postulates that significant brain activities would
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53 332 more likely occur in clusters rather than in a single voxel. ReHo measures the
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56 333 functional coherence of a given voxel with its nearest neighbors and can be used to
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4 334 evaluate resting-state brain activities.²⁵ Wu T et al. reported that ReHo, which was
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6 335 negatively correlated with UPDRS, decreased in extensive motor function-related brain
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9 336 regions, including the putamen, thalamus, and supplementary motor area, etc. in
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11 337 off-medication PD patients compared with normal controls. Administration of
12
13 338 levodopa relatively normalized ReHo.³⁴ Thus, changes in ReHo can happen secondary
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17 339 to dopamine deficiency, and can be related to the motor symptom severity of the disease.
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19 340 In the present study, decreased ReHo in the dorsal rostral putamen, which might also be
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21 341 secondary to dopamine deficiency, was associated with the impairment in acquisition
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23 342 learning, but not with motor-symptom severity. Decreased ReHo reflects asynchronous
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25 343 neural activity of the dorsal rostral putamen and might lead to impaired performance in
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27 344 associative learning.
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33 345 The putamen was classically regarded as motor-related structure. However, recent
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35 346 studies have revealed that the putamen's subdivisions were involved in comprehensive
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37 347 connectivity with motor, cognitive and emotional function.³⁵⁻³⁷ For example, caudal
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39 348 putamen exhibited co-activation with primary sensorimotor cortex, caudal
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41 349 supplementary motor cortices, and anterior cerebellum, demonstrating its role in motor
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43 350 function;^{31, 38} The rostral putamen had connectivity with dorsolateral prefrontal cortex
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45 351 (DLPFC), rostral anterior cingulate cortex and posterior parietal cortex, suggesting its
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47 352 participation in higher-level cognitive functions.^{31, 32} Moreover, the rostral putamen
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49 353 combined with most of the head of the caudate, referred to as associative striatum,³¹
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51 354 played a dominant role in instrumental learning.^{33, 39} The dorsal striatum was involved
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4 355 in both motor function and associative cognition, and has been implicated in
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6 356 maintaining information about reward outcomes and consequences.^{40, 41} Our results
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9 357 were consistent with previous studies, but more specifically, the dorsal rostral putamen
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11 358 was identified as the region closely related to feedback-based associative learning.

14 359 In our study, no correlation was found between the dorsal rostral putamen and the
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16
17 360 severity of motor symptoms, which further substantiated that the dorsal rostral putamen
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19 361 was mainly associated with cognitive function rather than motor function. ReHo in both
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21 362 sides of the putamen was associated with acquisition errors in L-naïve, but not in
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24 363 R-naïve patients. However, in the scatterplot of Figure 2D, there was no significant
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27 364 ReHo activity change in the left dorsal rostral putamen of L-naïve patients. Thus, this
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30 365 inverse correlation between acquisition errors and ReHo activity of the left dorsal
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32
33 366 rostral putamen does not have much clinical significance in those early-stage L-naïve
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35 367 PD patients. But we believe, with the disease progression, ReHo activity of the left
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38 368 dorsal rostral putamen will decrease and finally lead to associative learning impairment
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41 369 in R-naïve patients. This suggests a greater role for the dorsal rostral putamen in
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44 370 associative learning in left-onset rather than right-onset patients and may have
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47 371 implications for understanding of disease progression in relation to motor-symptom
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49 372 laterality.

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53 374 **Right and left dorsal rostral putamen might function differently following**
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56 375 **dopaminergic denervation**
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4 376 ReHo activity of the right dorsal rostral putamen was inversely correlated with the
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6 377 mean number of errors in acquisition in L-naïve. R-naïve, with intact function of the
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9 378 dorsal rostral putamen, performed equally well to NC in acquisition. The possible
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11 379 reason for different acquisition performance between L-naïve and R-naïve could be that
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14 380 the left and the right dorsal rostral putamen might function differently following
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17 381 dopaminergic denervation. Generally speaking, L-naïve had more dopaminergic
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19 382 neuronal loss in the right substantia nigra,² resulting in more severely reduced
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22 383 dopamine release in the right striatum.³ The reverse was true in R-naïve patients. Based
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25 384 on the fact that L-naïve and R-naïve patients were well matched in UPDRS-III scores in
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27 385 our study, we assumed that the degree of dopaminergic denervation contralateral to the
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30 386 onset side should be similar in the two groups. However, our fMRI results showed
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33 387 reduced neural activity in the right dorsal rostral putamen in L-naïve patients, while the
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35 388 activity of the left dorsal rostral putamen in R-naïve was similar to that of controls. This
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38 389 indicates that the right and the left dorsal rostral putamen might function differently
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41 390 after PD-related dopaminergic loss. The right dorsal rostral putamen might be more
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43 391 sensitive to dopamine depletion and finally led to impaired feedback-dependent
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46 392 associative learning function.

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48 393 There is no pathological or anatomical evidence to explain why the right and the
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51 394 left dorsal rostral putamen function differently following dopaminergic denervation.
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54 395 However, recent studies reported asymmetric dopamine signaling in the striatal and
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56 396 frontal regions caused by genetic variants of dopamine transporter and dopamine D2

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4 397 receptor,⁴² and left-right asymmetric dopamine D2/3 receptor availability in the
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6 398 dorsal putamen in healthy population.⁴³ Asymmetric dopamine receptors availability
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9 399 and asymmetric dopamine signaling might contribute to asymmetric functional
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11 400 changes to dopamine depletion between the right and the left dorsal rostral putamen.
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13 401 Asymmetric or uneven function between the left and the right striatum has been
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16 402 evidenced from ¹⁸F-dopa PET-scan, where tower of London scores correlated with
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19 403 activity in the right caudate nucleus. On the other hand, activity in the left putamen was
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22 404 related to verbal working memory task.⁴⁴ A task-related fMRI study of healthy subjects
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25 405 observed activity in the right striatum and the right inferior prefrontal cortexes during
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27 406 earlier phases of probability learning.⁴⁵ A study by Postuma et al. provided stronger
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30 407 evidence for asymmetric function of the putamen by analyzing the functional
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33 408 connectivity between the cortex and the striatum in a meta-analysis of 126 published
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35 409 functional neuroimaging studies.³⁷ The right and the left putamen co-activated in
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38 410 conjunction with different brain regions with different laterality. Briefly, the left
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41 411 putamen showed a large ipsilateral coactivation essentially with the entire primary
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43 412 motor and somatosensory cortex, while the right putamen showed a peak co-activation
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46 413 with the right DLPFC. These functional connectivity pictures delineated by the above
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49 414 study fully illustrated asymmetric function of the right and the left putamen. Therefore,
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51 415 the left and the right dorsal rostral putamen might co-activate with different regions and
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53 416 function unevenly and differently in feedback-based associative learning. Early-stage
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56 417 R-naïve patients would be spared in acquisition as long as the right dorsal rostral
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4 418 putamen was not affected. But with the progression of the disease, deficits in
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6 419 acquisition of learning will appear because both sides of the dorsal rostral putamen will
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9 420 be affected.

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11 421 Our results also showed that both retrieval and generalization function were
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14 422 normal in PD. It has been reported that PD might exhibit impaired retrieval function,
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17 423 which could benefit substantially from cueing.⁴⁶ Normal retrieval function in our study
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20 424 might be due to the fact that these early-stage PD patients had relatively normal
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22 425 executive function at that point, or because the faces shown on the computer screen
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25 426 acted as efficient cueing to help patients recall what they had learned. Normal
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27 427 generalization in our study indicated that in the early stage of PD, asymmetric
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30 428 dopamine depletion didn't affect MTL function and patients had normal cognitive
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33 429 flexibility to use learned knowledge in a new context, which is consistent with the
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35 430 previous studies.^{10, 11, 47}

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40 432 **Limitations and Conclusions**

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43 433 Although the relationship between asymmetric motor symptoms and laterality of
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45
46 434 dopaminergic depletion is well founded,^{3, 48} there are a considerable proportion of PD
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49 435 patients who have ipsilateral or bilateral deficits of dopaminergic function. Erro R et al.
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51 436 analyzed a dataset of 46 [¹²³I] FP-CIT scans of PD patients and reported a prevalence of
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54 437 4.3% of scans with predominant ipsilateral dopaminergic deficit.⁴⁹ The limitation in
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56 438 this study is that severity of motor symptoms instead of neuroimaging was used as the

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4 439 indicator for the extent of relative dopamine depletion between the hemispheres. In a
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6 440 study by Kaasinen V, motor asymmetry index and DAT binding asymmetry index
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9 441 showed good accordance with each other in both right-handed and left-handed PD
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11 442 patients, which provided evidence that motor asymmetry index could be used as an
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13 443 indicator for asymmetry evaluation.⁵⁰ Future studies should apply neuroimaging to
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15 444 directly measure dopaminergic asymmetry and analyze its associations with associative
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17 445 learning.

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22 446 In conclusion, our study showed that motor-symptom laterality could affect
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24 447 feedback-based associative learning in L-naïve PD patients. We conjecture that
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26 448 dysfunction of the right dorsal rostral putamen in L-naïve but not in R-naïve patients
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28 449 might be a rationale to explain why L-naïve patients performed worse than R-naïve
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30 450 patients in acquisition. Left and right dorsal rostral putamen might function differently
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32 451 or respond differently to dopamine depletion, which needs further exploration.
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40 **Authors' Roles:**

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43 454 Dr. Huang, Dr. Tan and Dr. Chen had full access to all the data in the study and take
44
45 455 responsibility for the integrity of the data and the accuracy of the data analysis. PH:
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47 456 provision of study material, collection and/or assembly of data, data analysis and
48
49 457 interpretation, manuscript writing, final approval of manuscript. YYT: conception and
50
51 458 design, subjects' recruitment and execution, administrative support, data analysis and
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53 459 interpretation, manuscript writing, final approval of manuscript. DL, YZ: fMRI data
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4 460 analysis and interpretation, revised manuscript writing, final approval of manuscript.
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6 461 MMH, EL, MAG: learning data analysis and interpretation, manuscript editing, final
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9 462 approval of manuscript. YW: subjects' recruitment and execution, final approval of
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11 463 manuscript. SC: conception and design, subjects' recruitment and execution,
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13
14 464 administrative support, manuscript writing, final approval of manuscript.
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37
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45 476 **Conflict of interests:** None.
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4 614 **Figure legends**

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6 615 **Fig.1 Learning performance on the Acquired Equivalence Task.**

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9 616 (A) L-naïve patients made significantly more errors than R-naïve patients and NC in the
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11 617 acquisition phase. R-naïve patients performed as well as NC in acquisition. No
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13 618 significant difference in accuracy was found either in the retention phase or in the
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15 619 generalization phase among three groups.

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19 620 (B) There was no significant difference in response time in the acquisition phase,
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21 621 retention phase and generalization phase among L-naïve, R-naïve and NC groups.

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24 622 L-naïve = left-onset medication-naïve patients with Parkinson's disease; R-naïve =
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26 623 right-onset medication-naïve patients with Parkinson's disease; NC = normal controls.

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32 625 **Fig. 2 Difference in neural activity asymmetry and its correlation with learning.**

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35 626 (A) The ANCOVA analysis among L-naïve, R-naïve and NC groups in the ReHo
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37 627 lateralization within the striatum (the left striatum was shown). A significant difference
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39 628 was found in the dorsal rostral putamen.

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43 629 (B) Post-hoc analysis between L-naïve and NC group. Increased ReHo lateralization
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45 630 was detected in the dorsal rostral putamen in L-naïve group.

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48 631 (C) Post-hoc analysis between L-naïve and R-naïve group. Increased ReHo
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50 632 lateralization was detected in the dorsal rostral putamen in L-naïve group compared to
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52 633 R-naïve group.

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55 634 (D) Scatter plot of ReHo activity in bilateral dorsal rostral putamen among groups. The
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4 635 horizontal line represents the mean level of ReHo. Group differences in ReHo
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6 636 lateralization were due to the decrease of ReHo in the right dorsal rostral putamen of
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9 637 L-naïve group.

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11 638 **(E)** The mean number of errors in acquisition was inversely correlated with the ReHo
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13 639 activity both of the right dorsal rostral putamen and the left dorsal rostral putamen in
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16 640 L-naïve group.

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19 641 L-naïve = left-onset medication-naïve patients with Parkinson's disease; R-naïve =
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21 642 right-onset medication-naïve patients with Parkinson's disease; NC = normal controls;
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23 643 ReHo = regional homogeneity.
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30 645 **Fig. 3 Correlation between ReHo activity of the dorsal rostral putamen and**

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32 646 **UPDRS-III score.** No significant correlation was found between UPDRS-III score and
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34 647 neural activity of either the right or the left dorsal rostral putamen in L-naïve patients.

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37 648 L-naïve = left-onset medication-naïve patients with Parkinson's disease; ReHo =
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Tables

Table 1 Clinical and demographic characteristics of medication-naïve Parkinson's patients and normal controls

	L-Naïve	R-Naïve	NC	P Value
	(n = 29)	(n = 34)	(n = 38)	
Age (y)	57.3 (8.6)	59.6 (9.2)	58.5 (8.5)	0.580
Gender (M/F)	16 / 13	19 / 15	14 / 24	0.190
Education (y)	11.6 (3.4)	12.9 (3.3)	12.6 (2.6)	0.288
Disease duration (y)	2.7 (2.2)	2.2 (1.4)	-	0.799
UPDRS-III				
Tremor	1.9 (1.9)	1.6 (1.7)	-	0.545
Rigidity	3.6 (2.2)	3.9 (1.6)	-	0.203
Bradykinesia	5.0 (3.6)	4.1 (2.0)	-	0.204
Left side symptoms	9.2 (4.0)	0.6 (1.2)	-	-
Right side symptoms	0.8 (2.7)	8.4 (2.8)	-	-
Dominant side symptoms	9.2 (4.0)	8.4 (2.8)	-	0.565
Non-dominant side symptoms	0.8 (2.7)	0.6 (1.2)	-	0.415

Total score	14.9 (8.5)	13.2 (5.6)	-	0.391
Motor asymmetry index	-0.9 (0.2)	0.9 (0.2)	-	-
H-Y score	1.2 (0.3)	1.4 (0.4)	-	0.104
BDI-II	5.2 (3.0)	5.6 (3.3)	5.0 (2.7)	0.740
MMSE	28.8 (1.0)	28.7 (1.4)	29.0 (1.2)	0.363

Data are mean (standard deviation). L-naïve = left-onset medication-naïve patients with Parkinson’s disease; R-naïve = right-onset medication-naïve patients with Parkinson’s disease; NC = normal controls; UPDRS-III = Unified Parkinson’s Disease Rating Scale III; Motor asymmetry index = (right side symptoms - left side symptoms) / (right side symptoms + left side symptoms); H-Y = Hoehn and Yahr; BDI-II = Beck Depression Inventory II; MMSE = Mini Mental State Examination.

Table 2 Differences in the asymmetry of ReHo in the striatum

Brain Regions	Voxels	Peak MNI coordinates			Maximum F/T Values
		X	Y	Z	
ANCOVA					
Dorsal rostral putamen	27	-24	12	-3	5.229 (F)
L-naïve > NC					
Dorsal rostral putamen	22	-24	12	-3	2.811 (T)
L-naïve > R-Naïve					
Dorsal rostral putamen	7	-12	12	-9	3.141 (T)

L-naïve = left-onset medication-naïve patients with Parkinson's disease; R-naïve = right-onset medication-naïve patients with Parkinson's disease; NC = normal controls; ReHo = regional homogeneity.

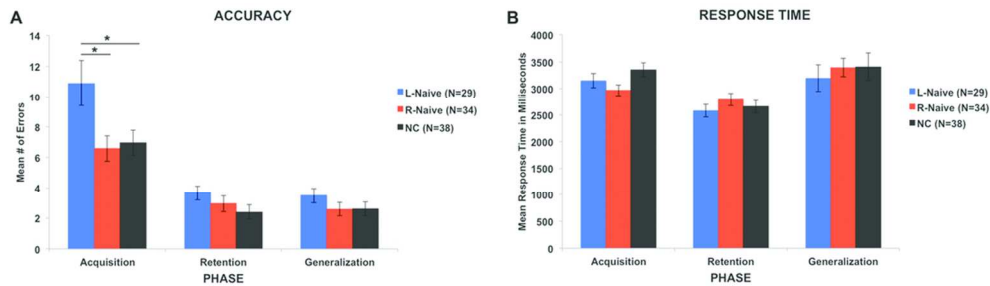


Fig.1 Learning performance on the Acquired Equivalence Task.

(A) L-naïve patients made significantly more errors than R-naïve patients and NC in the acquisition phase. R-naïve patients performed as well as NC in acquisition. No significant difference in accuracy was found either in the retention phase or in the generalization phase among three groups.

(B) There was no significant difference in response time in the acquisition phase, retention phase and generalization phase among L-naïve, R-naïve and NC groups.

L-naïve = left-onset medication-naïve patients with Parkinson’s disease; R-naïve = right-onset medication-naïve patients with Parkinson’s disease; NC = normal controls.

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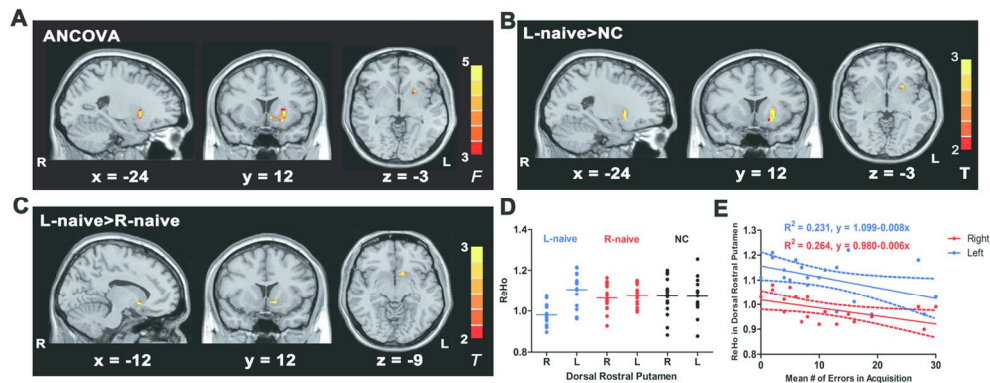


Fig. 2 Difference in neural activity asymmetry and its correlation with learning.

(A) The ANCOVA analysis among L-naïve, R-naïve and NC groups in the ReHo lateralization within the striatum (the left striatum was shown). A significant difference was found in the dorsal rostral putamen.

(B) Post-hoc analysis between L-naïve and NC group. Increased ReHo lateralization was detected in the dorsal rostral putamen in L-naïve group.

(C) Post-hoc analysis between L-naïve and R-naïve group. Increased ReHo lateralization was detected in the dorsal rostral putamen in L-naïve group compared to R-naïve group.

(D) Scatter plot of ReHo activity in bilateral dorsal rostral putamen among groups. The horizontal line represents the mean level of ReHo. Group differences in ReHo lateralization were due to the decrease of ReHo in the right dorsal rostral putamen of L-naïve group.

(E) The mean number of errors in acquisition was inversely correlated with the ReHo activity both of the right dorsal rostral putamen and the left dorsal rostral putamen in L-naïve group.

L-naïve = left-onset medication-naïve patients with Parkinson's disease; R-naïve = right-onset medication-naïve patients with Parkinson's disease; NC = normal controls; ReHo = regional homogeneity.

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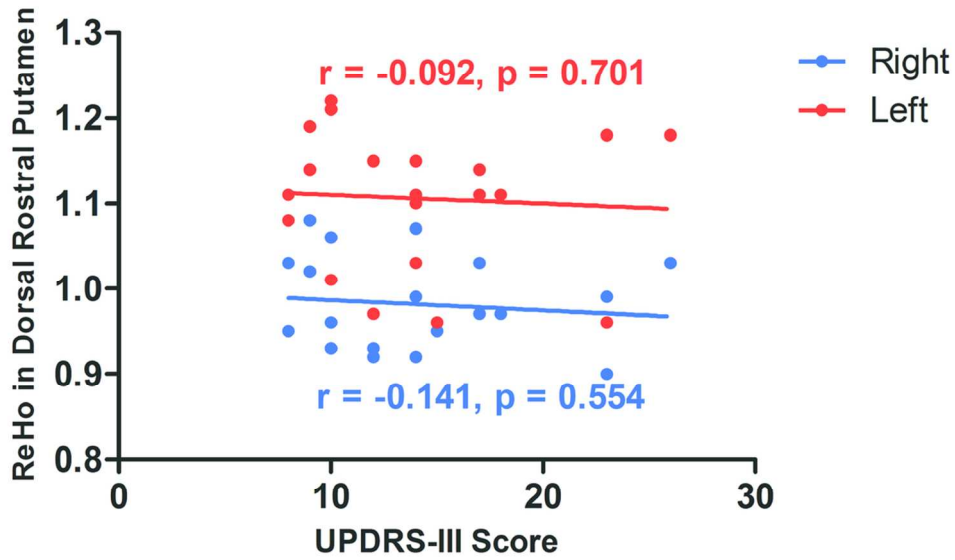


Fig. 3 Correlation between ReHo activity of the dorsal rostral putamen and UPDRS-III score. No significant correlation was found between UPDRS-III score and neural activity of either the right or the left dorsal rostral putamen in L-naïve patients. L-naïve = left-onset medication-naïve patients with Parkinson’s disease; ReHo = regional homogeneity.

49x30mm (600 x 600 DPI)

Review

Supplementary Online Content

eMethod 1 - Procedure of Acquired Equivalence Task

eMethod 2 - MRI data processing

eResult 1 - Behavioral performance of MRI subjects

eTable 1 - Acquired Equivalence Task

eTable 2 - Clinical and demographic characteristics of the MRI subjects

eFigure 1 - Learning performance of MRI subjects on the Acquired Equivalence Task

eFigure 2 - Correlation between ReHo activity of dorsal rostral putamen and left-side symptom scores

eReferences (e1-e8)

Supplemental Methods:

eMethod 1 Procedure of Acquired Equivalence Task

Stimuli

We used an Apple MacBook to run the acquired equivalence task.¹ Four drawings of faces (girl, boy, woman, man) were set as antecedent stimuli while the consequents were four drawings of colored fish (red, blue, purple, green). The girl and man had brown hair while the boy and woman wore yellow hair. So each antecedent stimulus shared one feature with another in “Age (adult vs. child), Gender (male vs. female), and Hair color (brown vs. yellow)”. For each participant, the antecedent (A1G1H1, A1G2H2, A2G1H2, A2G2H1) and consequent stimuli (X1, X2, Y1, Y2) were randomly assigned.

Acquisition phase

At the beginning of the test, instruction (Chinese Version) was presented on the screen as follows: “Welcome to the experiment. We will show you several drawings of people who have some pet fish. Remember that every person has his own pet fish, which may be different from others. Your task is to find the preference of each person. At the start, you will have to guess.” These words were read aloud to the subject by the tester and then acquisition phase started.

On each trial, participants were shown a face and two colored fish with the cue: “Which fish does this person prefer?” The left-right sequence of fish was randomized across each trial. Subjects must learn the association between face and fish according to the corrective feedback that was given after each choice.

The acquisition phase was composed of three stages, each had growing numbers of associations as shown in Table e-1. Since there were eight kinds of relationship between face and fish, stage 1 consisted of two associations and terminated after the subject had made four consecutive correct choices. Similarly, stage 2 and 3 that each included four and six associations ended after eight and twelve consecutive correct responses, respectively. However, the start of a new stage was not informed to the participant.

Transfer phase

The transfer phase followed the end of acquisition phase with instruction: “Good job!

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3 In the following phase of the experiment, you will use what you have learned. Correct
4 answers will not be given. But we will show you how many trials you got right at last.”

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7 In this part, forty-eight trials including thirty-six old associations (retention) that
8 had been trained during the acquisition phase and twelve new associations
9 (generalization) were tested for the examination of retrieval and learned equivalence.
10 The presence of new associations was not informed to the participant.
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13 Eventually, the mean number of incorrect choices and the mean response time in
14 each phase was recorded for behavioral measures.
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17 18 19 **eMethod 2 MRI data Processing**

20 MRI data were processed with Data Processing Assistant for Resting-State fMRI
21 (DPARSF) programs.² The first 10 frames were discarded and the remaining volumes
22 were slice-timing corrected. Then they were realigned to the first image to correct for
23 head motion. Individuals with the translation and rotation head motion parameters
24 larger than 2 mm or 2° were excluded. Then functional images were coregistered to the
25 corresponding T1 images. The coregistered T1 images were segmented using SPM8
26 software (<http://www.fil.ion.ucl.ac.uk/spm>), which takes more information outside the
27 brain into account, then the Diffeomorphic Anatomical Registration Through
28 Exponentiated Lie algebra (DARTEL) tool was employed to spatially normalize both
29 the T1 images and the functional images into MNI space. Finally, functional images
30 were resampled to $3 \times 3 \times 3$ mm³ voxels.³
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39 ReHo analysis was performed with the rs-fMRI Data Analysis Toolkit (REST,
40 <http://www.restfmri.net>).⁴ It is based on the hypothesis that the time courses of
41 neighboring voxels are similar with each other and such local synchronization can be
42 modulated by different states.⁵ First, the linear trend was removed and each voxel was
43 temporally band-pass filtered (0.01-0.08 Hz) to reduce the impact of low-frequency
44 drift and high-frequency noise. Second, the ReHo analysis was accomplished by
45 calculating the Kendall's coefficient of concordance (KCC) of the time series of a given
46 voxel with its 26 nearest neighboring voxels.
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3 the left striatum of left-onset patients and right striatum of right-onset patients should
4 be relatively spared. Thus, motor symptoms laterality might cause hemi-striatal
5 asymmetry in neural activity. In order to evaluate this impact, we used the ReHo
6 lateralization index.^{6,7} In consideration of the anatomical asymmetry of human brain, a
7 symmetric template was firstly made by averaging the gray matter probability template
8 in SPM and its mirror copy that was left-right flipped. In this symmetrical template,
9 each side of the image represents an average of both hemispheres. And individual
10 ReHo maps were then spatially normalized to this symmetrical template and further
11 divided by the global mean ReHo for the purpose of standardization.^{5, 8} Next, the
12 resulting ReHo maps were left-right flipped to obtain the mirror copies. The nonflipped
13 ReHo map was subtracted by flipped ReHo map, and then smoothed with a 4-mm
14 full-width at half-maximum (FWHM) Gaussian kernel. This produced a final ReHo
15 lateralization map, in which left side (meaning image of the left hemisphere minus the
16 right) had the same absolute value with the right side (meaning image of the right
17 hemisphere minus the left), but had different plus-minus sign. Therefore, both sides
18 could reflect hemispheric differences in the same patient. As the template was
19 symmetric, we can restrict statistical analyses to any half of hemisphere. Due to the
20 potential importance of the striatum in Parkinson's disease, a striatum mask was also
21 made. In detail, the gray matter concentration maps obtained during segmentation were
22 firstly thresholded by 0.5, and multiplied with the mask including putamen, caudate
23 and pallidum in the AAL template. Then these regions of interests (ROIs) were
24 normalized to the symmetric template and the intersection was made across subjects.
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56 **Supplemental Results:**

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eResult 1 Behavioral performance of MRI subjects**Acquisition was impaired in L-naïve but normal in R-naïve patients**

Mix-model ANOVAs showed that both the group [$F(2, 171) = 10.575, P < 0.001$] and phase [$F(2, 171) = 21.119, P < 0.001$] had significant effects on accuracy, and there was significant interaction between group and phase [$F(4, 171) = 2.603, P = 0.038$]. Post hoc analysis showed that accuracy was significantly different among L-naïve, R-naïve and NC. L-naïve patients made significantly more errors than R-naïve patients ($P = 0.002$) and NC ($P < 0.001$), while R-naïve patients performed as well as NC ($P = 0.140$) (Fig. e-1A). Significant differences were in the acquisition phase as the post hoc analysis indicated, rather than retention or generalization phase, indicating retrieval function and generalization were well preserved in both L-naïve and R-naïve patients (acquisition vs. retention, $P < 0.001$; acquisition vs. generalization, $P < 0.001$; retention vs. generalization, $P = 0.985$) (Fig. e-1A). Thus, L-naïve patients, rather than R-naïve patients, were selectively impaired in feedback-based associative learning, indicating that asymmetric dopamine depletion could affect feedback-based associative learning.

Phase had significant effect on the response time [$F(2, 171) = 6.552, P = 0.002$], but neither the effect of group [$F(2, 171) = 0.638, P = 0.530$] nor the interaction between group and phase [$F(4, 171) = 0.816, P = 0.517$] was significant (Fig. e-1B).

Supplemental Tables**eTable 1 Acquired Equivalence Task¹**

Acquisition Stage 1: Stimulus-outcome associations	Acquisition Stage 2: Stimulus-stimulus associations	Acquisition Stage 3: New stimulus-outcome associations	Transfer Phase: Old and new associations testing
A1G1H1→X1	A1G1H1→X1 A1G2H2→X1	A1G1H1→X1 A1G2H2→X1 A1G1H1→X2	A1G1H1→X2?
A2G1H2→Y1	A2G1H2→Y1 A2G2H1→Y1	A2G1H2→Y1 A2G2H1→Y1 A2G1H2→Y2	A2G1H2→Y2?

Transfer phase interleaved trials with old associations (a measure of retention) as well as new associations (a measure of generalization) without feedback. A = age, G = gender, H = hair color.

eTable 2 Clinical and demographic characteristics of the MRI subjects

	L-Naïve (n = 20)	R-Naïve (n = 21)	NC (n = 19)	P Value
Age (y)	56.6 (8.8)	61.4 (8.5)	60.8 (5.9)	0.117
Gender (M/F)	7 / 13	13 / 8	8 / 11	0.201
Education (y)	11.4 (2.8)	12.9 (3.3)	12.7 (2.6)	0.193
Disease duration (y)	2.9 (2.5)	2.2 (1.5)	-	0.717
UPDRS-III				
Tremor	1.8 (1.5)	1.4 (1.3)	-	0.641
Rigidity	3.3 (1.4)	3.9 (1.6)	-	0.231

Bradykinesia	4.8 (2.4)	4.4 (2.3)	-	0.334
Left side symptoms	9.1 (3.1)	0.8 (1.4)	-	-
Right side symptoms	0.4 (1.2)	8.3 (2.3)	-	-
Dominant side symptoms	9.1 (3.1)	8.3 (2.3)		0.545
Non-dominant side symptoms	0.4 (1.2)	0.8 (1.4)		0.199
Total score	14.2 (5.2)	13.4 (5.5)	-	0.565
Motor asymmetry index	-0.9 (0.2)	0.9 (0.2)	-	-
H-Y score	1.2 (0.3)	1.4 (0.4)	-	0.066
BDI-II	5.0 (3.0)	4.9 (3.2)	4.7 (2.1)	0.991
MMSE	28.8 (0.9)	28.9 (0.9)	29.3 (1.0)	0.127

Data are mean (standard deviation). L-naïve = left-onset medication-naïve patients with Parkinson's disease; R-naïve = right-onset medication-naïve patients with Parkinson's disease; NC = normal controls; UPDRS = Unified Parkinson's Disease Rating Scale; Motor asymmetry index = (right side symptoms - left side symptoms) / (right side symptoms + left side symptoms); H-Y = Hoehn-Yahr; BDI = Beck Depression Inventory; MMSE = Mini Mental State Examination.

Supplemental Figure Legends

eFig.1 Learning performance of MRI subjects on the Acquired Equivalence Task.

(A) L-naïve patients made significantly more errors than R-naïve patients and NC in the acquisition phase. R-naïve patients performed as well as NC in acquisition. No significant difference in accuracy was found either in the retention phase or in the generalization phase among three groups.

(B) There was no significant difference in response time in the acquisition phase, retention phase and generalization phase among L-naïve, R-naïve and NC groups.

L-naïve = left-onset medication-naïve patients with Parkinson's disease; R-naïve = right-onset medication-naïve patients with Parkinson's disease; NC = normal controls.

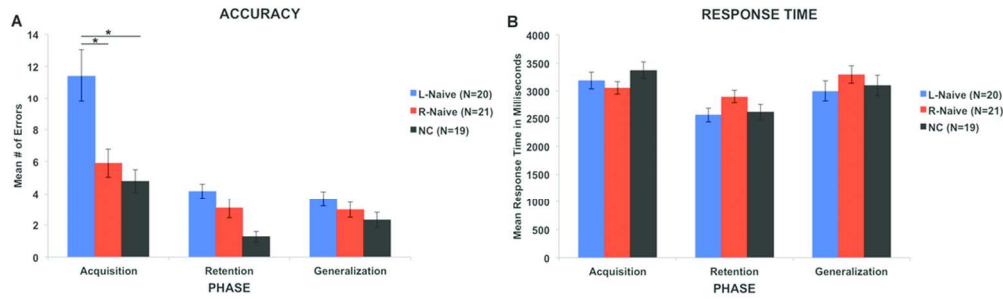
eFig.2 Correlation between ReHo activity of dorsal rostral putamen and left-side symptom scores.

No significant correlation was found between left-side symptom scores and neural activity of either right or left dorsal rostral putamen in L-naïve patients. L-naïve = left-onset medication-naïve patients with Parkinson's disease; ReHo = regional homogeneity.

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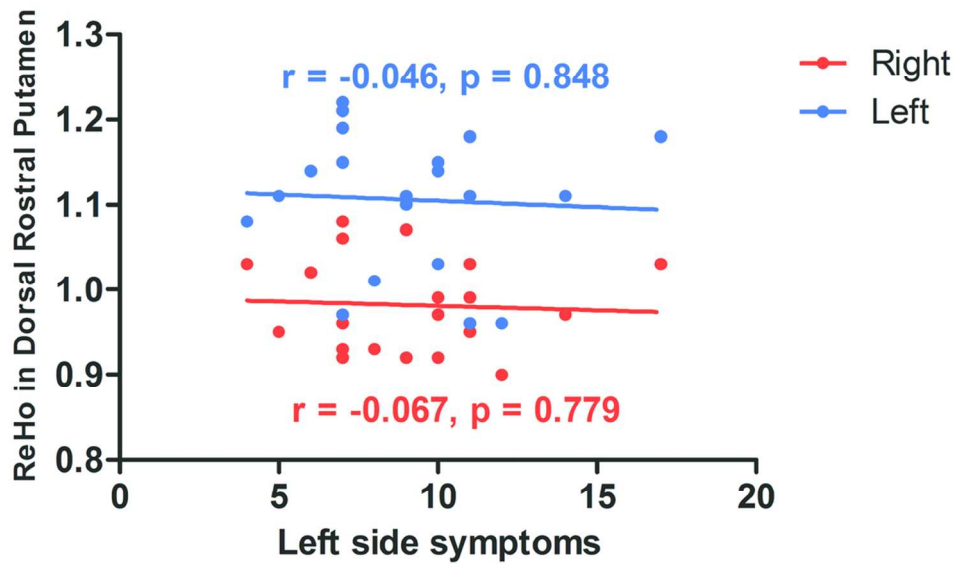
eFig.1 Learning performance of MRI subjects on the Acquired Equivalence Task.

(A) L-naïve patients made significantly more errors than R-naïve patients and NC in the acquisition phase. R-naïve patients performed as well as NC in acquisition. No significant difference in accuracy was found either in the retention phase or in the generalization phase among three groups.

(B) There was no significant difference in response time in the acquisition phase, retention phase and generalization phase among L-naïve, R-naïve and NC groups.

L-naïve = left-onset medication-naïve patients with Parkinson’s disease; R-naïve = right-onset medication-naïve patients with Parkinson’s disease; NC = normal controls.

50x14mm (600 x 600 DPI)



eFig.2 Correlation between ReHo activity of dorsal rostral putamen and left-side symptom scores. No significant correlation was found between left-side symptom scores and neural activity of either right or left dorsal rostral putamen in L-naïve patients. L-naïve = left-onset medication-naïve patients with Parkinson's disease; ReHo = regional homogeneity.

49x30mm (600 x 600 DPI)

1 **Title Page**2 **Motor-symptom Laterality Affects Acquisition in Parkinson's disease: a**3 **Cognitive and fMRI study**

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4 60 **Abstract**
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6 61 **Objective:** Asymmetric onset of motor symptoms in PD can affect cognitive function.
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9 62 We examined whether motor-symptom laterality could affect feedback-based
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11 63 associative learning and explored its underlying neural mechanism by fMRI in PD
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14 64 patients.
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19 66 **Methods:** We recruited 63 early-stage medication-naïve PD patients (29 left-onset
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22 67 medication-naïve patients, 34 right-onset medication-naïve patients) and 38 matched
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25 68 normal controls. Subjects completed an acquired equivalence task (including
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27 69 acquisition, retention and generalization) and resting-state fMRI scans. Learning
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30 70 accuracy and response time in each phase of the task was recorded for behavioral
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33 71 measures. Regional homogeneity was used to analyze resting-state fMRI data, with
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35 72 regional homogeneity lateralization to evaluate hemispheric functional asymmetry in
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37
38 73 the striatum.
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43 75 **Results:** Left-onset patients made significantly more errors in acquisition
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46 76 (feedback-based associative learning) than right-onset patients and normal controls,
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49 77 while right-onset patients performed as well as normal controls. There was no
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52 78 significant difference among these three groups in the accuracy of either retention or
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54 79 generalization phase. The three groups did not show significant differences in response
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56 80 time. In the left-onset group, there was an inverse relationship between acquisition
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4 81 errors and regional homogeneity in the right dorsal rostral putamen. There were no
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6 82 significant regional homogeneity changes in either the left or the right dorsal rostral
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9 83 putamen in right-onset patients when compared to controls.
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13
14 85 **Conclusions:** Motor-symptom laterality could affect feedback-based associative
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17 86 learning in PD, with left-onset medication-naïve patients being selectively impaired.
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19 87 Dysfunction in the right dorsal rostral putamen may **underlie** the observed deficit in
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22 88 associative learning in patients with left-sided onset.
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For Peer Review

103 Introduction

104 Parkinson's disease (PD) is the second most common neurodegenerative disorder,
105 characterized by resting tremor, rigidity, bradykinesia and postural instability. The
106 onset and progression of motor symptoms in PD are usually asymmetric, reflecting
107 asymmetric contralateral dopamine depletion in the basal ganglia.¹⁻⁴ Relationships
108 between cognitive performance and symptom asymmetry have been revealed that
109 left-onset PD patients performed worse on cognitive measures, such as spatial attention
110 and tasks of orientation and mental imagery, than right-onset PD patients.⁵⁻⁷ Cognitive
111 processes that are closely related with dopamine, such as cognitive flexibility and
112 motivation, showed different deficits between right-onset and left-onset PD patients.⁸
113 For example, left-onset PD patients with greater loss of dopamine in the right
114 hemisphere had impaired cognitive flexibility.^{5, 8}

115 Feedback-based associative learning, which involves learning through corrective
116 feedback provided on each trial, has been correlated to striatal dopamine release⁹ and
117 the function of the basal ganglia.^{10, 11} Previous studies have reported that
118 feedback-based associative learning was impaired in PD patients.^{12, 13} However, the
119 impairment in feedback-based learning in PD is not a universal finding, and many
120 factors could contribute to this variability. Wilkinson L et al. did not find a selective
121 impairment in PD in probabilistic feedback-based learning, but reported that there was
122 a significant correlation between disease severity and the impairment in
123 feedback-based learning.¹⁴ It has also been reported that off-medication PD patients

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4 124 learned stimulus-response associations equally well compared to healthy controls but
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6 125 learning was impaired by dopaminergic medication.¹³ Thus, in the underlying disease
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9 126 process, disease severity and dopaminergic medication might be all involved in
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11 127 modulating feedback-based learning. However, it is still not clear how the dopamine
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14 128 asymmetry affects feedback-based associative learning in PD patients.

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17 129 To control and minimize the effects of medication involvement and disease
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19 130 severity, we recruited early-stage medication-naïve right-handed PD patients including
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22 131 Left-onset medication-naïve patients (L-naïve) and Right-onset medication-naïve
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25 132 patients (R-naïve). We used a computer-based cognitive task of learning and
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27 133 generalization based on the acquired equivalence paradigm to test the effects of
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30 134 dopamine asymmetry on feedback-based associative learning. The acquired
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33 135 equivalence task, which includes tests of acquisition, retention and generalization, was
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36 136 repetitively used to evaluate feedback-based associative learning in patients with PD
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38 137 and other neurodegenerative disorders.^{10, 11} In the acquisition phase, learning through
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41 138 trial-by-trial feedback learning was shown to correlate to striatal function, while
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44 139 generalization without feedback was shown to correlate with hippocampal and medial
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46 140 temporal lobe (MTL) functionality.^{10, 11} Although striatal involvement in associative
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49 141 learning has been consistently reported in the previous task-based fMRI studies, such as
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52 142 caudate nucleus, amygdala and ventral striatum, the specific loci are not always the
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55 143 same.¹⁵⁻¹⁷ Thus, which subdivision of the basal ganglia is associated with
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57 144 feedback-based associative learning remains unclear, and resting-state fMRI (rs-fMRI)

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4 145 data were collected to explore the underlying neural mechanism of feedback-based
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6 146 learning.

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9 147 In the present study, we examined whether motor-symptom laterality could affect
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11 148 feedback-based associative learning and explored its underlying neural mechanism
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14 149 using rs-fMRI in PD patients.

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151 **Subjects and Methods**

152 **Subjects.** We recruited 63 right-handed, early stage (H-Y scores between 1 and 2),
153 medication-naïve PD patients and 38 right-handed normal controls (NC) during
154 2012-2015. Subjects in the PD and NC groups were matched for age, gender, education
155 and general cognitive status.¹⁸ According to the motor-symptom laterality, PD patients
156 were divided into L-naïve (N = 29) and R-naïve (N = 34) subgroups. All participants
157 were non-demented (Mini Mental State Examination, MMSE \geq 24) and scored less
158 than 15 on the Beck Depression Inventory II (BDI-II).^{19, 20} Participants were also
159 screened for history of cerebral trauma, cerebrovascular diseases, head surgery, severe
160 sleep disorders, hyperthyroidism, insulin-dependent diabetes, psychiatric or
161 neurological disorders, abuse of alcohol, tobacco use, use of hormonal contraceptives,
162 anticholinergic drugs, or antidepressants. For subjects with PD, only patients with
163 unilateral side of onset and asymmetrical motor symptoms were involved and diagnosis
164 was confirmed by two movement disorder specialists according to the UK Brain Bank
165 criteria for the diagnosis of PD.²¹ The side of onset was determined by medical history

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4 166 and physical examination. The severity of motor symptoms was evaluated by Unified
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6 167 Parkinson's Disease Rating Scale III (UPDRS-III).²² Motor asymmetry index (MAI)
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9 168 was calculated as (right side symptoms - left side symptoms) / (right side symptoms +
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171 **Standard protocol approvals, registrations, and patient consents.** We received
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20 172 approval from the Ethics Committee of Ruijin Hospital affiliated with Shanghai Jiao
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22 173 Tong University School of Medicine. We obtained written informed consents from all
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25 174 patients and controls prior to their participation in the study.

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30 176 **Behavioral data acquisition and evaluation.** We used an Apple MacBook to run the
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33 177 Acquired Equivalence Task.¹¹ This task is composed of two phases: acquisition and
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36 178 transfer. In the acquisition phase, participants acquire associations of colored faces and
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39 179 fish through trial-by-trial feedback-based learning. Following this acquisition, the
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42 180 transfer phase includes two types of trials: tests of previously learned associations
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45 181 (retention) and tests of new associations that are presented without feedback
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48 182 (generalization). The mean number of incorrect choices and the mean response time in
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51 183 each phase was recorded for behavioral measures. For detailed procedure, please refer
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54 184 to eMethod 1 and eTable 1 in the Supplement.

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186 **MRI data acquisition and processing.** MRI scan was performed after the acquired

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4 187 equivalence test with an interval of 8.6 ± 1.5 days. A subgroup of 70 subjects (23
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6 188 L-naïve, 25 R-naïve and 22 NC) participated in resting-state fMRI on a 3.0 T GE
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9 189 Medical System scanner based on the subjects' willingness. During the scan, the
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11 190 subjects were asked to remain motionless and awake with their eyes closed. For each
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13 191 participant, 210 functional images were collected using echo planar imaging
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16 192 T2*-weighted sequence (repetition time = 2000 ms, echo time = 30 ms, flip angle = 90
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18 193 °, 33/35/37 slices, matrix = 64×64 , voxel size = $3.75 \times 3.75 \times 4$ mm³). Then the
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21 194 high-resolution, three-dimensional T1-weighted structural images (repetition time =
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23 195 5.78 ms, echo time = 1.77 ms, flip angle = 12 °, 196 slices, matrix = 256×256 , voxel
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25 196 size = $1 \times 1 \times 1$ mm³) were acquired for registration and normalization of the functional
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32 198 After exclusion due to vascular diseases (1 L-naïve, 2 R-naïve and 3 NC) and
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34 199 obvious head motion (2 L-naïve and 2 R-naïve, with the translation and rotation head
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36 200 motion parameters larger than 2 mm or 2°), MRI data from 60 subjects (20 L-naïve, 21
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38 201 R-naïve, and 19 NC) qualified for analysis. MRI data were processed with Data
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41 202 Processing Assistant for Resting-State fMRI (DPARSF) programs.²³ Regional
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43 203 homogeneity (ReHo), as a commonly used method to analyze rs-fMRI data, was used
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46 204 with the rs-fMRI Data Analysis Toolkit (REST, <http://www.restfmri.net>) by calculating
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48 205 the Kendall's coefficient of concordance (KCC) of the time series of a given voxel with
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51 206 its 26 nearest neighboring voxels.^{24, 25} With the assumption that PD patients with
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54 207 unilateral onset of motor symptoms had asymmetric functional impairments in the
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4 208 brain, ReHo lateralization index was used to evaluate hemisphere asymmetry in neural
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6 209 activity as previously reported.^{26,27} Striatum subregions including the putamen, caudate
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9 210 and pallidum were chosen as regions of interest (ROIs). For detailed methods, please
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11 211 refer to eMethod 2 in the Supplement.
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17 213 **Statistical analysis.** The normality of clinical and demographic data distribution was
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19 214 checked by the Kolmogorov-Smirnov test. One-way ANOVA was used to compare the
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21 215 normally distributed continuous variables (age), and the chi-square test was employed
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23 216 to analyze categorical variables (gender). The continuous variables that were not
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25 217 normally distributed (education, disease duration, H-Y, BDI-II, MMSE, UPDRS-III
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27 218 score, MAI) were analyzed by Kruskal-Wallis test. Mix-model ANOVAs with group as
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29 219 between-subject factor and phase as within-subject factor were used to analyze the
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31 220 behavioral data. Post-hoc analysis was done using Tukey HSD test. In the correlational
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33 221 analysis, Spearman rho was calculated. The alpha level was set at 0.05. All P values less
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35 222 than the alpha level were considered statistically significant. SPSS version 17.0 (IBM,
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37 223 Chicago, IL, USA) was used for statistical analysis.
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45 224 For the fMRI data analysis, comparison of the hemispheric asymmetry among
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47 225 groups was performed using one-way ANCOVA. Age, gender, the mean frame-wise
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49 226 displacement (FD) corresponding to the temporal derivative of the head motion
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51 227 parameters, and mean gray matter (GM) volume of ROI were used as nuisance
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53 228 covariates.^{28, 29} Post-hoc analysis was performed within the significant regions. To
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4 229 control for family-wise error rates, Monte Carlo simulations were performed
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6 230 (3dClustSim; 10,000 iterations) using all brain voxels within the half-striatum ROI.³⁰
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9 231 The cluster threshold for a corrected alpha level of $P = 0.05$ was 27 voxels for
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11 232 ANCOVA and 7 voxels for post-hoc t-test, respectively.
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17 234 **Results**

19 235 **Clinical and demographic characteristics of subjects**

22 236 The clinical and demographic characteristics of subjects are presented in Table 1. All
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24 237 the groups were matched for age, gender, education, MMSE, and BDI-II ($P \geq 0.190$).
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27 238 There were no significant differences in disease duration, H-Y score, and UPDRS-III
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30 239 scores (including tremor, rigidity, bradykinesia sub-scores and total scores) between the
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32 240 L-naïve and R-naïve PD groups ($P \geq 0.104$). MAI was calculated as (right side
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35 241 symptoms - left side symptoms) / (right side symptoms + left side symptoms). The
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38 242 mean value of MAI for L-naïve and R-naïve groups were -0.9 (0.2) vs. 0.9 (0.2)
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41 243 respectively, indicating that motor-symptom asymmetry was also matched. In addition,
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43 244 subjects participating in the MRI examination were also matched across the three
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46 245 groups (see eTable 2 in the Supplement).
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51 247 **Behavioral performance**

53 248 **Acquisition was impaired in L-naïve but normal in R-naïve patients**

56 249 Mix-model ANOVAs showed that both group [$F(2, 294) = 7.228, P = 0.001$] and phase

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4 250 [F (2, 294) = 52.680, P < 0.001] had significant effects on accuracy. The interaction
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6 251 between group and phase was at a trend-level [F (4, 294) = 2.127, P = 0.077]. Fig. 1A
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9 252 indicated that the group effect is primarily driven by the acquisition phase. Post-hoc
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11 253 analysis showed that accuracy was significantly different among L-naïve, R-naïve and
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13 254 NC. L-naïve patients made significantly more errors than R-naïve patients (P = 0.003)
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15 255 and NC (P = 0.002), while R-naïve patients performed as well as NC (P = 0.996) (Fig.
16
17 256 1A). There were no significant differences between groups in retention or
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19 257 generalization phase, indicating that retrieval function and generalization were
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21 258 preserved in both L-naïve and R-naïve patients (retention, P = 0.201 vs. generalization,
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23 259 P = 0.331) (Fig. 1A). Thus, L-naïve patients, rather than R-naïve patients, were
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25 260 selectively impaired in feedback-based associative learning, indicating a potential
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27 261 effect of asymmetric dopamine depletion on associative learning.

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35 262 Phase had significant effect on the response time [F (2, 294) = 12.564, P < 0.001].
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37 263 However, there was neither an effect of group [F (2, 294) = 0.733, P = 0.481] nor an
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39 264 interaction between group and phase [F (4, 294) = 0.782, P = 0.538] (Fig. 1B).

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44 266 **Functional MRI results**

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47 267 **Dorsal rostral putamen was impaired in the right side in L-naïve but intact in**

48 268 **R-naïve patients**

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51 269 One-way ANCOVA analysis showed that L-naïve, R-naïve and NC groups were
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53 270 significantly different in ReHo lateralization in the dorsal rostral putamen (voxel level
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271 $P < 0.05$, cluster size > 27 voxels, corresponding to cluster-level corrected $P < 0.05$)
272 (Fig. 2A and Table 2). Post-hoc analysis showed that L-naïve patients had higher ReHo
273 lateralization in the dorsal rostral putamen compared with NC group (Fig. 2B and Table
274 2) and R-naïve group (Fig. 2C and Table 2) (voxel level $P < 0.05$, cluster size > 7
275 voxels, corresponding to cluster-level corrected $P < 0.05$). Further graphing using a
276 scatterplot in Fig. 2D indicated that higher ReHo lateralization in L-naïve patients was
277 due to decreased ReHo activity in the right side of the dorsal rostral putamen. There
278 was no significant difference between the left and the right dorsal rostral putamen in
279 R-naïve patients, suggesting neural function of the left dorsal rostral putamen in
280 R-naïve patients was relatively preserved in early stage PD. Our results showed that the
281 right dorsal rostral putamen of L-naïve patients had reduced neural activity compared
282 with the left dorsal rostral putamen in R-naïve patients, indicating that the right side of
283 dorsal rostral putamen might be more sensitive to dopamine depletion than the left side.

284

285 **Dorsal rostral putamen was correlated with feedback-based associative learning**

286 Correlational analysis in the L-naïve group showed that the mean number of errors in
287 acquisition was inversely correlated with ReHo activity of the right dorsal rostral
288 putamen ($r = -0.535$, $P = 0.015$) (Fig. 2E). This suggests that reduced activity in the
289 right dorsal rostral putamen might be associated with poor feedback-based associative
290 learning in L-naïve patients. In addition, poor performance in acquisition was also
291 inversely correlated with ReHo activity of the left dorsal rostral putamen in L-naïve

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4 292 patients ($r = -0.479$, $P = 0.033$) (Fig. 2E). However, there was no significant ReHo
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6 293 activity change in the left dorsal rostral putamen of L-naïve patients. Thus, this inverse
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9 294 correlation between acquisition and ReHo activity of the left dorsal rostral putamen has
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11 295 no clinical significance in those early-stage L-naïve PD patients.

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14 296 Since only 60 cases (20 L-naïve, 21 R-naïve and 19 NC) underwent resting-state
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16 297 fMRI examination based on subjects' willingness, performance in the acquired
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18 298 equivalence task was also analyzed in these 60 cases. Results were consistent with the
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20 299 earlier results from all 101 subjects (See eResult 1 and eFigure 1 in the Supplement).
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24 300 Our results showed that the dorsal rostral putamen activity might be specifically
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26 301 implicated in acquisition learning.
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33 303 **Function of the dorsal rostral putamen did not correlate with the severity of**
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35 304 **motor symptoms**

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38 305 In order to test whether the dorsal rostral putamen was associated with motor function,
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40 306 correlation analysis was done between UPDRS-III scores and ReHo activity in the
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42 307 dorsal rostral putamen in L-naïve patients. No significant correlation was found
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44 308 between UPDRS-III score and neural activity of either the right or the left dorsal rostral
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46 309 putamen (right $r = -0.141$, $P = 0.554$ vs. left $r = -0.092$, $P = 0.701$) (Fig. 3). In addition,
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48 310 neither the right nor the left dorsal rostral putamen was significantly associated with
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50 311 left-side motor symptom scores in L-naïve patients (right $r = -0.067$, $P = 0.779$ vs. left r
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52 312 $= -0.046$, $P = 0.848$) (see eFigure 2 in the Supplement), suggesting that activity of the
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4 313 dorsal rostral putamen did not correspond consistently with motor-symptom severity.
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9 315 **Discussion**

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11 316 The present study confirms previous reports regarding impaired acquisition and normal

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13 317 generalization in PD. The novel finding in our study in medication-naïve PD patients

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15 318 indicated that impaired acquisition was only detected in L-naïve patients, while

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17 319 R-naïve patients learned equally well as healthy controls. Results from rs-fMRI results

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19 320 indicated that there was a correlation between the impairment in acquisition and the

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21 321 activity in the dorsal rostral putamen, but not with motor-symptom severity.

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23 322 Dysfunction of the right dorsal rostral putamen was associated with acquisition deficit

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25 323 in L-naïve patients, which confirms the earlier reports that the dorsal rostral putamen is

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27 324 mainly involved in cognitive function rather than in motor function.³¹⁻³³
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37 326 **Dorsal rostral putamen resting-state activity correlated with performance in**

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39 327 **acquisition not motor symptom severity in Parkinson's disease**

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43 328 In the present study, the impairment in acquisition was inversely correlated with ReHo

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45 329 activity in the right dorsal rostral putamen, identifying that the dorsal rostral putamen

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47 330 could be an important region involved in feedback-based associative learning. The

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50 331 hypothesis of ReHo measurement postulates that significant brain activities would

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52 332 more likely occur in clusters rather than in a single voxel. ReHo measures the

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55 333 functional coherence of a given voxel with its nearest neighbors and can be used to

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4 334 evaluate resting-state brain activities.²⁵ Wu T et al. reported that ReHo, which was
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6 335 negatively correlated with UPDRS, decreased in extensive motor function-related brain
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9 336 regions, including the putamen, thalamus, and supplementary motor area, etc. in
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11 337 off-medication PD patients compared with normal controls. Administration of
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13 338 levodopa relatively normalized ReHo.³⁴ Thus, changes in ReHo can happen secondary
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16 339 to dopamine deficiency, and can be related to the motor symptom severity of the disease.
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19 340 In the present study, decreased ReHo in the dorsal rostral putamen, which might also be
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22 341 secondary to dopamine deficiency, was associated with the impairment in acquisition
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25 342 learning, but not with motor-symptom severity. Decreased ReHo reflects asynchronous
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27 343 neural activity of the dorsal rostral putamen and might lead to impaired performance in
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30 344 associative learning.

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33 345 The putamen was classically regarded as motor-related structure. However, recent
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35 346 studies have revealed that the putamen's subdivisions were involved in comprehensive
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37 347 connectivity with motor, cognitive and emotional function.³⁵⁻³⁷ For example, caudal
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40 348 putamen exhibited co-activation with primary sensorimotor cortex, caudal
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43 349 supplementary motor cortices, and anterior cerebellum, demonstrating its role in motor
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46 350 function;^{31, 38} The rostral putamen had connectivity with dorsolateral prefrontal cortex
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48 351 (DLPFC), rostral anterior cingulate cortex and posterior parietal cortex, suggesting its
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51 352 participation in higher-level cognitive functions.^{31, 32} Moreover, the rostral putamen
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53 353 combined with most of the head of the caudate, referred to as associative striatum,³¹
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56 354 played a dominant role in instrumental learning.^{33, 39} The dorsal striatum was involved
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4 355 in both motor function and associative cognition, and has been implicated in
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6 356 maintaining information about reward outcomes and consequences.^{40, 41} Our results
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9 357 were consistent with previous studies, but more specifically, the dorsal rostral putamen
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11 358 was identified as the region closely related to feedback-based associative learning.

14 359 In our study, no correlation was found between the dorsal rostral putamen and the
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16 360 severity of motor symptoms, which further substantiated that the dorsal rostral putamen
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18 361 was mainly associated with cognitive function rather than motor function. ReHo in both
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20 362 sides of the putamen was associated with acquisition errors in L-naïve, but not in
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22 363 R-naïve patients. However, in the scatterplot of Figure 2D, there was no significant
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24 364 ReHo activity change in the left dorsal rostral putamen of L-naïve patients. Thus, this
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26 365 inverse correlation between acquisition errors and ReHo activity of the left dorsal
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28 366 rostral putamen does not have much clinical significance in those early-stage L-naïve
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30 367 PD patients. But we believe, with the disease progression, ReHo activity of the left
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32 368 dorsal rostral putamen will decrease and finally lead to associative learning impairment
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34 369 in R-naïve patients. This suggests a greater role for the dorsal rostral putamen in
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36 370 associative learning in left-onset rather than right-onset patients and may have
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38 371 implications for understanding of disease progression in relation to motor-symptom
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40 372 laterality.

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53 374 **Right and left dorsal rostral putamen might function differently following**
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55 375 **dopaminergic denervation**

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4 376 ReHo activity of the right dorsal rostral putamen was inversely correlated with the
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6 377 mean number of errors in acquisition in L-naïve. R-naïve, with intact function of the
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9 378 dorsal rostral putamen, performed equally well to NC in acquisition. The possible
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11 379 reason for different acquisition performance between L-naïve and R-naïve could be that
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14 380 the left and the right dorsal rostral putamen might function differently following
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17 381 dopaminergic denervation. Generally speaking, L-naïve had more dopaminergic
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19 382 neuronal loss in the right substantia nigra,² resulting in more severely reduced
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22 383 dopamine release in the right striatum.³ The reverse was true in R-naïve patients. Based
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25 384 on the fact that L-naïve and R-naïve patients were well matched in UPDRS-III scores in
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27 385 our study, we assumed that the degree of dopaminergic denervation contralateral to the
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30 386 onset side should be similar in the two groups. However, our fMRI results showed
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33 387 reduced neural activity in the right dorsal rostral putamen in L-naïve patients, while the
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35 388 activity of the left dorsal rostral putamen in R-naïve was similar to that of controls. This
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38 389 indicates that the right and the left dorsal rostral putamen might function differently
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41 390 after PD-related dopaminergic loss. The right dorsal rostral putamen might be more
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43 391 sensitive to dopamine depletion and finally led to impaired feedback-dependent
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46 392 associative learning function.

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48 393 There is no pathological or anatomical evidence to explain why the right and the
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51 394 left dorsal rostral putamen function differently following dopaminergic denervation.
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54 395 However, recent studies reported asymmetric dopamine signaling in the striatal and
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56 396 frontal regions caused by genetic variants of dopamine transporter and dopamine D2
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4 397 receptor,⁴² and left-right asymmetric dopamine D2/3 receptor availability in the
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6 398 dorsal putamen in healthy population.⁴³ Asymmetric dopamine receptors availability
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9 399 and asymmetric dopamine signaling might contribute to asymmetric functional
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11 400 changes to dopamine depletion between the right and the left dorsal rostral putamen.
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14 401 Asymmetric or uneven function between the left and the right striatum has been
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17 402 evidenced from ¹⁸F-dopa PET-scan, where tower of London scores correlated with
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19 403 activity in the right caudate nucleus. On the other hand, activity in the left putamen was
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22 404 related to verbal working memory task.⁴⁴ A task-related fMRI study of healthy subjects
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25 405 observed activity in the right striatum and the right inferior prefrontal cortexes during
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27 406 earlier phases of probability learning.⁴⁵ A study by Postuma et al. provided stronger
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30 407 evidence for asymmetric function of the putamen by analyzing the functional
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33 408 connectivity between the cortex and the striatum in a meta-analysis of 126 published
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36 409 functional neuroimaging studies.³⁷ The right and the left putamen co-activated in
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38 410 conjunction with different brain regions with different laterality. Briefly, the left
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41 411 putamen showed a large ipsilateral coactivation essentially with the entire primary
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43 412 motor and somatosensory cortex, while the right putamen showed a peak co-activation
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46 413 with the right DLPFC. These functional connectivity pictures delineated by the above
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49 414 study fully illustrated asymmetric function of the right and the left putamen. Therefore,
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51 415 the left and the right dorsal rostral putamen might co-activate with different regions and
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54 416 function unevenly and differently in feedback-based associative learning. Early-stage
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56 417 R-naïve patients would be spared in acquisition as long as the right dorsal rostral
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4 418 putamen was not affected. But with the progression of the disease, deficits in
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6 419 acquisition of learning will appear because both sides of the dorsal rostral putamen will
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9 420 be affected.

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11 421 Our results also showed that both retrieval and generalization function were
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14 422 normal in PD. It has been reported that PD might exhibit impaired retrieval function,
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17 423 which could benefit substantially from cueing.⁴⁶ Normal retrieval function in our study
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20 424 might be due to the fact that these early-stage PD patients had relatively normal
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22 425 executive function at that point, or because the faces shown on the computer screen
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25 426 acted as efficient cueing to help patients recall what they had learned. Normal
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27 427 generalization in our study indicated that in the early stage of PD, asymmetric
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30 428 dopamine depletion didn't affect MTL function and patients had normal cognitive
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33 429 flexibility to use learned knowledge in a new context, which is consistent with the
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35 430 previous studies.^{10, 11, 47}

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40 432 **Limitations and Conclusions**

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43 433 Although the relationship between asymmetric motor symptoms and laterality of
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46 434 dopaminergic depletion is well founded,^{3, 48} there are a considerable proportion of PD
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49 435 patients who have ipsilateral or bilateral deficits of dopaminergic function. Erro R et al.
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51 436 analyzed a dataset of 46 [¹²³I] FP-CIT scans of PD patients and reported a prevalence of
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54 437 4.3% of scans with predominant ipsilateral dopaminergic deficit.⁴⁹ The limitation in
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56 438 this study is that severity of motor symptoms instead of neuroimaging was used as the

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4 439 indicator for the extent of relative dopamine depletion between the hemispheres. In a
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6 440 study by Kaasinen V, motor asymmetry index and DAT binding asymmetry index
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9 441 showed good accordance with each other in both right-handed and left-handed PD
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11 442 patients, which provided evidence that motor asymmetry index could be used as an
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13 443 indicator for asymmetry evaluation.⁵⁰ Future studies should apply neuroimaging to
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15 444 directly measure dopaminergic asymmetry and analyze its associations with associative
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17 445 learning.

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22 446 In conclusion, our study showed that motor-symptom laterality could affect
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24 447 feedback-based associative learning in L-naïve PD patients. We conjecture that
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26 448 dysfunction of the right dorsal rostral putamen in L-naïve but not in R-naïve patients
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28 449 might be a rationale to explain why L-naïve patients performed worse than R-naïve
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30 450 patients in acquisition. Left and right dorsal rostral putamen might function differently
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32 451 or respond differently to dopamine depletion, which needs further exploration.
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40 453 **Authors' Roles:**

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43 454 Dr. Huang, Dr. Tan and Dr. Chen had full access to all the data in the study and take
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45 455 responsibility for the integrity of the data and the accuracy of the data analysis. PH:
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47 456 provision of study material, collection and/or assembly of data, data analysis and
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49 457 interpretation, manuscript writing, final approval of manuscript. YYT: conception and
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51 458 design, subjects' recruitment and execution, administrative support, data analysis and
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53 459 interpretation, manuscript writing, final approval of manuscript. DL, YZ: fMRI data
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4 460 analysis and interpretation, revised manuscript writing, final approval of manuscript.
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6 461 MMH, EL, MAG: learning data analysis and interpretation, manuscript editing, final
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9 462 approval of manuscript. YW: subjects' recruitment and execution, final approval of
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11 463 manuscript. SC: conception and design, subjects' recruitment and execution,
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14 464 administrative support, manuscript writing, final approval of manuscript.
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46 476 **Conflict of interests:** None.
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614 **Figure legends**

615 **Fig.1 Learning performance on the Acquired Equivalence Task.**

616 (A) L-naïve patients made significantly more errors than R-naïve patients and NC in the
617 acquisition phase. R-naïve patients performed as well as NC in acquisition. No
618 significant difference in accuracy was found either in the retention phase or in the
619 generalization phase among three groups.

620 (B) There was no significant difference in response time in the acquisition phase,
621 retention phase and generalization phase among L-naïve, R-naïve and NC groups.

622 L-naïve = left-onset medication-naïve patients with Parkinson's disease; R-naïve =
623 right-onset medication-naïve patients with Parkinson's disease; NC = normal controls.

624

625 **Fig. 2 Difference in neural activity asymmetry and its correlation with learning.**

626 (A) The ANCOVA analysis among L-naïve, R-naïve and NC groups in the ReHo
627 lateralization within the striatum (the left striatum was shown). A significant difference
628 was found in the dorsal rostral putamen.

629 (B) Post-hoc analysis between L-naïve and NC group. Increased ReHo lateralization
630 was detected in the dorsal rostral putamen in L-naïve group.

631 (C) Post-hoc analysis between L-naïve and R-naïve group. Increased ReHo
632 lateralization was detected in the dorsal rostral putamen in L-naïve group compared to
633 R-naïve group.

634 (D) Scatter plot of ReHo activity in bilateral dorsal rostral putamen among groups. The

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4 635 horizontal line represents the mean level of ReHo. Group differences in ReHo

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6 636 lateralization were due to the decrease of ReHo in the right dorsal rostral putamen of

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9 637 L-naïve group.

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11 638 **(E)** The mean number of errors in acquisition was inversely correlated with the ReHo

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14 639 activity both of the right dorsal rostral putamen and the left dorsal rostral putamen in

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17 640 L-naïve group.

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19 641 L-naïve = left-onset medication-naïve patients with Parkinson's disease; R-naïve =

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22 642 right-onset medication-naïve patients with Parkinson's disease; NC = normal controls;

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25 643 ReHo = regional homogeneity.

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30 645 **Fig. 3 Correlation between ReHo activity of the dorsal rostral putamen and**

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32 646 **UPDRS-III score.** No significant correlation was found between UPDRS-III score and

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35 647 neural activity of either the right or the left dorsal rostral putamen in L-naïve patients.

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38 648 L-naïve = left-onset medication-naïve patients with Parkinson's disease; ReHo =

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41 649 regional homogeneity.

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