Reduced regional activity and functional connectivity within sensorimotor network in Parkinson’s patients with restless legs syndrome

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Abstract

Background: Restless legs syndrome is an important sleep disturbance in Parkinson's disease. Restless legs syndrome causes an urge to move the legs accompanying sensations which can be difficult to describe but include aching, burning, tingling, or crawling. However, the underlying pathophysiology of restless legs syndrome in Parkinson's disease remains unknown and no imaging investigation has been conducted to explore its mechanism to date.

Objective: This study is to investigate the brain functional changes in Parkinson's disease with restless legs syndrome (PD-RLS⁺) patients using functional magnetic resonance imaging.

Methods: Data of functional magnetic resonance imaging were collected from 14 PD-RLS⁺ patients, 20 Parkinson’s disease without restless legs syndrome (PD-RLS⁻) patients, as well as 19 normal controls during restless legs syndrome-free periods. Intraregional brain activity was evaluated by regional homogeneity method and compared between each pair of the three groups. Area with significantly altered regional homogeneity between two patient groups was further selected as seed in subsequent functional connectivity analysis. Correlations between clinical variables and the altered regional homogeneity and functional connectivity were then assessed in patient groups.

Results: Compared with PD-RLS⁻, PD-RLS⁺ had much reduced brain activity in the right precentral gyrus, which was negatively associated with restless legs scores in Parkinson's disease patients. Comparison between PD-RLS⁻ and normal controls revealed that brain activities were increased in the left brainstem and reduced in the left lingual, fusiform and inferior occipital gyri, middle cingulate and paracingulate gyri, and supplement motor area. Further functional connectivity analysis between right precentral gyrus and left postcentral/precentral gyri decreased dramatically within PD-RLS⁺ patients, which were also negatively correlated with restless legs symptoms in patient groups.

Conclusion: PD-RLS⁺ patients showed diminished regional homogeneity and functional connectivity within the precentral and postcentral gyri, which implies that the functional abnormalities in sensorimotor network may disrupt the lateral pain pathway, contributing to restless legs syndrome symptoms in Parkinson's disease patients. This may provide imaging evidence to explore the pathophysiology of Parkinson's disease-related restless legs syndrome.

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Keywords
Restless legs syndrome, Parkinson's disease, sensorimotor network, regional homogeneity, functional connectivity

Introduction
Parkinson’s disease (PD) is the most common neurodegenerative disorder presenting with motor and nonmotor symptoms, such as neuropsychiatric and sleep disturbances. Restless legs syndrome (RLS) is an important component of sleep disturbances in PD by an urge to move the legs accompanying unpleasant sensations begin or worsen during periods of rest or inactivity and partially or totally relieved by movement.1 The sensations can be difficult to describe but include aching, burning, tingling, crawling or numbness.2 Patients who experienced painful sensations had more severe RLS symptoms.3 A recent meta-analysis showed an increased risk for RLS in PD patients with a diagnostic odds ratio of 2.98 (2.12–4.16).4 The prevalence of RLS in PD patients is much higher than that in general adult population with 3.0%/24 versus 0.53%/18.8%.4 This disturbance can occur in the early or late stage of PD, which is often neglected by patients and physicians. Two large prospective cohort studies indicated that RLS could be an early clinical feature of PD, especially in men.6 The clinical characteristics of PD with RLS (PD-RLS+) patients were different from idiopathic RLS (iRLS).7 Taken together, there were possible different mechanisms between PD-RLS+ and iRLS. Over the last two decades, functional neuroimaging has enriched our understanding of brain networks correlated with iRLS. Several brain functional activities are changed in iRLS patients, including sensorimotor cortex, limbic system (hippocampus and parahippocampal gyri, corpus callosum, cingulate gyrus, and insula), basal ganglion (caudate and putamen), thalamus, and brainstem,8–12 among which the dysregulation of sensorimotor and limbic networks was of the most importance. Unfortunately, no imaging study has been reported regarding to PD-related RLS so far. The neural mechanisms lying in PD-related RLS remain unclear.

Resting-state functional magnetic resonance imaging (fMRI) is a valuable tool to investigate intrinsic functional abnormalities in brain. Regional homogeneity (ReHo) measures the degree of regional synchronization of fMRI time courses, providing information about temporal neural activities in the regional brain.13 Functional connectivity (FC) provides information about the functional interactions between brain regions.13 These two analyses are considered to be mutually complementary for detecting both local and remote brain activity synchronization,14 which may give more insights to PD-related RLS mechanisms than either method alone. Our study aimed to explore the local coherence of intrinsic brain activity and interregional connectivity features in PD patients with and without RLS by using ReHo and seed-based FC analyses. In consideration of the deficits of the sensorimotor and limbic networks vital to iRLS, we hypothesized that PD-RLS+ patients may present functional abnormalities in sensorimotor and limbic regions.

Materials and methods
Subjects
This study was conducted from March 2017 to May 2018. All the PD patients were diagnosed based on the Movement Disorder Society (MDS) clinical diagnostic criteria of PD.15 All the subjects wrote their agreement forms to participate in the study, and the project was approved by the Ethics Committee of the Second Affiliated Hospital of Guangzhou University of Chinese Medicine (No. Y2017-061-01). Patients were excluded due to secondary Parkinsonism, atypical parkinsonian disease, advanced PD stage (Hoehn–Yahr (H-Y) ≥4), age less than 30 or greater than 80 years, history of traumatic brain injury or other neuropsychological disorders (cognitive impairment, depression, etc.), left-handedness, and any contraindications for fMRI. All the PD patients were divided into two groups as PD-RLS+ and PD without RLS (PD-RLS−). RLS was diagnosed through clinical interview by a neurologist with sleep medicine expertise and according to the International Restless Legs Syndrome Study Group diagnostic criteria.1 Patients who had iron-deficiency anemia, peripheral neuropathy, myelopathy, or chronic kidney disease were excluded, since these disorders may cause secondary RLS. However, subjects with only peripheral iron deficiency without definite cause were included. Neuropsychological evaluation was conducted during the “off” medication state including the MDS-Unified PD Rating Scale (MDS-UPDRS), the H-Y scale, the PD Questionnaire (PDQ-39), Non-Motor Symptoms Scale (NMSS), PD Sleep Scale (PDSS), Mini Mental State Examination (MMSE),...
Hamilton Depressive Rating Scale (HAMD), and Chinese Handedness Inventory (CHI). Patients were then assessed by the International Restless Legs Syndrome Study Group Rating Scale (IRLS). Meanwhile, normal subjects were matched in terms of age and sex with patients. Normal subjects presented normal neurological status without RLS symptoms and without history of neurological, psychiatric, or other medical illness. Detailed examination included IRLS, MMSE, HAMD, and CHI to exclude RLS, cognitive impairment, depression, and left-handedness in all normal subjects.

Image acquisition

The brains’ images of all subjects were generated by a Siemens 3.0T scanner (Erlangen, Germany) with an eight-channel head coil. fMRI scans were performed during RLS-free periods and in “off” medication state to reduce the effect of the medication on the images. During the data acquisition process, all subjects were asked to close their eyes and lie quietly for magnetic resonance scanning. The three-dimensional structural images were produced with a T1-weighted Magnetization-Prepared Rapid Gradient-Echo (MP-RAGE) sequence on the condition of repetition time = 1900 ms, echo time = 2.27 ms, flip angle = 9°, thickness = 1.0 mm, field of view = 256 × 256 mm², and matrix = 256 × 256. Resting-state functional images were collected using anecho-planar imaging sequence with 31 axial slices, repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, thickness = 3.5 mm, gap = 0.35 mm, field of view = 224 × 224 mm², and matrix = 64 × 64 and 240 time points.

fMRI data preprocessing

The fMRI data preprocessing was performed using Data Processing & Analysis for Brain Imaging (DPABI) based on MATLAB R2013a (The Math Works, Natick, MA, USA). The first 10 time points of each participant were discarded to allow for scanner stabilization. The remaining functional images were then corrected for the intravolume acquisition time delay using slice-timing and realignment. One PD-RLS patient was excluded based on the criteria of displacement >2.5 mm or angular rotation >2.5° in any direction. All corrected functional data were spatially normalized to the Montreal Neurological Institute space and resampled to 3 × 3 × 3 mm³. Linear trends were removed and a temporal band-pass filter (0.01–0.08 Hz) was applied to eliminate the low-frequency drift and high-frequency physiological noise. Finally, 24 head-motion parameters, white matter signals, and cerebrospinal fluid signals were regressed using a general linear model.

ReHo analysis

Individual ReHo maps were generated for each subject. Twenty-seven nearest neighboring voxels were defined as a cluster and a Kendall’s coefficient of concordance (KCC) value (ranging from 0 to 1) was given to the voxel at the center of this cluster referring to the temporal sequences of its 26 neighboring voxels. The individual ReHo map was normalized by dividing the KCC among each voxel by the average KCC of the whole brain to reduce the influence of individual variations in the KCC value. The ReHo maps were then spatially smoothed by a 4-mm full-width half-maximum Gaussian filter.

Seed-based FC analysis

The brain regions which were significantly different in ReHo between the two patient groups were saved as masks separately and used as seeds in subsequent FC analyses. The average time series of each mask seed was extracted and correlated to the time series of all of the voxels in the whole brain for each subject. In this way, FC maps of each seed were produced. Finally, these maps were transformed by Fisher’s r-to-z transformation to improve normality.

Statistical analysis

One-way analysis of variance (ANOVA) was used to compare the age, MMSE, and HAMD among the three groups. The Kruskal–Wallis test was performed to compare sex distributions. Two-sample t tests were applied to compare the PD onset age, levodopa equivalent doses, MDS-UPDRS, H-Y scale, PDQ-39, NMSS, PDSS, and IRLS between the two patient groups. The above-mentioned statistical analysis was all conducted in SPSS 22.0 (Chicago, IL, USA). The level of significance was set as P < 0.05.

For ReHo and FC analyses, one-way ANOVA were conducted in DPABI to explore the differences among the three groups. Post hoc t tests were performed to identify group differences between each pair of the three groups. The resulting statistical map was set at P < 0.05 corrected via Gaussian random field (GRF) theory (voxel significance: P < 0.005 and cluster significance: P < 0.05) and were visualized with the DPABI viewer. Subsequently, brain regions that showed significant differences between the two patient groups were identified as regions of interest, and the mean ReHo values and z values of FC were extracted using DPABI. Pearson’s correlation analyses were administrated to examine the relationship between the altered ReHo/FC and clinical variables (e.g., IRLS, UPDRS, PDQ-39, NMSS, PDSS scores, and H-Y scales) within
PD patients in SPSS. The statistical significance level was set as $P < 0.05$.

Results

Demographic and clinical data

The demographic and clinical characteristics of the three groups were extracted from the Chronic Disease Management System in the Second Affiliated Hospital of Guangzhou University of Chinese Medicine and are described in Table 1. All the subjects were normally cognitive, free of depression and right handedness according to the measurement of MMSE, HAMD, and CHI. No statistically significant differences in gender and age were observed among the three groups ($P > 0.05$). Nor were the PD onset age, levodopa equivalent doses, MDS-UPDRS, H-Y scale, PDQ-39, and NMSS between the two patient groups ($P > 0.05$). There were significant differences in PDSS and IRLS between the two patient groups ($P < 0.05$). Based on the item 7 in IRLS, six of PD-RLS$^+$ patients had very severe RLS symptoms, one was severe, two were moderate, and five were mild. Half of them reported a sensation of electrical, prickling, burning, tingling, or itching. As for the severity on an average day based on the item 8 in IRLS, half of them had RLS symptoms less than 1 h per day, four had 1–3 h per day, while three suffered 8 h or more per day.

ReHo differences between groups

The one-way ANOVA test showed significant differences in ReHo among the three groups in the following brain regions: the precentral and postcentral gyri, caudate nucleus, paragigocampal gyrus, middle cingulate and paracingulate gyri, lingual and fusiform gyri, and inferior temporal gyrus ($P < 0.05$) (Table 2).

The PD-RLS$^+$ group presented significant reduced ReHo in the right precentral gyrus in contrast with PD-RLS$^-$/C0 group ($P < 0.05$, GRF corrected) (Table 3 and Figure 1(a)). Compared to the normal controls (NC) group, the PD-RLS$^+$ group demonstrated significant increase of regional activity in the left brainstem and significant decreases of ReHo in the left lingual gyrus, fusiform gyrus, inferior occipital gyrus, middle cingulate and paracingulate gyri, and supplement motor area (SMA) ($P < 0.05$, GRF corrected) (Table 3 and Figure 1(b)). There was a significant increase of ReHo observed in the right inferior temporal gyrus and decrease of ReHo in the right caudate nucleus, middle cingulate and paracingulate gyri, and bilateral parahippocampal gyrus in the PD-RLS$^-$/C0 group compared to the NC group ($P < 0.05$, GRF corrected) (Table 3 and Figure 1(c)).

FC differences between groups

The ReHo analysis revealed that the regional activity in the right precentral gyrus exhibited significant difference

Table 1. Participants’ demographic and clinical characteristics.

|                           | PD-RLS$^+$ (n = 14) | PD-RLS$^-$ (n = 20) | NC (n = 19) | $P$  |
|---------------------------|---------------------|---------------------|-------------|------|
| Gender (M/F)              | 5/9                 | 12/8                | 7/12        | 0.252|
| Age (years)               | 62.86 ± 2.25        | 64.60 ± 1.29        | 62.84 ± 1.61| 0.678|
| MMSE                      | 28.21 ± 0.47        | 27.90 ± 0.36        | 28.21 ± 0.38| 0.803|
| HAMD                      | 4.21 ± 0.51         | 3.65 ± 0.53         | 3.42 ± 0.48 | 0.576|
| PD onset age              | 57.57 ± 2.68        | 58.60 ± 1.95        | –           | 0.753|
| Levodopa equivalent doses (mg/day) | 296.43 ± 42.08 | 377.50 ± 46.24 | –           | 0.226|
| MDS-UPDRS                 | 54.14 ± 6.27        | 50.30 ± 4.11        | –           | 0.596|
| UPDRS I                   | 8.29 ± 1.00         | 7.45 ± 1.23         | –           | 0.625|
| UPDRS II                  | 12.36 ± 1.72        | 11.35 ± 1.15        | –           | 0.615|
| UPDRS III                 | 31.14 ± 4.23        | 29.20 ± 2.61        | –           | 0.682|
| UPDRS IV                  | 2.36 ± 0.96         | 2.30 ± 0.79         | –           | 0.963|
| H&Y stage                 | 2.11 ± 0.20         | 1.92 ± 0.11         | –           | 0.394|
| PDQ-39                    | 31.79 ± 5.23        | 32.80 ± 4.29        | –           | 0.881|
| NMSS                      | 39.25 ± 5.66        | 40.83 ± 9.89        | –           | 0.891|
| PDSS                      | 106.50 ± 6.09       | 121.80 ± 4.58       | –           | 0.049*|
| IRLS                      | 14.50 ± 1.70        | 0.00                | –           | 0.000*|

HAMD: Hamilton Depressive Rating Scale; H&Y: Hoehn & Yahr scale; IRLS: International Restless Legs Syndrome Study Group Rating Scale; MDS-UPDRS: Movement Disorder Society- Unified Parkinson’s Disease Rating Scale; MMSE: Mini Mental State Examination; NC: normal controls; NMSS: Non-Motor Symptoms Scale; PD: Parkinson’s disease; PDQ-39: Parkinson’s Disease Questionnaire-39; PD-RLS$^+$: Parkinson’s disease with restless legs syndrome; PD-RLS$^-$: Parkinson’s disease without restless legs syndrome; PDSS: Parkinson’s Disease Sleep Scale.

*P < 0.05.
between the PD-RLS\(^+\) and PD-RLS\(^-\) groups. Therefore, the right precentral gyrus was selected as seed for subsequent FC analysis. One-way ANOVA showed significant differences of the FC between the right precentral gyrus and the left postcentral gyrus among the three groups \((P < 0.05, \text{GRF corrected})\). PD-RLS\(^-\) group presented a significant decrease of FC in the left postcentral and precentral gyri compared to the PD-RLS\(^+\) group \((P < 0.05, \text{GRF corrected})\) (Table 3 and Figure 2(a) and in the left postcentral gyrus compared to the NC group \((P < 0.05, \text{GRF corrected})\) (Table 3 and Figure 2(b)). No significant difference of the right precentral gyrus based FC in brain was found between the PD-RLS\(^-\) and NC groups.

**Correlations between abnormal ReHo/FC and clinical variables in PD patients**

Highly negative correlation was calculated between the ReHo values of the right precentral gyrus and the IRLS

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**Table 2.** The one-way analysis of variance result of the regional homogeneity differences among the three groups.

| Brain region                          | Cluster size | Peak MNI coordinates | Peak F values |
|---------------------------------------|--------------|----------------------|---------------|
|                                       |              | X        | Y     | Z     |            |
|                                       |              | 39       | -18   | 45    | 8.45       |
| Right precentral gyrus                 | 186          | 39       | -18   | 45    | 8.45       |
| Right inferior temporal gyrus          | 349          | 51       | -9    | -42   | 8.43       |
| Right caudate nucleus                  | 330          | 21       | 9     | 21    | 13.04      |
| Right parahippocampal gyrus            | 722          | 18       | 0     | -21   | 13.58      |
| Left parahippocampal gyrus             | 232          | -21      | 3     | -21   | 9.21       |
| Left lingual, fusiform, and inferior occipital gyri | 219     | -18      | -78   | -9    | 8.39       |
| Bilateral middle cingulate and paracingulate gyri, and supplement motor area | 330 | 9        | -30   | 30    | 9.57       |

**MNI:** Montreal Neurological Institute.

**Table 3.** Brain regions with different ReHo and FC between each pair of the three groups.

| Brain region                                      | Cluster size | Peak MNI coordinates | Peak T values\(^a\) |
|---------------------------------------------------|--------------|----------------------|--------------------|
|                                                   |              | X        | Y     | Z     |                  |
| ReHo                                              |              |            |       |       |                  |
| PD-RLS\(^-\) vs. PD-RLS\(^+\)                    |              |            |       |       |                  |
| Right precentral gyrus                            | 50           | 39       | -18   | 45    | -4.38          |
| PD-RLS\(^-\) vs. NC                               |              |            |       |       |                  |
| Left brainstem                                     | 38           | -6       | -24   | -45   | 4.52           |
| Left lingual, fusiform, and inferior occipital gyri | 54           | -18      | -78   | -9    | -4.14          |
| Left middle cingulate and paracingulate gyri, and supplement motor area | 47           | -6       | -18   | 48    | -4.61          |
| PD-RLS\(^-\) vs. NC                               |              |            |       |       |                  |
| Right inferior temporal gyrus                      | 69           | 51       | -9    | -42   | 3.98           |
| Left parahippocampal gyrus                        | 36           | -21      | 3     | -21   | -4.35          |
| Right parahippocampal gyrus                       | 79           | 18       | 0     | -21   | -5.36          |
| Right caudate nucleus                             | 34           | 21       | 6     | 21    | -5.27          |
| Right middle cingulate and paracingulate gyri      | 39           | 9        | -30   | 30    | -4.11          |
| FC of the right precentral gyrus                   |              |            |       |       |                  |
| PD-RLS\(^-\) vs. PD-RLS\(^+\)                    |              |            |       |       |                  |
| Left postcentral gyrus                            | 20           | -24      | -33   | 66    | -3.78          |
| Left precentral gyrus                             | 3            | -30      | -24   | 57    | -3.62          |
| PD-RLS\(^-\) vs. NC                               |              |            |       |       |                  |
| Left postcentral gyrus                            | 82           | -27      | -33   | 69    | -6.07          |

**FC:** functional connectivity; **MNI:** Montreal Neurological Institute; **NC:** normal controls; **PD-RLS\(^-\):** Parkinson’s disease with restless legs syndrome; **PD-RLS\(^+\):** Parkinson’s disease without restless legs syndrome; **ReHo:** regional homogeneity.

\(^a\)A positive/negative t value represents an increased/decreased ReHo or FC.
Figure 1. Brain regions with ReHo differences across the three groups ($P < 0.05$, Gaussian random field corrected). (a) Compared with PD-RLS–, PD-RLS+ showed a reduced ReHo in the right precentral gyrus. (b) Compared with normal controls (NC), PD-RLS+ demonstrated significant increase in the left brainstem and significant decreases in the left lingual gyrus, fusiform gyrus, inferior occipital gyrus, middle cingulate and paracingulate gyri, and supplement motor area. (c) Compared with NC, PD-RLS+ shows a significant increase in the right inferior temporal gyrus and decrease in the right caudate nucleus, middle cingulate and paracingulate gyri, and bilateral parahippocampal gyri. (d) Highly negative correlation was calculated between the ReHo values of the right precentral gyrus and IRLS total scores in PD patients. IRLS: International Restless Legs Syndrome Study Group Rating Scale; PD-RLS+: Parkinson’s disease with restless legs syndrome; PD-RLS–: Parkinson’s disease without restless legs syndrome; ReHo: regional homogeneity.

Figure 2. Significant differences of FC of the right precentral gyrus across the three groups ($P < 0.05$, Gaussian random field corrected). (a) Compared with PD-RLS–, PD-RLS+ showed significant lower FC in the left postcentral and precentral gyri. (b) Compared with normal controls, decreased FC in the left postcentral gyrus was found in PD-RLS+ patients. (c) Significantly reduced z values of FC between the right precentral gyrus and left postcentral/precentral gyri in PD patients were negatively correlated with IRLS total scores in PD patients. FC: functional connectivity; IRLS: International Restless Legs Syndrome Study Group Rating Scale; PD-RLS+: Parkinson’s disease with restless legs syndrome; PD-RLS–: Parkinson’s disease without restless legs syndrome.
total scores in PD patients (r = −0.679, P = 0.000) (Figure 1(d)). Significantly reduced z values of FC between the right precentral gyrus and left postcentral/precentral gyri in PD patients were also negatively correlated with severe RLS symptoms (left postcentral gyrus r = −0.486, P = 0.004; left precentral gyrus r = −0.495, P = 0.003) (Figure 2(c)). No significant correlation was found between abnormal ReHo/FC and other clinical variables.

**Discussion**

The prevalence of RLS in PD patients is much higher than that in general adult population. Since dopaminergic agents can improve symptoms in RLS and PD, and the nigrostriatal dopaminergic system is primarily involved in PD, it is possible that the extrastriatal dopaminergic systems, for example diencephalic dopaminergic system, may be variably involved in those PD patients generating RLS symptoms. Qu et al. performed stereotaxic bilateral 6-hydroxydopamine (6-OHDA) lesions into the diencephalic dopaminergic spinal neurons (A11) nucleus and pathologic examination demonstrated a 94% reduction in A11 tyrosine hydroxylase staining cells in mice injected with 6-OHDA but minimal effects on other areas. Locomotor activities were significantly increased in the A11-lesioned mice compared with controls, which could be normalized after treatment with the D2/D3 agonist ropinirole, as is seen in human RLS, but was worsened by the D1 agonist SKF38393. Impairment in dopaminergic transmission, common in the etiology of PD and RLS, may explain why the prevalence of RLS in patients with PD is high. Dysfunction of dopaminergic signaling can directly change the brain network. Hence, we did fMRI analysis to investigate the altered patterns of brain activity and functional connections in PD patients with and without RLS by combining both ReHo and seed-based FC analyses. We demonstrate that PD patients with or without RLS show abnormalities in cortical and subcortical functional networks, and some of these alterations are associated with clinical characteristics. The present findings provide information on the underlying pathophysiology mechanism of PD-RLS$^+$ patients in relation to distributed networks dysfunctions.

A marked downtick of ReHo values was found in the right precentral gyrus and left SMA of PD-RLS$^+$ patients compared to PD-RLS$^-$ and NC. Furthermore, the FC between the right precentral gyrus and left postcentral/precentral gyri decreased dramatically within PD-RLS$^+$ patients. The ReHo values of the right precentral gyrus as well as the z values of FC between the right precentral gyrus and left postcentral/precentral gyri were all negatively correlated with IRLS total scores but not correlated with UPDRS, H-Y, or MMSE scores in PD patients. In addition, the motor and cognitive function of two patient groups were indistinguishable according to their UPDRS III and MMSE scores; hence, we believe such dysfunction of sensorimotor network is related to RLS in PD. The sensorimotor system comprises of the precentral gyrus, postcentral gyrus, SMA, and so on. Many studies reported the impaired sensorimotor integration existed in RLS patients. RLS patients often reported abnormal feeling such as spontaneous electrical, prickling, burning, tingling, and itching sensations, which is similar to those of neuropathic pain. Unpleasant sensations were perceived as painful by 47% to 61% of iRLS patients in large clinical studies, and 59% of individuals with RLS reported pain in a general population survey. In our study, 50% PD-RLS$^+$ patients reported painful sensations. The pain experience includes sensory and affective motivational components, which are controlled by the lateral and medial pain system, respectively. The lateral pain system is laterally projecting spinothalamic and trigeminothalamic pathways that terminate in lateral thalamic nuclei, which in turn project to primary and secondary somatosensory cortices that process the sensory-discriminative dimension of the pain. Evidence shows that the primary somatosensory cortex has nociceptive neurons which are involved in the encoding the process of perceiving the intensity of noxious stimulation. The pain messages emerge internally but not externally in RLS patients. Rana et al. reported the frequency of reporting pain was significantly higher in PD-RLS$^+$ patients than PD-RLS$^-$ patients. The reduced regional activity and FC of sensorimotor network in PD patients could be an imaging biomarker for distinguishing PD-related RLS in the early or late stage of the disease, which may help to start early initiation of appropriate medication.

While PD-RLS$^+$ patients displayed malfunction in lateral pain system, the functional abnormality of the lateral and medial pain systems was confirmed obviously in iRLS patients. The medial pain system comprises anterior cingulated cortex, insula, prefrontal cortex, and amygdale, which underlie the processing of the affective-motivational dimension of pain. Study conducted in iRLS patients showed the gray matter volume of bilateral postcentral and the left precentral gyri was correlated negatively with the severity of RLS symptoms and disease duration, and RLS severity was positively correlated with the FC in anterior cingulate network. Thus, it is reasonable to infer that less severe in RLS-related symptoms of PD-RLS$^+$ than iRLS patients, which was supported by Zhu et al.’s study.

It is noteworthy that higher ReHo signals in brainstem and lower in lingual, fusiform, and inferior occipital gyri were detected in PD-RLS$^+$ patients than in NC. The activation of brainstem and red nuclei was found to be
associated with periodic limb movements in iRLS. The lingual, fusiform, and inferior occipital gyri pertain to visual processing regions. An fMRI study conducted in iRLS patients revealed that amplitude of low-frequency fluctuations was lower in the visual processing region compared with controls. Because motor responses are closely linked to visual stimuli, visual information processing is an important part of the sensorimotor network. The low activity in visual processing region together with sensorimotor cortex of PD-RLS patients may weaken the inhibitory effects of descending pathways, leading to the abnormal central somatosensory processing.

Several limitations of the study should be addressed. First, relatively small sample size in each group restricts the ability to investigate the full extent of ReHo and FC. Therefore, the results should be interpreted cautiously. Second, all of the PD-RLS patients were under fMRI scan during RLS-free periods, which may have biased the outcomes measures. Third, we used MMSE to screen for the cognitive impairments as it is quite specific and easy to complete. Nonetheless, MMSE may not be as sensitive as the Montreal Cognitive Assessment to detect mild cognitive impairments. Finally, the data are cross-sectional; whether these alterations of brain function change dynamically after long-term medication remains to be established in the longitudinal studies.

Conclusion

Diminished ReHo and FC were detected at the sensorimotor network in PD-RLS patients in this study. Data proposed that the functional abnormalities of sensorimotor network may result in the disruption of lateral pain pathway, thereby affect the discrimination of sensory features of the pain, and participate in the dysfunctional mechanism contributing to PD-related RLS development.

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Authors’ Contributions

Z. Li and P. Xu conceived and designed the experiments; J. Chen, X. Li, and B. Liu performed the functional magnetic resonance imaging scans and analyzed the functional magnetic resonance imaging data; Z. Wu and X. Zhu analyzed the clinical data; M. Zhou, Q. Cai, and X. Chen collected the clinical data; X. Yang, J. Lu, L. Zhang, and X. Luo recruited potential participants; and Z. Li, Y. Lin, and P. Xu wrote the manuscript.

Declaration of Conflicting Interests

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