

## Original Article

# Regional homogeneity changes in early and advanced Parkinson's disease: a resting state functional magnetic resonance imaging study

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**Abstract:** Objective: Previous work has shown regional homogeneity (ReHo) differences in Parkinson's disease (PD) patients. So looking in more detail at differences between early and late stages is valuable. The aim of our study was to investigate brain activity of early and advanced PD in the resting state by using a ReHo approach. Methods: Functional magnetic resonance images were acquired in 35 patients with PD at in early stage and advanced stage, as well as in 17 age- and sex-matched normal controls (NC). Results: In PD patients compared with NC, we observed decreased ReHo in motor cortex and increased ReHo in the right cuneus and frontal eye field. In early stage of PD, decreased ReHo was located in bilateral posterior insular cortex, dorsolateral prefrontal cortex, angular gyrus, supramarginal gyrus, left precuneus, right superior temporal gyrus, and right cerebellar posterior lobe, in addition to motor cortex; and increased ReHo in the left cerebellar anterior lobe. During disease evolution, decreased ReHo was found in more brain areas, including right cerebellar posterior lobe, bilateral orbitofrontal cortex, gyrus rectus and left middle and inferior temporal gyrus; and increased ReHo in bilateral middle occipital gyrus, insular cortex, cingulate gyrus, superior temporal gyrus, and right middle temporal gyrus and thalamus. Whereas no changes were observed in bilateral motor cortex. Conclusion: Our results indicate that neuronal activity decrease in motor cortex with no marked variation during disease progression in a resting state, and decreased cognitive function may be associated with worsening motor symptoms in PD.

**Keywords:** Parkinson's disease, regional homogeneity, resting state, functional magnetic resonance imaging

## Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease which is characterized by distinct motor symptoms. However, the pathogenesis of PD is unclear. Currently, functional magnetic resonance imaging (fMRI) is anticipated to allow new insight into the pathophysiology of PD.

Of fMRI methods, regional homogeneity (ReHo) method has been used to analyze the blood oxygen level-dependent signal of the brain. ReHo is a voxel-based measure of brain activity which evaluates the similarity or synchronization between the time series of a given voxel and its nearest neighbors [1]. It has been successfully used to investigate the functional

modulations in the resting state in the patients with Alzheimer's disease (AD) [2], schizophrenia [3], attention deficit hyperactivity disorder [4, 5], multiple system atrophy [6], and normal aging subjects [7].

In recent years, the resting-state fMRI method has also been applied to investigate PD-related modulations of neural activity. Wu et al. [8] showed that ReHo in PD patients not taking medication was generally decreased in the putamen, thalamus, and SMA, and increased in the cerebellum, primary sensorimotor cortex, and premotor areas compared with controls. These changes were normalized by instant administration of levodopa. Another study [9] examined ReHo changes in less affected PD patients tested when not taking medication.

## ReHo changes in early and advanced PD

**Table 1.** Clinical details of patients with Parkinson's disease (mean  $\pm$  SD)

Variables	Earlier group	Advanced stage group
Age (year)	60.28 $\pm$ 10.14	63.81 $\pm$ 9.16
Sex, No.		
M	8	13
F	7	7
H & Y score	1.06 $\pm$ 0.17	2.53 $\pm$ 0.69
Disease duration (years)	4.18 $\pm$ 2.95	5.42 $\pm$ 4.23
MMSE score	28.29 $\pm$ 1.38	28.43 $\pm$ 1.16
UPDRS score	3.43 $\pm$ 2.30	4.86 $\pm$ 2.32

UPDRS, Unified Parkinson's disease rating scale; MMSE, Mini-Mental State Examination; H & Y, Hoehn and Yahr staging; M, male; F, female.

The most consistent findings between these studies are reduced ReHo in the putamen and increased ReHo in the cerebellum, medial frontal gyrus, and middle temporal gyrus in PD patients compared with controls. However, these studies showed opposite changes in ReHo in PD patients versus controls in several other areas. Such discrepancies point to the need for further studies that could inform our understanding of how ReHo is affected by dopaminergic medication and disease severity in PD [10].

The aim of this study was to investigate whether disease severity impacts on ReHo. To explore these issues, we investigated the fMRI data from patients with PD in early and advanced stages and normal controls using ReHo analysis.

### Materials and methods

#### Participants

This study was conducted in accordance with the Declaration of Helsinki and approved by the local Institutional Review Board. Written informed consent was obtained from each subject.

Thirty-five patients with PD (21 men and 14 women; age range, 38-77 years; mean age, 62.41 $\pm$ 9.50 years) and 17 age- and sex-matched control subjects (10 men and 7 women; age range, 38-75 years; mean age, 60.44 $\pm$ 9.74 years) were included in the study. All patients were right-handed according to the

Edinburgh Handedness Inventory [11]. The duration of the disease was 4.81 $\pm$ 3.43 years. The diagnosis of PD was made by a neurologist using the criteria of the Parkinson's Disease Society Brain Bank, London, England [12]. Patients were assessed with the UPDRS (Unified Parkinson's Disease Rating Scale) [13], and the Hoehn & Yahr disability scale [14]. Patients with PD were divided into two groups according to the severity of the disease: early group (Hoehn & Yahr  $\leq$ 1.5) and advanced stage group (Hoehn & Yahr  $>$ 1.5). All patients completed the Mini-Mental State Examination (MMSE). Baseline characteristics are summarized in **Table 1**.

Exclusion criterion were: 1) Patients with secondary parkinsonism; 2) Patients with Parkinson-plus syndromes; 3) Patients with other internal medicine diseases apart from PD or Parkinsonism which may affect the brain and cognition function evaluation; 4) Patients with a history of acute cerebrovascular disease within 3 months; 5) Patients with active epilepsy; 6) Patients with a history of mental disorder including delirium, depression and anxiety.

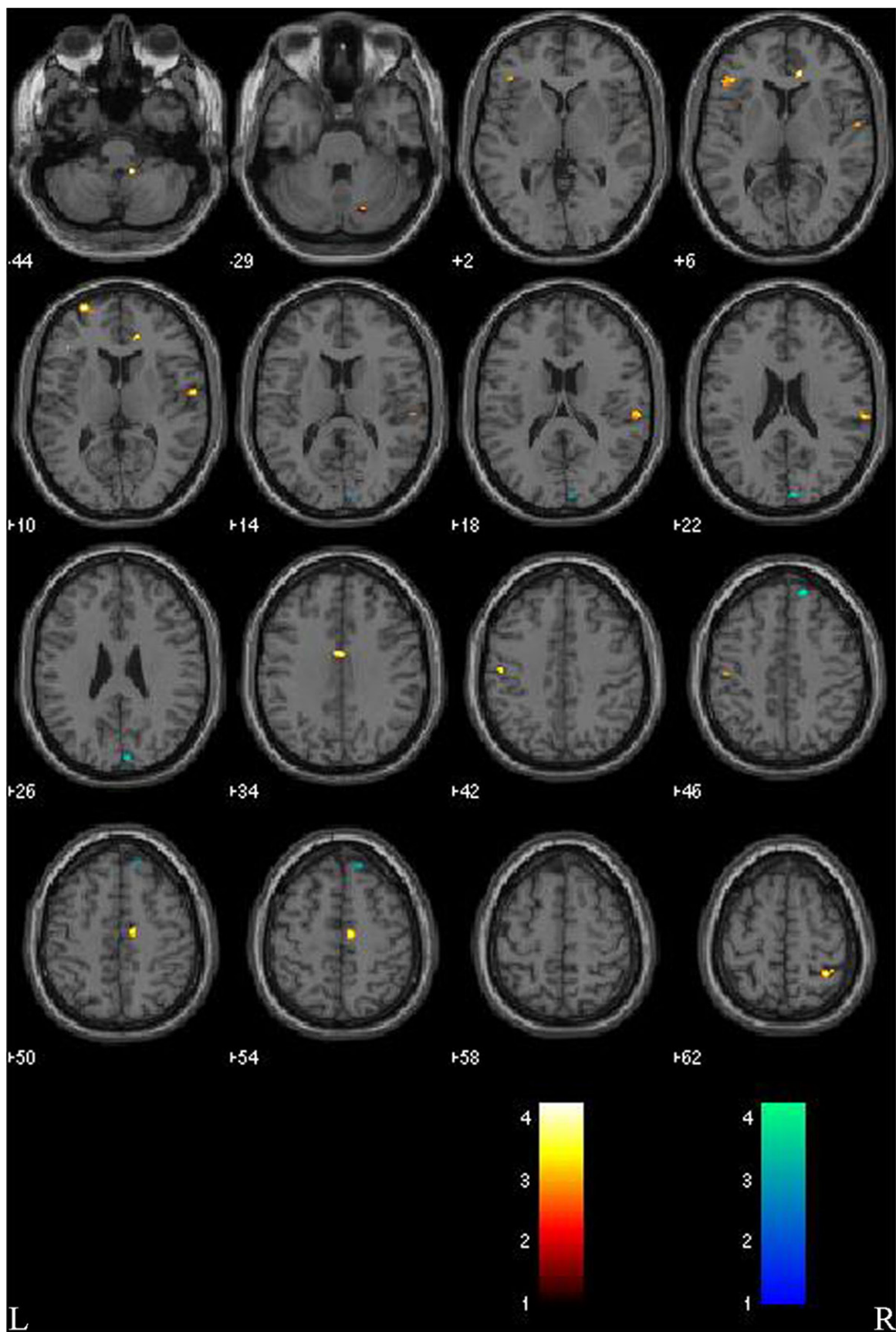
Healthy controls were recruited from the healthy volunteers and from relatives of patients with PD. The controls had no active neurological or psychiatric disorder. They had no cognitive deficits, and were not taking drugs that could affect their cognition. Routine brain MRI showed no abnormalities.

#### MRI data acquisition

Images were acquired on a 3.0-T MR scanner (Signa HDxt, GE Healthcare, Milwaukee, WI). All subjects were placed in a standard head coil and fitted to foam padding to reduce head motion. During resting state fMRI, subjects were instructed to keep their eyes closed, to remain motionless, and to not to think of anything in particular.

Functional images were acquired using a single-shot, gradient echo type echo planar imaging (GRE-EPI) sequence (TR = 2000 ms, TE = 30 ms and flip angle = 90°). Thirty-two transverse slices (FOV = 24 cm, matrix = 64 $\times$ 64, slice thickness = 4 mm, section gap = 1 mm) were acquired. Resolution was 3.75 $\times$ 3.75 mm<sup>2</sup> in-plane. The fMRI scanning lasted for 6 min, so 180 time points were obtained. Subsequently,

ReHo changes in early and advanced PD



## ReHo changes in early and advanced PD

**Figure 1.** Alterations of ReHo in PD patients compared with normal controls ( $P < 0.05$ , corrected). The patients with PD had significantly lower ReHo in the left primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC), and right posterior central gyrus, ACC, premotor cortex (PMC), supplementary motor area (SMA), cerebellar posterior lobe, and superior temporal gyrus, whereas the regions with increased ReHo in the PD patients included the right cuneus and frontal eye field (FEF), compared to normal controls. Red and yellow, and blue and green colors indicate PD-related ReHo decreases and increases, respectively. L, left; R, right.

for spatial normalization and localization, a set of high-resolution T1-weighted anatomical images was acquired in axial orientation using a 3D brain volume imaging (BRAVO) sequence (TR = 8.4 ms, TE = 3.3 ms, flip angle = 13, NEX = 1, section thickness = 1 mm, gap = 0, FOV = 24 cm, matrix size = 228×256 and voxel size = 0.47×0.47×1 mm<sup>3</sup>) on each subject.

### Data preprocessing

Data preprocessing was carried out using Statistical Parametric Mapping software (SPM5, <http://www.fil.ion.ucl.ac.uk/spm>). The first 10 volumes of the functional images were discarded for the signal equilibrium and participants' adaptation to the scanning circumstance. The remaining 170 time points were left for further analysis. They were slice-time-corrected and realigned for head motion. The participants with head movement exceeding 1.5 mm of maximum translation in any of the x, y, and z directions or 1.5° of maximum rotation about the three axes were excluded from this study. The resulting images were normalized spatially to the normal EPI template and resampled to 2 mm×2 mm×2 mm voxels, and then smoothed by convolution with an isotropic Gaussian kernel of 4 mm full width at half maximum (FWHM) to decrease spatial noise. To further reduce the effects of confounding factors unlikely to be involved in specific regional correlation, a temporal filter (0.01-0.08 Hz) was used to reduce the low-frequency drift and physiological high frequency noise. Finally, we removed several sources of spurious variance by linear regression, including six head motion parameters, linear drift and average signals from whole brain.

### ReHo analysis

ReHo analysis was performed for each participant by calculating Kendall's coefficient concordance (KCC) of the time series of a given voxel with those of its nearest neighbors (26 voxels) on a voxel-wise basis. The KCC can be computed by the following formula:

$$W = \frac{\sum (R_i)^2 - n(\bar{R})^2}{(1/12)K^2(n^3 - n)}$$

where W is the KCC among given voxels, ranging from 0 to 1;  $R_i$  is the sum rank of the  $i$ th time point;  $\bar{R} = [(n + 1)K]/2$  is the mean of the  $R_i$ 's; K is the number of time series within a measured cluster (K = 27, one given voxel plus the number of its neighbors) and n is the number of ranks (here, n = 170). Through calculating the KCC value of every voxel in the whole brain, an individual ReHo map was obtained for each subject. In this study, gray matter was the region of interest, so the gray matter voxels were extracted to make a mask using the AAL Toolbox (created by WFU PickAtlas, <http://www.fmri.wfubmc.edu/download.htm>).

### Group statistical analysis

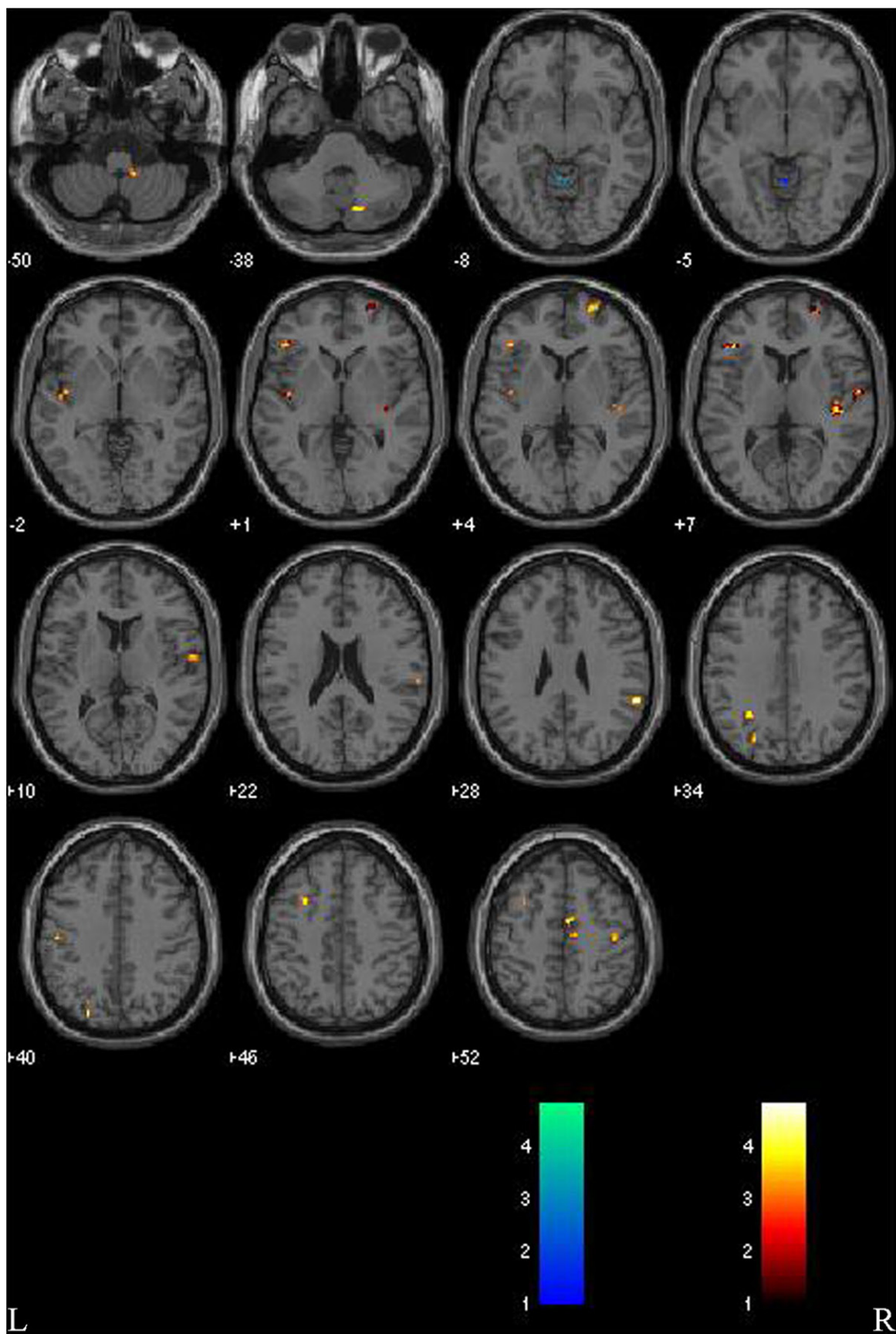
Two-sample t tests were applied to compare the ReHo results: (1) between the patients with PD and NC; (2) between the patients with PD in the early stages and NC; (3) between the patients with PD in the advanced stages and NC; and (4) between the patients with PD in the early stages and in the advanced stages. Age and sex were included as covariates to exclude the possible influences of these two factors on the results. The resulting statistical map was set at a combined threshold of  $P < 0.005$  and a minimum cluster size of 20 voxels, which resulted in a corrected threshold of  $P < 0.05$  determined by AlphaSim in AFNI (Analysis of Functional NeuroImages), (B.D. Ward, <http://afni.nih.gov/afni/docpdf/AlphaSim.pdf>). Statistical analysis were performed with the software SPSS, version 13.0 (SPSS, Chicago, IL, USA). Differences were considered statistically significant when  $P < 0.05$ .

## Results

### ReHo results within the normal controls

The default mode network including the anterior cingulate cortex (ACC), precuneus, and medi-

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## ReHo changes in early and advanced PD

**Figure 2.** Alterations of ReHo in early PD patients compared with normal controls ( $P < 0.05$ , corrected). We observed decreased ReHo in the PMC, SMA, M1, primary sensory cortex, posterior insular cortex, and dorsolateral prefrontal cortex (DLPFC), angular gyrus, supramarginal gyrus (both sides), posterior lobe of cerebellum and superior temporal gyrus (right side), and precuneus (left side) in early stage of PD patients. Conversely, ReHo was increased in the left cerebellar anterior lobe. Red and yellow, and blue and green colors indicate PD-related ReHo decreases and increases, respectively. L, left; R, right.

al prefrontal cortex (MPFC) exhibited significant higher ReHo than other brain areas, suggesting that ReHo can reflect the spontaneous brain activity.

### *ReHo alteration in patients with PD compared with NC*

Compared with the NC, the patients with PD had significantly lower ReHo in the left primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC), and right posterior central gyrus, ACC, premotor cortex (PMC), supplementary motor area (SMA), cerebellar posterior lobe, and superior temporal gyrus, whereas the regions with increased ReHo in the PD patients included the right cuneus and frontal eye field (FEF) (**Figure 1**).

### *ReHo alteration in patients with PD in the early stage compared with NC*

We observed decreased ReHo in the PMC, SMA, M1, primary sensory cortex, posterior insular cortex, and dorsolateral prefrontal cortex (DLPFC), angular gyrus, supramarginal gyrus (both sides), posterior lobe of cerebellum and superior temporal gyrus (right side), and precuneus (left side) in early stage of PD patients. Conversely, ReHo was increased in the left cerebellar anterior lobe (**Figure 2**).

### *ReHo alteration in patients with PD in the advanced stage compared with NC*

Compared to the NC, ReHo of the PD patients in the advanced stage group decreased in the posterior lobe of cerebellum and precentral gyrus (both sides), orbitofrontal cortex (OFC), gyrus rectus, DLPFC, fusiform gyrus and middle temporal gyrus (left side), and post-central gyrus, ACC, inferior parietal lobule, supramarginal gyrus, SMA, and superior temporal gyrus (right side) significantly ( $P < 0.05$ ) and increased in the bilateral cuneus, right middle frontal gyrus and right mediodorsal thalamic nuclei, lingual gyrus, precuneus, and FEF significantly ( $P < 0.05$ , **Figure 3**).

### *ReHo alteration in early and advanced with PD patients*

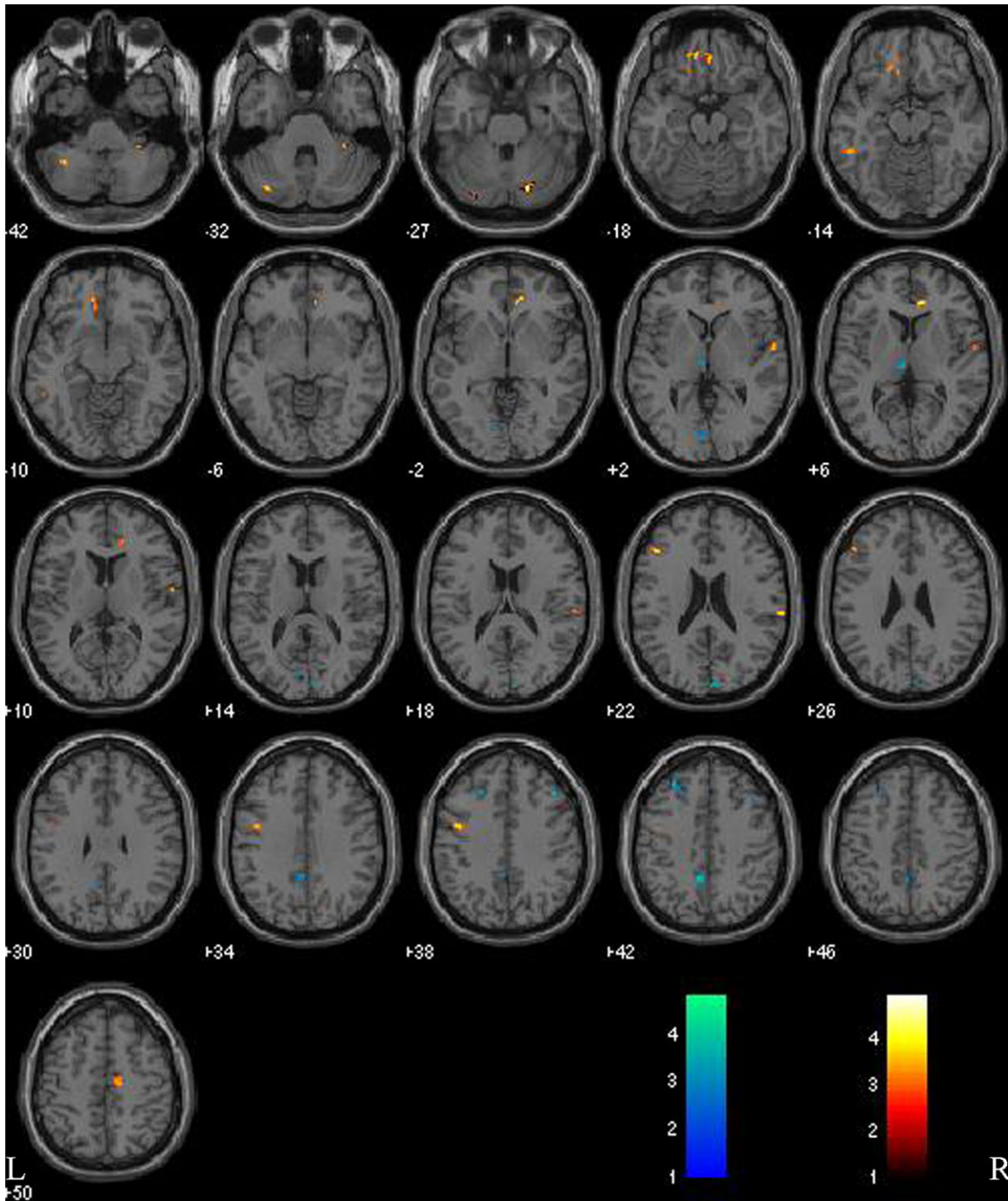
PD patients in the advanced stage group showed a decrease in ReHo in the resting state over the right posterior lobe of cerebellum, left middle frontal gyrus and middle and inferior temporal gyrus, and bilateral OFC, gyrus rectus, and an increase in ReHo over the bilateral middle occipital gyrus, insular cortex, cingulate gyrus, superior temporal gyrus, right middle temporal gyrus and thalamus, compared with those in early stage group (**Figure 4**).

## Discussion

In the present study, we used resting state fMRI to investigate the ReHo alteration in PD patients at different disease severity and normal controls. We found that patients with PD showed decreased ReHo mainly in the M1, SMA, ACC, DLPFC, and right cerebellar posterior lobe, and superior temporal gyrus compared with NC. Consistent with findings of previous resting state fMRI studies [8, 9, 15], our results indicated that abnormal brain activity might be widely distributed in PD during the resting state. We found decreased ReHo in some cortical motor areas, like the PMA and M1. The M1 is important in planning and initiation of movements. The SMA is suggested to be critical in planning and initiation of movements, particularly for those internally generated [16, 17], self-paced movement sequences [18]. The decreased ReHo in the M1 and SMA supports the findings reported by a previous study [19].

DLPFC are functionally implicated in cognitive control [20], more specifically in self-control [21], as well as in bringing about norm-related behavior [22] and in making strategic decisions [23]. In our study, decreased ReHo in DLPFC suggests that PD patients had a lower local neuronal activity, which contribute to explain why patients with PD had characteristic motor symptoms of the disorder are frequently accompanied by impairments in cognition.

## ReHo changes in early and advanced PD

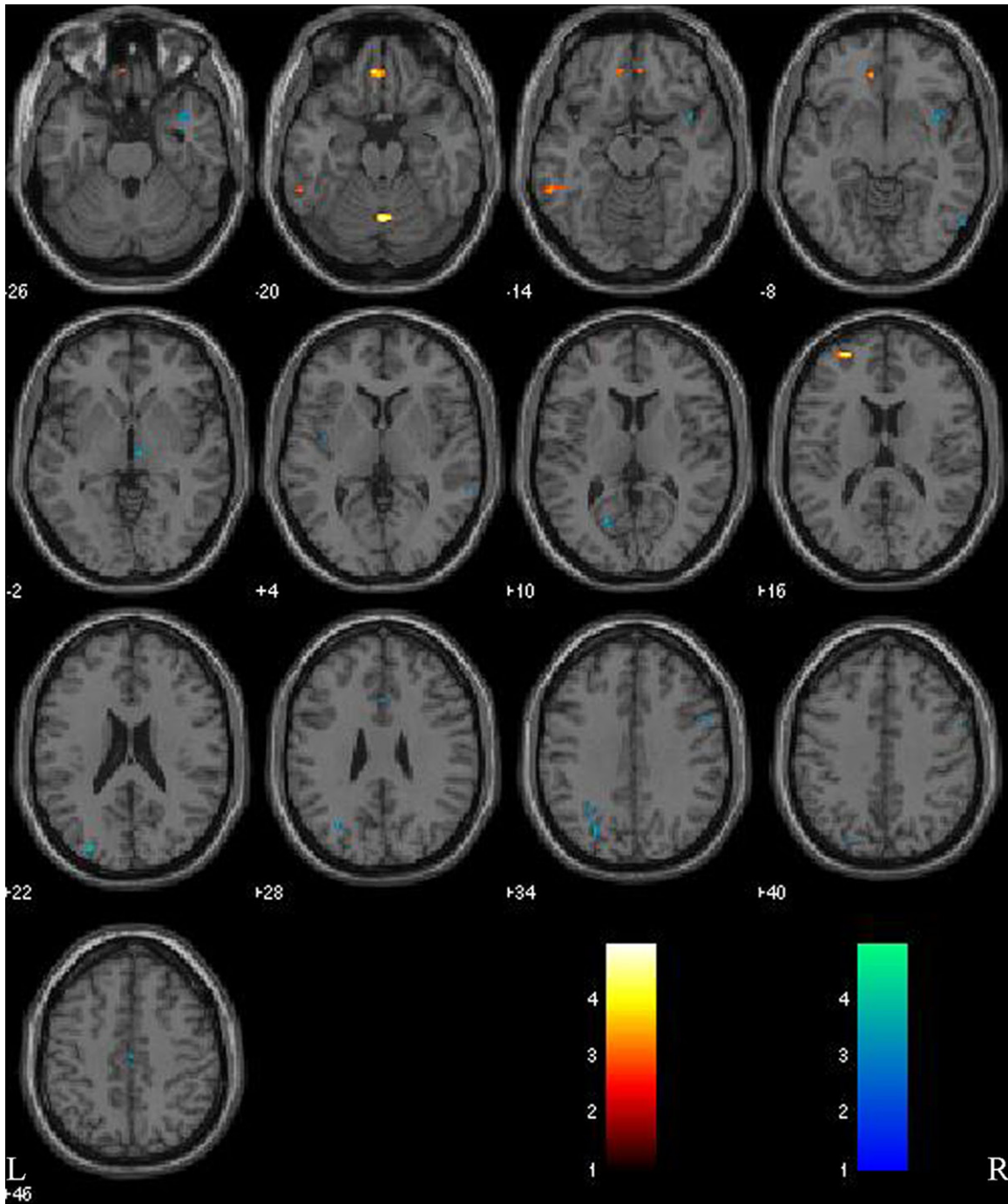


**Figure 3.** Alterations of ReHo in advanced PD patients compared with normal controls (two sample *t* test;  $P < 0.05$ , corrected). Compared to the NC, ReHo of the PD patients in the advanced stage group decreased in the posterior lobe of cerebellum and precentral gyrus (both sides), orbitofrontal cortex (OFC), gyrus rectus, DLPFC, fusiform gyrus and middle temporal gyrus (left side), and post-central gyrus, ACC, inferior parietal lobule, supramarginal gyrus, SMA, and superior temporal gyrus (right side) significantly ( $P < 0.05$ ) and increased in the bilateral cuneus, right middle frontal gyrus and right mediodorsal thalamic nuclei, lingual gyrus, precuneus, and FEF significantly. Red and yellow, and blue and green colors indicate PD-related ReHo decreases and increases, respectively. L, left; R, right.

In contrast to other studies, we not only compared PD patients with healthy controls but also investigated ReHo changes in different

physiological stage in PD. In early stage of PD, we observed decreased ReHo in bilateral posterior insular cortex, DLPFC, angular gyrus,

## ReHo changes in early and advanced PD



**Figure 4.** Alterations of ReHo in advanced PD patients compared with early PD patients (two sample *t* test;  $P < 0.05$ , corrected). PD patients in the advanced stage group showed a decrease in ReHo in the resting state over the right posterior lobe of cerebellum, left middle frontal gyrus and middle and inferior temporal gyrus, and bilateral OFC, gyrus rectus, and an increase in ReHo over the bilateral middle occipital gyrus, insular cortex, cingulate gyrus, superior temporal gyrus, right middle temporal gyrus and thalamus, compared with those in early stage group. Red and yellow, and blue and green colors indicate PD-related ReHo decreases and increases, respectively. L, left; R, right.

supramarginal gyrus, left precuneus, right superior temporal gyrus, and right cerebellar posterior lobe, in addition to motor cortex.

These findings suggest that parietal lobe and superior temporal gyrus cortex are associated with the integration of visual-spatial informa-

tion and attention. Levin et al. [24] reported that PD subjects did significantly worse on embedded figures, facial recognition, proverbs, verbal and figural memory measures, whereas made more perseverative responses on a set shifting task as compared to the normal controls. Huang et al. [25] found that early stage PD are associated with progressive decreases in regional metabolism in the prefrontal and inferior parietal regions using a longitudinal PET method. Lewis et al. [26] revealed significant signal intensity reductions during a working-memory paradigm in specific striatal and frontal lobe sites in patients with cognitive impairment compared with those patients who were not cognitively unimpaired. Our results are consistent with the above findings.

With disease progression, advanced PD patients had decreased ReHo in more brain areas, mainly involved in right cerebellar posterior lobe, bilateral OFC, gyrus rectus and left middle and inferior temporal gyrus. The OFC appears to play a special role in adjusting affect and appropriate behavioral responses to the society. Damage to OFC can lead to the euphoria, irresponsibility, lack of affect, and lack of concern for the present or future [27]. Helen et al. [28] reported that depressed patients with PD had lower relative metabolic activity in the caudate and orbital-inferior region of the frontal lobe as compared to both nondepressed patients and normal controls. In the current study, we found that advanced PD patients showed a lower ReHo, whereas no abnormality was observed in the early PD patients. These findings suggest that OFC alteration often occurs later, which addressed that PD patients may display different degrees of psychiatric and/or behavioural problems, such as depression and apathy with the progression of the disease [29].

During disease evolution, we found increased ReHo values in bilateral middle occipital gyrus, insular cortex, cingulate gyrus, superior temporal gyrus, and right middle temporal gyrus and thalamus. Occipital lobe is considered to play an important role in visual information processing, memory-related information processing, and the perceptive priming. The present study showed a decreased ReHo in the prefrontal lobe suggesting that PD patients may develop cognitive impairment such as memory disorder,

decreased learning ability, and visual-spatial agnosia; whereas an increased ReHo values in the occipital lobe which may represent a compensation for dysfunction. In the study, early PD patient did not show an increased ReHo in occipital lobe. Conversely, advanced PD patients showed an increased ReHo in occipital. These findings may represent a compensation for dysfunction.

In addition to occipital cortex, we observed an increased ReHo value in the bilateral insular lobe and right mediodorsal thalamic nuclei. These findings suggest that cognition-related anteroventral portion of insular cortex and mediodorsal thalamic nuclei involve in the primary compensatory mechanism for neuronal dysfunction [30]. Our results showed an increased ReHo in right mediodorsal thalamic nuclei and decreased ReHo over the prefrontal and parietal lobe in PD patients. It may also be the compensatory results for impairment of prefrontal and association cortex.

In this study, we observed that PD patients both in early and advanced stages showed significantly decreased ReHo in motor cortex as compared to normal controls. However, we did not observe significant alteration of ReHo values when compared advanced PD group with early PD group. However, cognition-related brain regions had an obvious alteration. These findings seems to be contrary with the notion that motor symptom in PD worsen with the disease progression. But it may illustrate that decreased cognitive function may play a critical role in worsening motor symptoms in PD.

In the current study, advanced PD patients showed an increased ReHo value in bilateral superior temporal gyrus and right middle temporal gyrus compared to the early PD patients, and a decreased ReHo over the left middle and inferior temporal gyrus. However, the ReHo of early PD and advanced PD patients was still lower in middle temporal cortex as compared to the normal controls. Therefore, it is not sufficient to conclude that the increased ReHo in advanced PD patients was the results of the compensation for local neuronal activity dysfunction. It just reflects that early and advanced PD patients had different degrees of ReHo alteration in temporal lobe, which may be explained by small sample size or individual difference.

Interestingly, PD patients showed decreased and increased ReHo in cerebellar hemisphere and insula, which seems to be contradictory. However, in practice, there was distinct difference between increased and decreased regions after careful observation. Cerebellum and insula are considered to participate in motor and cognitive function. Postuma et al. [31] present a meta-analysis of 126 functional imaging studies. They found different functional areas in the cerebellum and insula. Among these regions, cerebellar anterior lobe is strongly coactivated with the left putamen and is involved in movement; cerebellar posterior lobe is coactivated with caudate nucleus and is involved in cognitive function. Dorsal insula is coactivated with the putamen and participate in the motor function, whereas anterior-ventral insula is coactivated with caudate nucleus and participate in tasks involving in language and language planning. Compared to NC, we observed significant decreased ReHo in cognition-related right cerebellar posterior lobe in early PD patients, and more significantly in that of advanced PD patients, suggesting local neuronal impairment. Conversely, increased ReHo was observed in left cerebellar anterior in early PD patients. These findings may be due to the motor-related compensatory results for impairment of cerebellum in the early stage. Early PD patients showed a decreased ReHo value in motor-related bilateral dorsal insula, suggesting an impaired motor function. Whereas advanced PD patients showed an increased ReHo in cognition-related anterior-ventral insula. We speculated that cognitive function impairment increased with the disease progression, and it may be the language-related compensatory results for impairment of insula. Besides, ReHo of PD patients including early and advanced stages increased in the eye field, it may be caused by involuntary eye movements during examination.

In conclusion, our results suggested that abnormal brain activity of PD may exist in the resting state, and a pattern of decreased ReHo mainly in motor cortex and DLPFC. In early stage of PD, brain impairment occurs in more brain regions in addition to motor cortex. During disease progression, neuronal activity decrease in motor cortex exhibited no marked variation in a resting state, suggesting motor cortex impairment achieve steady state during disease evolution,

and decreased cognitive function may play an important role in worsening motor symptoms in PD. The ReHo analysis may be potentially valuable for detecting the development from early PD to advanced PD.

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### Disclosure of conflict of interest

None.

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