Neuroanatomy and Functional Connectivity in Patients with Parkinson’s Disease with or without Restless Legs Syndrome

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ABSTRACT

Introduction: Restless legs syndrome (RLS) is a common non-motor symptom in Parkinson’s disease (PD), but its pathogenesis remains unclear. This study aimed to explore the potential neural substrates of RLS in a large sample of patients with PD.

Methods: A total of 42 patients with PD with RLS and 124 patients with PD without RLS were prospectively recruited at our hospital between February 2019 and October 2020 and underwent structural and resting-state functional magnetic resonance imaging. Differences between the two patient groups were assessed using voxel-based morphometry and functional connectivity analysis. PD duration, Part III of the Movement Disorder Society’s Unified Parkinson’s Disease Rating Scale (MDS-UPDRS-III) score, and levodopa equivalent daily dose were treated as covariates.

Results: Patients with PD with RLS had significantly larger gray matter volume in the bilateral posterior cingulate cortex than patients with PD without RLS (FDR-adjusted $P < 0.05$). Compared to patients without RLS, those with RLS had significantly lower functional connectivity between the left central opercular cortex and the bilateral precentral gyri and postcentral gyri (FDR-adjusted $P < 0.001$).

Conclusion: Our study provides the first evidence that in patients with PD, RLS is associated with significantly larger gray matter volume in the posterior cingulate cortex and lower resting-state functional connectivity within the sensorimotor network. Our results may help clarify the pathophysiology of RLS in PD and identify possible therapeutic targets.

Keywords: Parkinson’s disease; Restless legs syndrome; fMRI; Posterior cingulate gyrus; Functional connectivity
INTRODUCTION

Restless legs syndrome (RLS) is a common sensorimotor disease characterized by an irresistible urge to move the legs, especially at rest [1]. RLS occurs in approximately 14% of patients with Parkinson’s disease (PD), one of the most common chronic neurological disorders, whereas RLS occurs in only 1.9–4.6% of the general population [2, 3]. Primary RLS has been associated with decreased dopamine transport in the striatum [4], decreased iron content in the substantia nigra [5], poor functional connectivity within the dopaminergic network [6], and altered sensorimotor circuits [7]. How RLS arises in PD has not yet been elucidated. This is an important question to address because RLS has been associated with greater anxiety, worse nutritional status, and lower quality of life among patients with PD [8].

Dopaminergic dysfunction and response to dopaminergic agents are consistent features in both RLS and PD, suggesting that the two diseases may have a common pathophysiology [9]. Both PD and primary RLS involve decreased dopamine transport in the nigro-striatal system [10, 11]. However, the two conditions differ in that PD, but not primary RLS, involves loss of dopaminergic neurons in the substantia nigra [12]. In the nigro-striatal system, PD involves reduced dopamine levels, while the opposite is true of primary RLS [10, 11]. In addition, the iron content in the substantia nigra is higher in patients with PD but lower in individuals with primary RLS [5, 13].

Voxel-based morphometry (VBM) studies in primary RLS have reported sometimes conflicting findings. Most VBM studies of patients with primary RLS have reported no changes in brain volume [14–18]. On the other hand, some VBM studies of individuals with primary RLS detected volume or density changes in diverse brain areas: larger gray matter volume or density has been reported in the thalamus, hippocampus, and middle orbitofrontal gyrus, right middle frontal gyrus, left primary somatosensory cortex, left primary motor cortex, right primary somatosensory cortex, right temporal area, inferior parietal lobe, bilateral putamen, and bilateral brainstem [7, 19, 20]. Smaller gray matter volume or density has been reported in the medial frontal areas, right anterior cingulate gyrus, left central opercular cortex, right middle temporal gyrus, bilateral lateral temporal areas, left occipital region, left hippocampus, bilateral parietal lobes, right thalamus, and cerebellum [21, 22]. We are unaware of VBM studies on RLS in PD, so we wanted to examine whether patients with PD and RLS show structural changes in the brain similar to those of individuals with primary RLS.

A recent functional magnetic resonance imaging (fMRI) study has shown that patients with PD and RLS show lower functional connectivity of the right precentral gyrus with the left post- and precentral gyri than patients with PD without RLS [23]. This implies that functional abnormalities in sensorimotor networks may contribute to RLS symptoms, but the sample in that study was small. Therefore, we wanted to examine whether patients with PD and RLS have abnormal functional connectivity in sensorimotor networks.

Here we exploited VBM and analysis of functional connectivity between regions of
interest (ROIs) to explore differences in local brain structure and functional connectivity in patients with PD with or without RLS.

METHODS

Subjects

Patients with idiopathic PD were prospectively recruited at our hospital between February 2019 and October 2020. The inclusion criteria were (1) clinically established PD based on the Movement Disorder Society Clinical Diagnostic Criteria [24]; (2) no family history of PD in first-degree relatives; (3) a score on the Mini-Mental State Examination above the lowest quartile, after adjusting for age and education level [25]; (4) no history of nervous system surgery; and (5) no severe psychosis or psychological diseases. The exclusion criteria were (1) MRI evidence of structural lesions related to other neurological disorders; (2) head movement artifacts during the MRI session; or (3) the presence of iron deficiency anemia, diabetes, renal dysfunction, or peripheral neuropathy.

This study was approved by the Ethics Committee of Henan Provincial People’s Hospital (approval 202282). The study was conducted in accordance with the Declaration of Helsinki and its later amendments. Informed consent was obtained from all participants in the study.

Clinical Assessment

All clinical and MRI examinations were performed while patients were on medication, because MRI examinations are difficult for many patients when off medication, especially for those with tremor. Clinicodemographic data were collected on each patient, including name, age, sex, disease duration, and medication in terms of the levodopa equivalent daily dose (LEDD) [26]. PD severity was assessed using Part III of the Movement Disorder Society’s Unified Parkinson’s Disease Rating Scale (MDS-UPDRS-III) [27].

Patients with PD were divided into those with or without RLS, which was diagnosed according to the 2014 diagnostic criteria of the International Restless Legs Syndrome Study Group [28]. To reduce risk of misdiagnosis, we diagnosed our patients with RLS only when two neurologists concurred.

Structural MRI

MRI images were acquired using a 3-T MAGNETOM Prisma scanner (Siemens, Erlangen, Germany) with a 64-channel head coil. The parameters for T1-weighted sequences were as follows: sequence, 3-dimensional magnetization-prepared rapid gradient-echo; echo time = 3.43 ms; repetition time = 5,000 ms; inversion time = 755 ms; flip angle = 4°; slice thickness = 1.00 mm; number of slices = 208; bandwidth = 240 Hz/pixel; matrix size = 256 × 256; field of view = 256 mm × 256 mm; and voxel size = 1.0 × 1.0 × 1.0 mm³.

MRI scans were visually checked, and those containing severe vascular lesions, space-occupying lesions, or motion artifacts were excluded. Statistical Parametric Mapping version 12b (SPM12b; www.fil.ion.ucl.ac.uk/spm) was used to preprocess images and analyze VBM data. All the structural images were segmented into gray matter, white matter, and cerebrospinal fluid using the standard segmentation model. After an initial affine registration of the gray/white matter concentration map into Montreal Neurological Institute (MNI) space, the gray/white matter concentration images were non-linearly warped using the diffeomorphic anatomical registration through the exponentiated Lie algebra (DARTEL) technique [29], then resampled to a voxel size of 1.0 × 1.0 × 1.0 mm³. The map of gray matter volume (GMV) and white matter volume (WMV) was obtained by multiplying the gray/white matter concentration map by the non-linear determinants that were derived from the spatial normalization step. Finally, the resulting GMV/WMV images were smoothed using a Gaussian kernel with a full width at half-maximum (FWHM) of 8 mm.
Resting-State fMRI

Participants were asked to lie still, relax, and keep their eyes open throughout the scanning session. Functional images were obtained using axial echo-planar imaging with the following parameters: TR = 2000 ms; TE = 35 ms; flip angle = 80°; FOV = 240 mm × 240 mm; matrix size = 94 × 94; voxel size = 2.20 mm × 2.20 mm × 2.20 mm; slice thickness = 2.2 mm; number of slices = 75; and number of time points = 180.

SPM12b and the CONN functional connectivity toolbox version 18_b [30] (http://www.nitrc.org/projects/conn) were used to preprocess images and analyze resting-state fMRI data. Functional axial echo-planar MRI image preprocessing were performed as described [31]. In the denoising step, white matter, cerebrospinal fluid, and head motion were regressed. Low-frequency drift and high-frequency physiological noise were removed by bandpass filtering (0.01 < frequency < 0.08 Hz), while systematic shifts were removed by detrending.

Statistical Analysis

Comparison of Clinicodemographic Characteristics

Differences in demographic and clinical characteristics between the two patient groups were assessed for significance using Student’s t and χ² tests. Statistical analyses were performed using the Statistical Package for Social Sciences for Windows (version 22.0; IBM, Chicago, IL, USA). Differences associated with P < 0.05 were considered statistically significant.

Analysis of VBM Data

Voxel-based comparisons of GMV or WMV between the two patient groups were conducted using the parametric two-samples t test in SPM12. In order to regress the influence of covariates, a general linear model was used. To correct for multiple comparisons, the significance threshold was defined as an uncorrected P = 0.001 at the initial voxel level and as a false discovery rate (FDR)-corrected P = 0.05 at the cluster level.

Functional Connectivity Analysis

To evaluate functional connectivity in the brain, we analyzed neurological activity among 132 regions comprising 91 cortical and 15 subcortical ROIs from the FSL Harvard–Oxford Atlas [32] and 26 cerebellar ROIs from the Anatomical Automatic Labeling Atlas [33] in the CONN toolbox. Potential correlations in resting-state activity were explored by applying a general linear model and performing bivariate correlation analysis based on first-level analysis of the CONN pipeline [30]. To evaluate changes in ROI-to-ROI functional connectivity, differences from the

| Characteristic | PD with RLS | PD without RLS | P value |
|---------------|-------------|----------------|---------|
| n             | 42          | 124            | –       |
| Male          | 23 (54.8)   | 79 (63.7)      | 0.303   |
| Age, years    | 62.8 ± 7.5  | 61.9 ± 6.7     | 0.495   |
| PD duration, years | 8.4 ± 4.6   | 6.0 ± 3.9     | 0.003   |
| MDS-UPDRS-III score | 46.0 ± 15.6 | 37.2 ± 18.3 | 0.006   |
| LEDD          | 587.0 ± 297.1 | 411.6 ± 315.4 | 0.002   |

Values are n, n (%) or mean ± SD, unless otherwise noted

LEDV levodopa equivalent daily dose, MDS-UPDRS-III Part III of Movement Disorder Society Unified Parkinson’s Disease Rating Scale, PD Parkinson’s disease, RLS restless legs syndrome
second-level analysis of the CONN pipeline were assessed using a two-samples $t$ test \[30\]. In order to regress the influence of covariates, a general linear model was used. To correct for multiple comparisons, the significance threshold was defined as an FDR-corrected $P = 0.05$ at the seed level.

**RESULTS**

Clinicodemographic Features

Of 248 patients initially considered for enrollment, 166 patients, of whom 42 had RLS (25%), were included in the final analysis based on the inclusion and exclusion criteria. Patients with PD and RLS had significantly longer duration of PD as well as significantly higher MDS-UPDRS-III score and LEDD than patients with PD without RLS (Table 1). However, the two patient groups did not differ significantly in age or sex distribution.

**Table 2** Voxel-based morphometry showing areas in which gray matter volume was greater in patients with PD and RLS than in patients with PD without RLS

| Region       | R/ L | Cluster size | Montreal Neurological Institute coordinates $(x, y, z)$ | $T$ score |
|--------------|------|--------------|--------------------------------------------------------|----------|
| IPL R        | 155  | 45 $-42$     | 42 3.99                                                |          |
| MTG L        | 199  | $-57$ $-67.5$| 9 3.72                                                 |          |
| PCC L/R      | 1065 | 3 $-45$      | 27 4.44                                                |          |

Single-voxel $p < 0.001$ uncorrected for multiple comparisons, cluster size $> 100$ voxels

Cluster-level false discovery rate correction (single-voxel $p < 0.001$, cluster size $\geq 1065$ voxels)

| Region       | R/ L | Cluster size | Montreal Neurological Institute coordinates $(x, y, z)$ | $T$ score |
|--------------|------|--------------|--------------------------------------------------------|----------|
| PCC L/R      | 1065 | 3 $-45$      | 27 4.44                                                |          |

IPL inferior parietal lobule, L left, MTG middle temporal gyrus, PCC posterior cingulate cortex, PD Parkinson’s disease, R right, RLS restless legs syndrome

**Comparison of GMV and WMV Between Patients with PD and with or Without RLS**

VBM was used to assess GMV and WMV differences between patients with PD and RLS or without RLS. PD duration, MDS-UPDRS-III score, and LEDD differed significantly between the two groups. In order to minimize the influence of PD duration, disease severity, and dopaminergic drugs, we treated PD duration, MDS-UPDRS-III score, and LEDD as covariates. GMV was significantly greater in the bilateral posterior cingulate cortex (PCC) of patients with PD and RLS than in patients without RLS (Table 2, Fig. 1). Unlike GMV, WMV did not differ significantly between the two groups in any brain region.

**Comparison of ROI-to-ROI Functional Connectivity Between Patients with PD and with or Without RLS**

In order to minimize the influence of PD duration, disease severity, and dopaminergic drugs,
we treated PD duration, MDS-UPDRS-III score, and LEDD as covariates. Compared to patients without RLS, those with RLS showed significantly lower functional connectivity between various brain regions as follows (Table 3, Fig. 2): (1) between the left central opercular cortex and the bilateral precentral gyrus and postcentral gyrus (all FDR-adjusted $P < 0.001$); (2) between the right central opercular cortex and the left postcentral gyrus (FDR-adjusted $P = 0.019$); (3) between the right supplemental motor area and the left precentral gyrus (FDR-adjusted $P = 0.011$); (4) between the left caudate nucleus and the posterior cingulate cortex (FDR-adjusted $P = 0.041$); (5) between the right superior frontal gyrus and the right middle frontal gyrus, right cerebellum 9 and right frontal pole (all FDR-adjusted $P < 0.030$); (6) between the right cerebellum 3 and the left amygdala (FDR-adjusted $P = 0.029$); and (7) between the temporo-occipital part of the left middle temporal gyrus and the left cerebellum 7 (FDR-adjusted $P = 0.024$). Conversely, patients with PD with RLS showed significantly greater functional connectivity between the left planum temporale and left thalamus (Table 3, Fig. 2; FDR-adjusted $P = 0.029$).

**DISCUSSION**

In the present study, we explored neural substrates related to the RLS in patients with PD. Our work shows for the first time that patients with PD and RLS have significantly greater GMV in the bilateral PCC than patients without RLS. We also demonstrated that RLS in PD is associated with significantly altered functional connectivity between multiple brain regions, especially lower functional connectivity between the left central opercular cortex and the pre- and postcentral gyri on both sides of the brain. These neuroanatomical and functional differences may hold clues to the pathogenesis of RLS in PD.

RLS is a common sensorimotor disorder characterized by an urge to move the legs and other unpleasant sensations. These symptoms often occur at rest, especially in the evening, and they improve or disappear during movement [28]. The PCC is a central node in the default mode network (DMN), which is usually involved in the processing of internally generated information, especially in the resting state [34]. Individuals with primary RLS have disturbances of the DMN that may influence the thalamic relay sensory-motor-associated circuit [35], which are associated with greater spontaneous neural activity in the PCC [36]. Stimulation of the PCC may induce sensory responses (e.g., tingling, formication) and tonic motor responses, suggesting that PCC may be related to sensory and motor functions [37]. Among patients with PD, we found that those with RLS

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**Table 3** Differences in functional connectivity between patients with PD and with or without RLS

| Connection          | $T$ value | FDR-corrected $P$ |
|---------------------|-----------|-------------------|
| **Lower connectivity with RLS** |           |                   |
| CO L–PostCG L       | $-4.98$   | $0.001$           |
| CO L–PreCG L        | $-4.85$   | $0.001$           |
| CO L–PreCG R        | $-4.50$   | $0.001$           |
| CO L–PostCG R       | $-4.44$   | $0.001$           |
| CO R–PostCG L       | $-3.59$   | $0.019$           |
| SMA R–PreCG L       | $-3.84$   | $0.011$           |
| Caudate L–PCC       | $-3.68$   | $0.041$           |
| SFG R–MidFG R       | $-4.23$   | $0.005$           |
| SFG R–Cereb9 R      | $-4.07$   | $0.005$           |
| SFG R–FP R          | $-3.50$   | $0.026$           |
| Cereb3 R–Amygdala L | $-3.77$   | $0.029$           |
| toMTG L–Cereb7 L    | $-3.83$   | $0.024$           |
| **Higher connectivity with RLS** |           |                   |
| PT L–Thalamus L     | $3.77$    | $0.029$           |

*Cereb3* cerebellum 3, *Cereb7* cerebellum 7, *Cereb9* cerebellum 9, CO central opercular cortex, FDR false discovery rate, FP frontal pole, L left, MidFG middle frontal gyrus, PCC posterior cingulate cortex, PD Parkinson’s disease, PostCG postcentral gyrus, PreCG precentral gyrus, PT planum temporale, R right, RLS restless legs syndrome, SFG superior frontal gyrus, SMA supplemental motor area, toMTG temporo-occipital part of middle temporal gyrus.
showed significantly lower functional connectivity between the PCC and the left caudate nucleus than patients without RLS. Acute infarcts in the caudate nucleus have been linked to RLS after stroke [38]. Our findings here lead us to speculate that greater GMV in the bilateral PCC may be related to RLS in PD.

The precentral gyrus, postcentral gyrus, central opercular cortex, and supplemental motor area are key parts of the sensorimotor network [39–43]. Patients with PD and RLS have considerably lower brain activity in the right precentral gyrus than patients with PD without RLS, as well as reduced functional connectivity between the right precentral gyrus and the left post- and precentral gyri [23]. In fact, repetitive, low-frequency transcranial magnetic stimulation over the pre- and postcentral gyri can alleviate the sensory–motor complaints of patients with primary RLS [44]. Consistent with these results, we found that functional connectivity within the sensorimotor network was significantly lower in our patients with PD and RLS than in those without it. It would be interesting to investigate whether repetitive, low-frequency transcranial magnetic stimulation over the primary motor and somatosensory cortical areas can alleviate the symptoms of RLS in PD.

Our study also revealed abnormal functional connections between the cerebellum and multiple brain regions, including the amygdala, middle temporal gyrus, and superior frontal gyrus. A resting fMRI study of individuals with

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**Fig. 2** Differences between patients with Parkinson’s disease (PD) with or without restless legs syndrome (RLS) in functional connectivity. Patients with PD and RLS showed significantly lower functional connectivity (1) between the left central opercular cortex (CO) and the bilateral precentral gyri (PreCG) and postcentral gyri (PostCG); (2) between the right CO and the left PostCG; (3) between the right supplemental motor area (SMA) and the left PreCG; (4) between the left caudate nucleus and the posterior cingulate cortex (PCC); (5) between the right superior frontal gyrus (SFG) and the right middle frontal gyrus (MidFG), right cerebellum 9 (Cereb9), and right frontal pole (FP); (6) between the right cerebellum 3 (Cereb3) and the left amygdala; and (7) between the temporo-occipital part of the left middle temporal gyrus (toMTG) and the left cerebellum 7 (Cereb7). Patients with PD and RLS showed significantly greater functional connectivity between the left planum temporale (PT) and left thalamus. a Differences associated with FDR-corrected $P < 0.05$ are shown. b Differences associated with FDR-corrected $P < 0.001$ are shown. L left, R right.
primary RLS also showed lower cerebello-parietal connectivity than in healthy controls [45]. A high-resolution fMRI study detected cerebellar activity during sensory leg discomfort in individuals with primary RLS [46]. These studies implicate the cerebellum in primary RLS.

In patients with PD and RLS, we found weaker functional connections between the right superior frontal gyrus and multiple brain regions, including the middle frontal gyrus, cerebellum 9, and frontal pole. The superior frontal gyrus has been implicated in RLS. For example, hub analysis of a resting-state fMRI showed stronger functional connectivity within the superior frontal gyrus in drug-naïve individuals with idiopathic RLS than in healthy controls [47]. In addition, individuals on hemodialysis who have RLS show greater cerebral blood flow in the left medial superior frontal gyrus than healthy controls [48].

The thalamus is a key part of the sensorimotor network [6]. Individuals with primary RLS show significantly greater connectivity between the thalamus and frontal regions [45] and between the DMN and thalamus [35] than healthy controls do. Compared to healthy controls, individuals with primary RLS show reduced thalamic connectivity with the right parahippocampal gyrus, right precuneus, right precentral gyrus, and bilateral lingual gyri, but strengthened thalamic connectivity with the right superior temporal gyrus, bilateral middle temporal gyrus, and right medial frontal gyrus [49]. Individuals with primary RLS show thalamic activity during the combined periodic limb movement and sensory leg discomfort, based on high-resolution fMRI [46]. Our study found that patients with PD and RLS had significantly greater functional connectivity between the left planum temporale and left thalamus than patients with PD without RLS. Together, these studies implicate the thalamus in both primary RLS and RLS in the context of PD.

Patients with PD and RLS in our study had PD for significantly longer and had higher MDS-UPDRS-III scores than patients with PD without RLS, consistent with a longitudinal study that showed that RLS prevalence in patients with PD increased from 4.6% to 6.5% after 2 years and to 16.3% after 4 years [50]. Indeed, the longer PD duration and more serious disease in our patients with PD and RLS may explain their significantly higher LEDD. In order to reduce potential confounding of our analyses of VBM and functional connectivity, we treated impact of PD duration, MDS-UPDRS-III score, and LEDD as covariates.

Our study had some limitations. Since RLS in PD may be confused with chronic dopaminergic treatment, more studies are needed to investigate RLS in drug-naïve patients with PD. Moreover, certain PD symptoms, such as motor- and non-motor sensory fluctuations and akathisia, are not easily distinguished from RLS symptoms, which may lead to overdiagnosis of RLS among patients with PD. To reduce misdiagnosis, we diagnosed our patients with RLS only when two neurologists concurred. Patients with common diseases that can cause RLS were excluded from the study, although we relied only on patients’ current condition and medical history to decide such exclusion, which increases the risk of confounding. Although we treated disease duration and MDS-UPDRS-III score as covariates, we cannot exclude that more advanced disease in patients with PD and RLS contributed to their differences from the patients without RLS. Lastly, we did not assess severity of RLS, so it remains unclear whether the observed alterations in brain GMV and functional connectivity correlate with RLS severity.

**CONCLUSIONS**

Our study provides the first evidence that patients with PD and RLS have significantly greater GMV in the bilateral PCC and significantly lower functional connectivity between the left central opercular cortex and the bilateral pre- and postcentral gyri than patients with PD without RLS. We expect that our results will help elucidate the pathophysiology of RLS in PD, as well as provide new insights into potential therapeutic targets.
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Author Contributions. All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Qiuling Zang, Jinhua Zheng and Qi Zhang. The first draft of the manuscript was written by Qiuling Zang. The manuscript was revised by Jianjun Ma, Peipei Huang, Nannan Shen and Wang Miao.

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Compliance with Ethics guidelines. This study was approved by the Ethics Committee of Henan Provincial People’s Hospital (approval 202282). The study was conducted in accordance with the Declaration of Helsinki and its later amendments. Informed consent was obtained from all participants in the study.

Data Availability. The data that support the findings of the present study are available from the corresponding authors upon reasonable request.

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