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ORIGINAL RESEARCH

Effects of levodopa therapy on voxel-based degree centrality in Parkinson's disease

Miao Zhong[1] · Wanqun Yang[2] · Biao Huang[2] · Wenjie Jiang[1] · Xiong Zhang[3] · Xiaojin Liu[1] · Lijuan Wang[3] · Junjing Wang[1,5] · Ling Zhao[1] · Yuhu Zhang[3] · Yingjun Liu[4] · Jiabao Lin[1] · Ruiwang Huang[1]

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Abstract

Levodopa therapy is widely recognized as an effective treatment for PD patients, however, it is rare of the study looking at effects of levodopa therapy on the whole-brain network. This study was to evaluate the effects of levodopa on whole-brain degree centrality (DC) and seed-based functional connectivity (FC) in PD patients. We recruited 26 PD patients and acquired their resting-state fMRI data before ('OFF' state) and after ('ON' state) taking a dose of 400 mg levodopa. Through constructing the voxel-based brain functional network, we calculated distant and local DC and seed-based FC. We found that compared to the healthy controls, the PD patients at 'OFF' state showed significantly decreased distant DC in several occipital regions and left postcentral gyrus, but increased distant DC in the right precentral gyrus, supplementary motor area, and several frontal regions. Meanwhile, we detected decreased local DC in the left cuneus and bilateral insula but increased local DC in several temporal regions in the PD patients at 'OFF' state compared to the controls. Using paired-sample *t*-tests, we found that levodopa effectively normalized the distant DC abnormalities in the PD patients particularly in the occipital regions and postcentral gyrus. Additionally, compared to 'OFF' state, the PD patients at 'ON' state showed decreased FC of the left median cingulate gyrus to brain regions in default mode network. The decreased FC of the left median cingulate gyrus to right temporal pole was associated with improved UPDRS-III score. This study provided new evidence for understanding the neural effects of levodopa therapy on the whole-brain network in PD patients.

Keywords Resting-state fMRI · Network centrality · Distant DC · Local DC · Functional connectivity

Miao Zhong and Wanqun Yang contributed equally to this work.

Highlights

1. The PD patients at 'OFF' state showed altered distant DC mainly in several occipital, frontal and motor areas compared to the healthy controls.
2. Levodopa therapy can normalize the abnormal distant DC in the PD patients in the occipital areas and left PoCG.
3. Levodopa therapy decreased FC of the left MCG to brain regions in DMN in the PD patients. The decreased FC of the left MCG to right TPOmid was associated with improved UPDRS-III score.

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✉ Biao Huang
cjr.huangbiao@vip.163.com

✉ Ruiwang Huang
ruiwang.huang@gmail.com

[1] School of Psychology, Institute of Brain Science and Rehabilitation, Key Laboratory of Mental Health and Cognitive Science of Guangdong Province, South China Normal University, Guangzhou 510631, People's Republic of China

[2] Department of Radiology, Guangdong Academy of Medical Sciences, Guangdong General Hospital, Guangzhou, People's Republic of China

[3] Department of Neurology, Guangdong Academy of Medical Sciences, Guangdong General Hospital, Guangzhou, People's Republic of China

[4] School of Biomedical Engineering, Southern Medical University, Guangzhou, People's Republic of China

[5] Department of Applied Psychology, Guangdong University of Foreign Studies, Guangzhou, People's Republic of China

Abbreviations

ALFF	amplitude of low-frequency oscillations
ANG	angular gyrus
CUN	cuneus
DC	degree centrality
DMN	default mode network
FWHM	Full-Width at Half Maximum
FC	functional connectivity
H-Y	Hoehn and Yahr stage
ICA	independent component analysis
INS	insula
IFGoperc	opercular part of inferior frontal gyrus
IFGtriang	triangular part of inferior frontal gyrus
IOG	inferior occipital gyrus
LING	lingual gyrus
MMSE	Mini-Mental State Examination
MFG	middle frontal gyrus
MTG	middle temporal gyrus
MCG	median cingulate gyrus
MOG	middle occipital gyrus
MCI	mild cognitive impairment
ORBinf	orbital part of inferior frontal gyrus
PMC	premotor cortex
PoCG	postcentral gyrus
PreCG	precentral gyrus
PHG	parahippocampal gyrus
PCUN	precuneus
ReHo	regional homogeneity
ROI	region of interest
SMA	supplementary motor area
STG	superior temporal gyrus
SFGmed	medial superior frontal gyrus
SOG	superior occipital gyrus
TPOmid	temporal pole of middle temporal gyrus
THA	thalamus
UPDRS-III	Unified Parkinson's Disease Rating Scale-motor

Symbol

'OFF' state	before levodopa therapy
'ON' state	after levodopa therapy
DC_i	degree centrality for a given voxel i
d_{ij}	connection or edge weight from voxel i to voxel j
$\overline{DC}$	mean degree across all voxels in the whole brain degree centrality map
σDC	standard deviation of degree centrality
zDC	z-score of degree centrality
szDC	smoothed z-score of degree centrality
zFC	z-score of functional connectivity
ΔDC	difference in degree centrality between 'ON' and 'OFF' state
ΔFC	difference in functional connectivity between 'ON' and 'OFF' state
ΔUPDRS-III	difference in UPDRS-III score between 'ON' and 'OFF' state
ΔMMSE	difference in MMSE score between 'ON' and 'OFF' state

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder associated with motor symptoms such as tremor, slowness of movement (bradykinesia), rigidity, difficulty in initiating movements (akinesia), gait disturbance and postural instability (Jankovic 2008; Braak et al. 2003). PD may also lead to non-motor symptoms, such as cognitive impairments, affective symptoms, and hallucination (Diederich et al. 2014; Dubbelink et al. 2014; Cardoso et al. 2009). It has been widely recognized that the neuropathology of PD is related to degeneration of dopaminergic neurons loss in the pars compacta of the substantia nigra which results in dopamine depletion in the striatum (Forno 1981; Kish et al. 1988; Braak et al. 2006). Previous functional Magnetic Resonance Imaging (fMRI) studies (Helmich et al. 2010; Kurani et al. 2014) demonstrated abnormal functional connectivity (FC) in the cortico-striatothalamic-cortical loop in PD patients. Other studies (Wu and Hallett 2005; Wu et al. 2009a) showed altered brain functional activity in intensive motor regions such as the supplementary motor area (SMA), lateral premotor cortex (PMC), cerebellum, and parietal cortex in PD patients, compared to healthy controls. The result of these studies suggested that PD patients present a wide range of brain functional impairments outside of the striatal system. In addition, cognitive impairments in PD has also been revealed, a previous study (Dubbelink et al. 2014) showed a loss of global resting-state FC in several brain regions in PD, such as the superior, middle, and inferior occipital gyrus, calcarine cortex, cuneus (CUN), and superior temporal gyrus (STG), and found that the decreased FC was associated with cognitive decline across 3 years. These studies (Wu and Hallett 2005; Dubbelink et al. 2014; Wu et al. 2009a) suggest that whole-brain FC analysis is needed to study the abnormalities of the functional network in PD.

To date, levodopa has become one of the most widely used therapies for PD patients to temporarily increase dopamine level in the striatum (Xie et al. 2015; Salat and Tolosa 2013) and is highly effective in ameliorating disease symptoms in PD patients (Stanley Fahn 1999; Group 2004). Wu et al. (2011) found that levodopa therapy can relatively normalize the hypoactivation of the SMA and decrease the overactivation of the cerebellum, and improve the motor functions in PD patients. Other studies (Esposito et al. 2013; Kwak et al. 2010) indicated that levodopa therapy exerted influences on cognitive functions in PD patients. Esposito et al. (2013) found that levodopa can modulate FC in the striatal cognitive network, and Kwak et al. (2010) revealed that

decreased FC between striatal and the thalamus (THA) was related to improved cognitive performance. Overall, these studies (Wu et al. 2011; Esposito et al. 2013; Kwak et al. 2010) suggested that levodopa therapy could influence motor as well as cognitive functions in PD patients. However, most of the previous studies (Kelly et al. 2009; Bell et al. 2015; Wu et al. 2009b) focused on the motor network or striatal circuits, and the study to explore effects of levodopa therapy on the whole-brain FC is rare. Therefore, it is necessary to carry out a study to explore the levodopa-induced changes on the whole-brain FC in PD patients.

Previous neuroimaging studies (Bell et al. 2015; Tessitore et al. 2012b) explored the altered resting-state FC in PD patients using region of interest (ROI) based temporal correlation analysis and independent component analysis (ICA) approaches. However, the ROI-based approach depends on the selected region which is quite subjective, and the connectivity patterns derived from the ICA approach depends on the input number of components which is also quite subjective. Recently, several studies (Bullmore and Sporns 2009; Rubinov and Sporns 2010) used voxel-based degree centrality (DC) to characterize FC in the whole-brain network and suggested that DC is a very reliable metric among several nodal network metrics (Buckner et al. 2009; Wang et al. 2011). DC measures the number of functional connections between a voxel and rest voxels of the entire brain (Hagmann et al. 2008; Takeuchi et al. 2015). It provides novel insights into the patterns of FC of brain functional network (Tomasi and Volkow 2010; Di Martino et al. 2013; Wang et al. 2014; Wang et al. 2015). Furthermore, to describe interactions between adjacent brain regions and interactions between distantly distributed brain regions in the whole brain, several studies (Sepulcre et al. 2010; Achard et al. 2006; Liu et al. 2015; Beucke et al. 2013) proposed distant and local DC, which is defined by using anatomical distance as a cutoff. By now, it is rare of the study to explore distant and local DC in PD patients (Zhang et al. 2015). The aim of this study was to evaluate levodopa-induced acute changes on the whole-brain DC and seed-based FC in PD patients.

Materials and methods

Subject

Thirty-nine PD patients were recruited between April 2012 and February 2015 from Guangdong General Hospital in Guangzhou. The patients were diagnosed by an experienced neurologist according to clinical diagnostic criteria of the UK Parkinson's Disease Society Brain Bank (Gibb and Lees 1988). All PD patients were evaluated with the Unified Parkinson's Disease Rating Scale-motor (UPDRS-III) (Fahn and Elton 1987), Mini-Mental State Examination (MMSE) (Folstein et al. 1975), and the Hoehn and Yahr (H-Y) stage (Hoehn and Yahr 1998). The exclusion criteria for the PD patients were (1) acute cerebrovascular disease history in the recent 3 months; (2) history of mental illness such as delirium, depression, or anxiety disorders; (3) diagnosed with atypical Parkinsonian disorders or secondary Parkinson syndrome; (4) severe claustrophobia or contraindications to MRI (e.g., pacemaker, metallic foreign bodies); (5) MRI findings of severe cerebral atrophy; (6) MRI findings of severe impairments or intracranial space-occupying lesions (such as tumors, parasites, or vascular malformations) or other brain lesions. We also recruited 28 age- and gender-matched healthy subjects as a control group. All healthy controls (HC) were assessed with the MMSE. The exclusion criteria for the HC were (1) abnormal neurological examination; (2) history of any psychiatric or neurological disease; (3) MRI finding of cerebral atrophy. We excluded 13 PD patients and 7 HC from the sample pool due to the following reasons, 5 PD patients and 2 HC were excluded because of excessive head motion (our criteria were displacement < 2 mm in any plane and rotation < 2° in any direction), 3 PD patients and 2 HC were excluded because of poor spatial normalization to the EPI template, 2 PD patients and 3 HC were excluded due to severe MRI artifacts and frontal lobe deformation, and 1 PD patient was excluded for severe cerebral atrophy, 2 patients were excluded for tumor. Thus, we obtained 26 PD patients (9 M / 17 F, aged 45–79 years old, mean ± SD = 63.77 ± 8.89 years) and 21 HC (7 M /14F, aged 50-81 years old, mean ± SD = 63.67 ± 10.32 years) for further analyses.

All subjects were right-handed according to the Edinburgh Handedness Inventory (Oldfield 1971). Akinesia was the predominant symptom in PD patients, which was dominant on the binary sides in 15 patients, on the right side in 6 patients and on the left side in 5 patients. All PD patients had an obvious delay in movement initiation and a mild tremor. The demographic and clinical characteristics of both patients and controls are shown in Table 1.

The protocol of this study was approved by the Institutional Review Board of Guangdong General Hospital. Written informed consents were obtained from all PD patients and HC prior to the study.

Medication procedure

Each PD patient underwent two fMRI scans on two consecutive days corresponding to before ('OFF' state) and after ('ON' state) levodopa therapy, respectively. The 'OFF' state was withdrawal from treatment for more than 12 h (PD patients took the levodopa before 7:00 pm the day before the testing day to avoid disturbing for clinical therapy). The 'ON' state was defined as 60–90 min after the patient received a dose of 400 mg levodopa, which is consistent with the expected time peaks of plasma levodopa levels (Contin and Martinelli 2010).

Table 1 Demographic and clinical characteristics of the patients with Parkinson's disease (PD) and the healthy controls (HC) in this study

Parameter	PD ($n = 26$) Mean ± SD	HC ($n = 21$) Mean ± SD	p-value
Age (years old)	63.77 ± 8.89	63.67 ± 10.32	0.97[a]
Gender (male/female)	9 / 17	7 / 14	0.93[c]
Education (years)	7.42 ± 4.50	9.62 ± 3.15	0.07[a]
Disease duration (years)	3.47 ± 2.40		
Symptom-dominant side (bilateral / right / left)	15 / 6 / 5		
H & Y stage ('OFF' state)	2.02 ± 0.62		
UPDRS-III			
'OFF' state	35.08 ± 13.86		0.00[b]
'ON' state	26.87 ± 10.52		
MMSE			
'OFF' state	26.50 ± 2.53 ($n = 14$)	29 ± 1.10 ($n = 26$)	0.00[a]
'ON' state	26.21 ± 2.81 ($n = 14$)		0.39[b]
Levodopa dose (mg/day)	400		

UPDRS-III, Unified Parkinson's Disease Rating Scale-motor; H & Y, Hoehn and Yahr stage; MMSE, Mini-Mental State Examination

[a] The P-value was obtained by independent-sample t-test

[b] The P-value was obtained by paired-sample t-test

[c] The P-value was obtained by chi-square test

MRI data acquisition

All MRI data were acquired on a 3T GE Signa Excite II HD MRI scanner equipped with a standard 8-channel phased-array head coil. Foam padding and earplugs were used to limit head movement and to reduce scanner acoustic noise. The resting-state fMRI data were obtained by using a single-shot gradient-echo EPI sequence with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 80°, field of view (FOV) = 240 × 240 mm^2, data matrix = 64 × 64, slice thickness = 4 mm, interslice gap = 1 mm, voxel size = 3.75 × 3.75 × 4 mm^3, 30 axial interleaved slices covering the whole brain, and 186 volumes acquired in 6 min 12 sec. During fMRI acquisition, subjects were instructed to keep their eyes closed and to move as little as possible, but not to fall asleep. In addition, we also acquired high-resolution brain structural images by using a T1-weighted 3D rapid interference phase gradient echo flip recovery pulse sequence (FSPGRIR) for each subject. The sequence parameters were as follows: TR = 7.58 ms, TE = 3.31 ms, FA = 13°, FOV = 240 × 240 mm^2, data matrix = 256 × 256, slice thickness = 1 mm, voxel size = 0.94 × 0.94 × 1 mm^3, and 146 sagittal slices covering the whole brain. The high-resolution brain structural images were used to check for brain structural anomalies, such as atrophies, cysts, and tumors.

Preprocessing of fMRI data

All images were preprocessed by using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and DPARSF (Yan and Zang 2010). For each subject, the first 5 volumes of functional data were discarded for the signal equilibrium and adaptation to scanning noise. Then the remaining functional images were processed using the following steps: corrected for the acquisition time delay between slices in the same TR, realigned to the first volume to correct for inter-TR head motions, spatial normalization to the standard Montreal Neurological Institute (MNI) EPI template in SPM8 and resample to 3 × 3× 3 mm^3, detrending and bandpass filtering within 0.01–0.08 Hz to reduce the effect of low-frequency drift and high-frequency physiological noise. The realignment calculation provided a record of head motions. All subjects in this study satisfied our criteria for head motions, displacement < 2 mm in any plane and angular rotation < 2° in any direction. Finally, we regressed out nuisance variables, including head motion profiles derived from the Friston 24-parameter model, signals of the brain white matter and cerebrospinal fluid in each voxel in the whole brain. In this study, we did not perform spatial smoothing in the data preprocessing as it may introduce artificial local correlations between voxels which are unrelated to the real connectivity (Zuo et al. 2012).

Voxel-based degree centrality (DC)

DC is a measure of the brain network indexing the sum of weights from edges between a given node and the rest nodes of the entire brain. To calculate voxel-based DC, we first constructed a voxel-based whole-brain functional network for each subject. In the calculation, we restricted the voxel-based DC analysis in a predefined gray matter (GM) mask (GM tissue probability > 20%) (Zuo et al. 2012) to exclude artificial

correlations from non-GM voxels. Then we took each voxel in the GM mask as a node, estimated Pearson's correlation between the time series of any two voxels across the whole brain, and selected each significant inter-nodal Pearson's correlation as functional connection to define the edge weight (Buckner et al. 2009; Di Martino et al. 2013). Thus, we obtained a weighted voxel-based functional network for each subject by using inter-nodal correlation $r_{ij} = 0.3$ as the threshold, which was set to eliminate weak correlations possibly arising from noise (Liu et al. 2015; Wang et al. 2014). In the calculation, we excluded negative correlations as their ambiguous interpretation (Wang et al. 2011; Murphy et al. 2009; Weissenbacher et al. 2009). Finally, we estimated DC value for each voxel according to the following equation (Zuo et al. 2012)

$$DCi = \sum_{j=1}^{N} d_{ij}(i \neq j) \quad (1)$$

where DC_i is DC for a given voxel i, d_{ij} represents a connection or edge weight from voxel i to voxel j, and N is a number of voxels in the GM mask. We obtained a whole-brain DC map for each subject. A voxel has a high DC value if it has more direct connections to other voxels.

The local and distant DC map for each subject were also calculated to describe interactions between adjacent brain regions and interactions between distantly distributed brain regions, respectively, in the whole brain. For a selected voxel, we calculated its local DC value by considering voxels inside a sphere (radius = 12 mm) around the selected voxel, while its distant DC value by counting voxels outside the 12-mm sphere (Sepulcre et al. 2010; Beucke et al. 2013). In this way, we obtained the local and distant DC map for each subject. In order to improve normality, we transformed DC indices to z-score (Di Martino et al. 2013; Zuo et al. 2012) according to the following equation

$$zDCi = \frac{DCi\text{-}\overline{DC}}{\sigma DC}(i = 1\ldots\ldots\mathrm{N}) \quad (2)$$

where $\overline{DC}$ represents the mean degree across all the voxels in the whole-brain DC map and σDC is the standard deviation of the map. We then smoothed the local and distant DC map, zDC_{local} and zDC_{distant}, for each subject by using a Gaussian kernel with Full-Width at Half Maximum (FWHM) of 4-mm, obtained the smoothed z-score of local and distant DC map, $szDC_{\mathrm{local}}$ and $szDC_{\mathrm{distant}}$, which were used as inputs for further group-level analyses.

Seed-based FC

To trace the locations to which the altered brain clusters were linked, we performed seed-based connectivity analysis. First, we determined brain clusters with significant differences in distant and local DC in the PD patients between 'ON' and 'OFF' state. Second, for each patient, we computed the difference in clinical variables in UPDRS-III and MMSE score between 'ON' and 'OFF' state in the PD patients (ΔUPDRS-III and ΔMMSE). We also calculated the difference in distant and local DC between 'ON' and 'OFF' state for each identified cluster ($\Delta DC_{\mathrm{distant}}$ and $\Delta DC_{\mathrm{local}}$). In the calculation, the mean DC value across all voxels in each identified cluster was used. We further performed correlation analyses of $\Delta DC_{\mathrm{distant}}$ against ΔUPDRS-III and ΔMMSE as well as $\Delta DC_{\mathrm{local}}$ against ΔUPDRS-III and ΔMMSE. Age, gender, and education were considered as confounding factors. The clusters in which the $\Delta DC_{\mathrm{distant}}$ or $\Delta DC_{\mathrm{local}}$ were significantly correlated with ΔUPDRS-III or ΔMMSE were selected as the seed clusters. Third, for each seed cluster, we extracted its time series by averaging the signal time series of all voxels in the given seed cluster, and calculated its Pearson's correlation coefficients with each voxel in the rest of brain, and transformed the correlation coefficients to z-score. Thus, the seed-based zFC map was obtained for each subject, which was smoothed using a Gaussian kernel with Full-Width at Half Maximum (FWHM) of 4-mm. The smoothed zFC maps were used as inputs for further statistical analyses.

Statistical analysis

Distant and local DC

Independent-sample t-tests were used to determine statistical differences in distant and local DC maps between the PD patients and the HC. In the calculation, we regressed out the effects of age, gender, education, and head motion. Meanwhile, paired-sample t-tests were used to compare statistical differences in distant and local DC maps in the PD patients between 'ON' and 'OFF' state. We used cluster-extent thresholding at an uncorrected voxel-wise $p < 0.001$ and a minimum cluster size computed by Monte Carlo simulations (Ledberg et al. 1998), which was implemented with AlphaSim utility (Yan et al. 2016), to maintain a corrected alpha threshold at the cluster level of 0.05. Once a significant difference was observed for the distant and local DC between groups, we estimated the effect size (Cohen d) according to Cohen's definition (Cohen 1992). Levels of small, medium and large effect size corresponding to 0.2, 0.5, and 0.8, respectively.

Additionally, we determined brain clusters show a significant difference in either distant or local DC between the PD patients at 'OFF' state and the HC. To explore if the distant or local DC correlates with the disease severity in the PD patients, we performed partial correlation analyses of the DC value against the clinical variables (duration, H-Y stage, UPDRS-III score, and MMSE score) in the PD patients at 'OFF' state. In the calculation, we used the mean DC value

across all voxels in each identified cluster and regressed out the effects of age, gender and education.

Seed-based FC

Paired-sample *t*-tests were used to compare differences in seed-based FC maps between 'ON' and 'OFF' state in the PD patients. We used cluster-extent thresholding at an uncorrected voxel-wise $p < 0.001$ and a minimum cluster size computed by Monte Carlo simulations (Ledberg et al. 1998), which was implemented with AlphaSim utility (Yan et al. 2016), to maintain a corrected alpha threshold at the cluster level of 0.05.

For each PD patient, we calculated the difference in FC between 'ON' and 'OFF' state for each identified brain cluster (ΔFC). Then, we performed correlation analyses between ΔFC and ΔUPDRS-III as well as between ΔFC and ΔMMSE. In the calculation, we used the mean FC value across all voxels in each identified cluster and regressed out the effects of age, gender and education.

Robustness

Inter-nodal correlation threshold When computing voxel-based DC above, we selected a threshold of the correlation coefficient ($r_{ij} = 0.3$) to eliminate weak correlations possibly arising from noise (Wang et al. 2014; Liu et al. 2015). To check if our main results depended on the choices of the threshold of inter-nodal correlation, we recomputed voxel-based distant and local DC in the same GM mask by selecting two different thresholds of inter-nodal correlation, $r_{ij} = 0.2$ and 0.4, and repeated the network analysis.

Global signal regression We reanalyzed the resting-state fMRI data by regressing out the global signal (GS) to examine the robustness of our main results. Recent studies suggested that the GS is related with the oscillatory neuronal signal and may be biologically meaningful (Schölvinck et al. 2010) and the removal of the GS can dramatically shift the resting-state correlation patterns (Saad et al. 2012). We also noticed that several studies suggested that the GS is associated with physiological noise (Birn et al. 2006; Chang and Glover 2009) and should be removed (Fox et al. 2009). In fact, regressing out the GS or not in analyzing resting-state fMRI data is still in dispute (Anderson et al. 2011).

Network type In the constructing of the voxel-based whole-brain functional network, we obtained a weighted voxel-based functional network for each subject. To verify if our main results were robust in terms of network type, we recalculated distant and local DC by using the binary network (Wu et al. 2015). For a binary network, the DC of a node is calculated as the number of edges connecting to the node.

Results

Demographic and clinical characteristics

Table 1 lists demographic and clinical information for both the PD patients and the HC. No significant difference was found in age, gender and years of education between the PD patients and the HC, while a significant difference was found in MMSE score between the PD patients at 'OFF' state and the HC ($p < 0.05$). Paired-sample *t*-test showed a significant difference in UPDRS-III score in the PD patients between 'ON' and 'OFF' state ($p < 0.05$).

Abnormal distant and local DC in the PD patients at 'OFF' state

Figure 1 shows 9 clusters with significantly altered distant DC between the patients at 'OFF' state and the HC. Compared to the HC, the PD patients at 'OFF' state had significantly decreased distant DC in 5 clusters, the right inferior occipital gyrus (IOG), left middle occipital gyrus (MOG), left cuneus (CUN), left lingual gyrus (LING) and left postcentral gyrus (PoCG), but significantly increased distant DC in 4 clusters, the left medial superior frontal gyrus (SFGmed), right triangular part of inferior frontal gyrus (IFGtriang), right precentral gyrus (PreCG) and right supplementary motor area (SMA). The size and the locations of these clusters are listed in Table 2.

Figure 2 shows 7 clusters with significantly altered local DC in the patients at 'OFF' state compared to the HC. Four clusters with significantly decreased local DC are located in the left CUN, bilateral insula (INS) and right middle temporal gyrus (MTG). Three clusters with significantly increased local DC are located in the right parahippocampal gyrus (PHG), left MTG and left superior temporal gyrus (STG). The size and the locations of these clusters are listed in Table 3.

The relationship between brain network parameters and clinical variables

No significant correlation was found between the clinical variables (duration, H-Y stage, UPDRS-III score, and MMSE score) and distant DC or local DC of any of the altered clusters in the PD patients.

Effects of levodopa therapy on distant and local DC in the PD patients

Figure 3a shows the effects of levodopa therapy on distant DC in the PD patients. We detected 6 clusters with significantly altered distant DC between 'ON' and 'OFF' state in the PD patients. Compared to 'OFF' state, the patients at 'ON' state had significantly increased distant DC in the right IOG, right

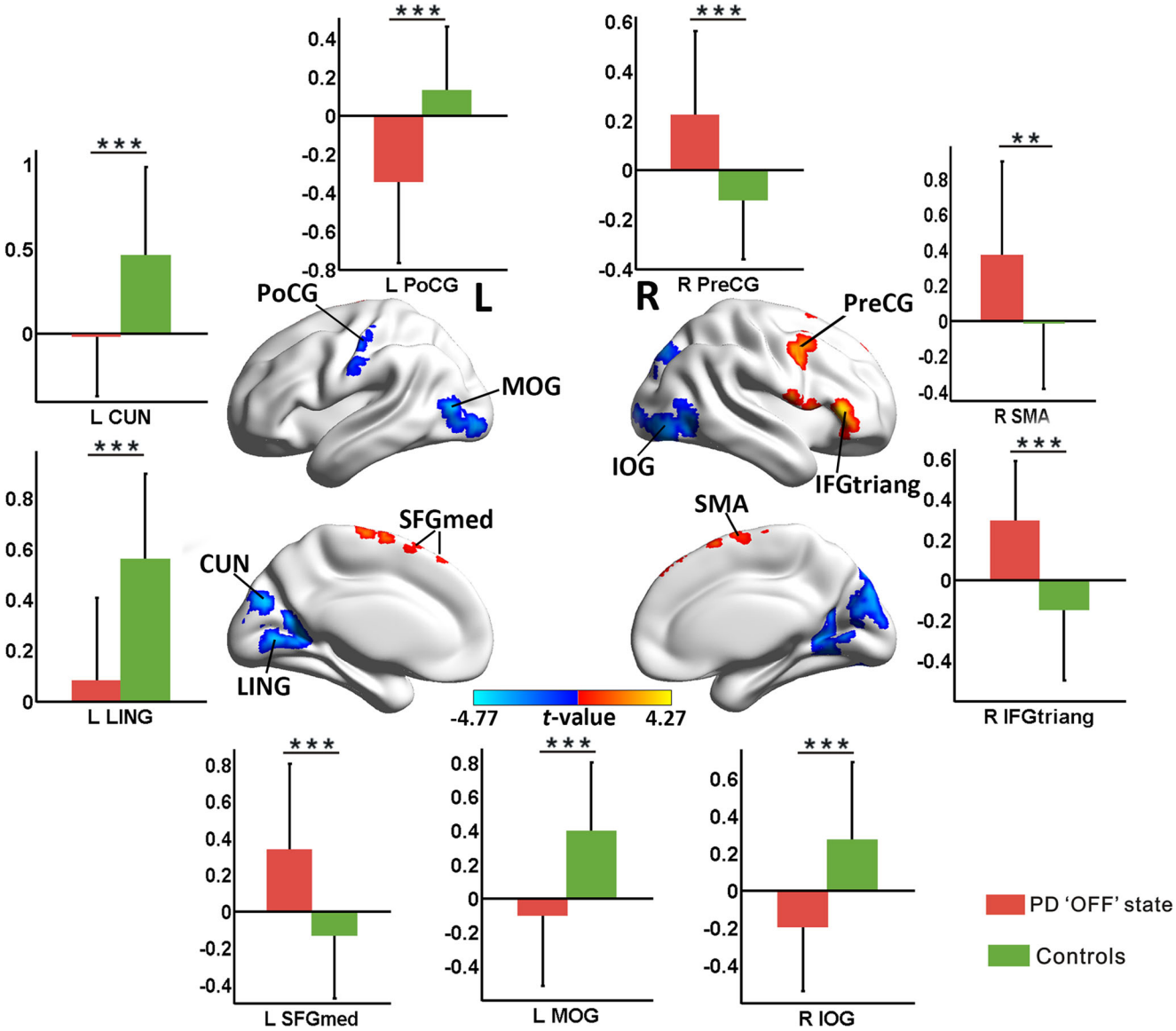

Fig. 1 Comparison of distant degree centrality (DC) between the PD patients at 'OFF' state and the healthy controls (HC). Clusters with a significant group difference in distant DC were detected at the threshold of voxel-wise $p < 0.001$ and cluster level $p < 0.05$ (Monte Carlo simulations). Warm (cold) color indicates significantly increased (decreased) distant DC in the PD patients at 'OFF' state compared to the HC. The bar plots show distant DC values for these clusters. The bar height indicates the mean value and the error bar indicates the standard deviation for a given group. **, $p < 0.01$; ***, $p < 0.001$. PreCG, precentral gyrus; PoCG, postcentral gyrus; MOG, middle occipital gyrus; IOG, inferior occipital gyrus; CUN, cuneus; SFGmed, medial superior frontal gyrus; LING, lingual gyrus; SMA, supplementary motor area; IFGtriang, triangular part of inferior frontal gyrus; L (R), left (right) hemisphere

LING, left superior occipital gyrus (SOG) and left PoCG, but significantly decreased local DC in the right INS and left median cingulate gyrus (MCG). The size and the locations of these clusters are listed in Table 2.

Figure 4 shows the effects of levodopa therapy on local DC in the PD patients. We detected 9 clusters with significantly altered local DC between 'ON' and 'OFF' state in the PD patients. Compared to 'OFF' state, the patients at 'ON' state had significantly increased local DC in 3 clusters, the left cerebellum (lobule VII B), right PoCG and right STG, but significantly decreased local DC in 6 clusters, the right opercular part of inferior frontal gyrus (IFGoperc), left orbital part of inferior frontal gyrus (ORBinf), right angular gyrus (ANG), right SMA and bilateral middle frontal gyri (MFG). The size and the locations of these clusters are reported in Table 3.

Effects of levodopa therapy on seed-based FC in the PD patients

Figure 3b shows a significant positive correlation between ΔUPDRS-III and $\Delta DC_{distant}$ in the left MCG ($r = 0.487$,

Table 2 Brain clusters showing significantly altered distant degree centrality (DC) in the PD patients compared to the healthy controls (HC)

Region	Cluster size (voxels)	MNI coordinate (*x*, *y*, *z*)			*t*-value	Cohen *d*
PD ('OFF' state) vs. HC						
L medial superior frontal gyrus	95	−6	35	60	4.27	1.13
R triangular part of inferior frontal gyrus	233	51	30	6	3.87	1.35
R precentral gyrus	93	45	3	36	3.32	1.17
R supplementary motor area	81	6	0	74	2.89	0.83
R inferior occipital gyrus	204	36	−78	−15	−3.63	1.22
L postcentral gyrus	87	−57	−9	48	−3.71	1.24
L middle occipital gyrus	96	−48	−75	6	−3.88	1.21
L cuneus	291	−9	−81	27	−4.37	1.06
L lingual gyrus	318	−6	−72	3	−4.77	1.44
PD ('ON' state) vs. HC						
R orbital part of superior frontal gyrus	354	30	60	−3	4.32	1.41
L supplementary motor area	94	−6	−11	75	4.04	0.92
L orbital part of inferior frontal gyrus	85	−48	45	−9	3.42	0.88
L superior temporal gyrus	122	−42	−12	−2	−3.97	1.35
PD ('ON' state) vs. PD ('OFF' state)						
R inferior occipital gyrus	113	42	−78	−3	4.20	0.97
R lingual gyrus	131	6	−75	−3	3.98	0.92
L superior occipital gyrus	327	−24	−78	36	3.76	0.98
L postcentral gyrus	113	−51	−27	54	3.42	0.71
R insula	129	42	12	3	−4.16	0.82
L median cingulate gyrus	530	−12	21	36	−5.25	1.09

The coordinates correspond to the peak voxel location of *t*-value map in the MNI space. The *t*-value indicates a significant level of between- and within- group difference in distant DC. Positive (negative) *t*-value means significantly increased (decreased) distant DC in the PD patients compared to the healthy controls or in the PD patients at 'ON' state compared to 'OFF' state. L (R), left (right) hemisphere

$p = 0.018$) in the PD patients. No significant correlation was found between ΔMMSE or ΔUPDRS-III and ΔDC_{local} of any of the altered clusters in the PD patients.

Figure 5a shows significantly altered FC between 'ON' and 'OFF' state in the PD patients. We found that the left MCG was significantly connected to 8 clusters in the PD patients at 'ON' state compared to 'OFF' state, the left IFGtriang, left cerebellum (crus I), left SFG, left PoCG, left MTG, right temporal pole of middle temporal gyrus (TPOmid), right ANG and right precuneus (PCUN). All these 8 connections were significantly decreased in the PD patients at 'ON' state compared to 'OFF' state. The size and the locations of these clusters are reported in Table 4. Figure 5b shows a significant positive correlation between ΔUPDRS-III and ΔFC of the left MCG to right TPOmid ($r = 0.577$, $p = 0.004$) in the PD patients.

Robustness

Our main results were largely preserved after selecting different correlation thresholds and a binary network (Supplementary Materials Fig. S1 and S2). In contrast to the main results without GSR (global signal regression), the results with GSR showed that the pattern of local DC was not influenced, but the pattern of distant DC was changed a lot. With GSR, we observed that the PD patients at 'OFF' state had significantly altered distant DC in several brain regions (cerebellum, bilateral PreCG, and temporal regions) compared to the HC, and levodopa therapy changed distant DC in the right ORBinf and vermis in the PD patients. From these results, we infer that performing GSR in the preprocessing may bias the pattern of distant DC, although it exerted a negligible effect on the local DC.

Discussion

In this study, we constructed the voxel-based whole-brain functional network, estimated the distant and local DC, and analyzed the effects of levodopa therapy on distant and local DC as well as seed-based FC in the PD patients. We reached the following results: (a) Compared to the HC, the PD patients at 'OFF' state showed significantly decreased distant DC in several occipital regions and left PoCG, but increased distant

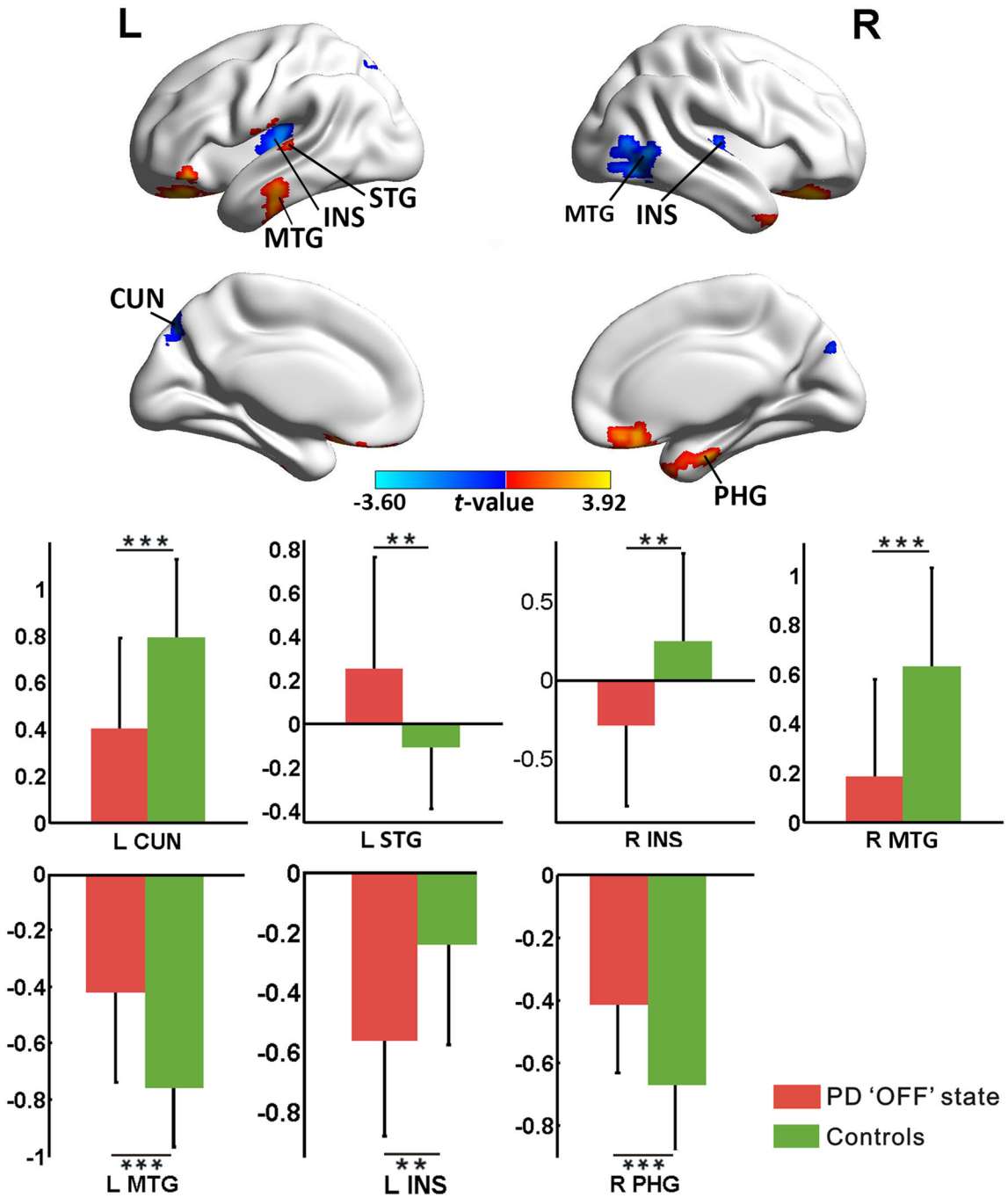

Fig. 2 Comparison of local degree centrality (DC) between the PD patients at 'OFF' state and the healthy controls (HC). Clusters with a significant group difference in local DC were detected at the threshold of voxel-wise $p < 0.001$ and cluster level $p < 0.05$ (Monte Carlo simulations). Warm (cold) color indicates significantly increased (decreased) local DC in the PD patients at 'OFF' state compared to the HC. The bar plots show local DC values for these clusters. The bar height indicates the mean value and the error bar indicates the standard deviation for a given group. **, $p < 0.01$; ***, $p < 0.001$. STG, superior temporal gyrus; INS, insula; MTG, middle temporal gyrus; CUN, cuneus; PHG, parahippocampal gyrus; L (R), left (right) hemisphere

DC in frontal area and several motor regions, including the right PreCG and right SMA. Meanwhile, we detected decreased local DC in the left CUN and bilateral INS but increased local DC in several temporal regions in the PD patients at 'OFF' state compared to the HC. (b) Levodopa therapy is capable of reversing the DC abnormality in the PD patients at 'OFF' state. Levodopa increased distant DC in the occipital regions and PoCG in the PD patients at 'ON state compared to 'OFF' state. (c) Compared to 'OFF' state, the PD patients at 'ON' state showed decreased FC of the left MCG to brain regions in DMN, including the precuneus, angular gyrus, temporal and frontal regions. The decreased FC of the left MCG to

Table 3 Brain clusters showing significantly altered local degree centrality (DC) in the PD patients compared to the healthy controls (HC)

Region	Cluster size (voxels)	MNI coordinate (*x*, *y*, *z*)			*t*-value	Cohen *d*
PD ('OFF' state) vs. HC						
R parahippocampal gyrus	172	21	−9	−30	3.92	1.19
L middle temporal gyrus	100	−66	−9	−21	3.61	1.24
L superior temporal gyrus	84	−63	−21	14	3.59	0.85
R middle temporal gyrus	150	54	−57	3	−3.18	1.12
L insula	104	−39	−18	3	−3.18	0.97
R insula	76	44	−12	4	−3.42	0.97
L cuneus	92	0	−78	36	−3.60	1.06
PD ('ON' state) vs. HC						
L inferior temporal gyrus	211	−54	−15	−24	4.52	1.67
R median cingulate gyrus	105	1	−30	33	4.32	1.15
L cerebellum (lobule VII B)	90	−38	−70	−54	4.07	0.97
R inferior temporal gyrus	92	48	−12	−36	3.26	1.13
L insula	109	−33	−21	15	−3.11	1.06
L median cingulate gyrus	75	−6	15	33	−3.19	1.09
PD ('ON' state) vs. PD ('OFF' state)						
L cerebellum (lobule VII B)	98	−39	−70	−53	3.72	0.70
R postcentral gyrus	78	26	−27	56	3.39	0.56
R superior temporal gyrus	88	45	−21	3	3.23	0.93
R opercular part of inferior frontal gyrus	102	60	9	12	−3.29	0.76
R middle frontal gyrus	111	36	21	51	−3.53	0.75
L orbital part of inferior frontal gyrus	139	−24	51	−9	−3.71	0.87
R angular gyrus	107	54	−48	30	−4.32	0.77
L middle frontal gyrus	234	−36	42	27	−4.34	1.12
R supplementary motor area	376	6	12	48	−4.54	1.00

The coordinates correspond to the peak voxel location of *t*-value map in the MNI space. The *t*-value indicates a significant level of between- and within-group difference in local DC. Positive (negative) *t*-value means significantly increased (decreased) local DC in the PD patients compared to the healthy controls or in the PD patients at 'ON' state compared to 'OFF' state. L (R), left (right) hemisphere

right TPOmid was correlated with improved UPDRS-III score in the PD patients at 'ON' state relative to 'OFF' state. These findings reflect the neural effects of levodopa therapy on the voxel-based whole-brain network in PD patients.

Abnormal distant DC in the PD patients at 'OFF' state

In this study, we found abnormal distant DC in motor areas, including increased distant DC in the right supplementary motor area (SMA) and precentral gyrus (PreCG), while decreased in the left postcentral gyrus (PoCG) in the PD patients at 'OFF' state compared to the HC (Fig. 1, Table 2). The SMA plays a role in movement selection, preparation, and initiation (Tanji and Hoshi 2001; Jenkins et al. 2000; Roland et al. 1980). The PreCG is suggested involving in hand action, finger movements or object grasping (Buccino et al. 2004), and PoCG is involved in sensory feedback during the motor planning and execution (Chéron et al. 2000). Our observations are in line with several previous studies (Kwak et al. 2012; Fang et al. 2017; Tuovinen et al. 2018). Kwak et al. (2012) analyzed amplitude of low-frequency fluctuations (ALFF) in the whole brain and found increased FC in SMA and PreCG in PD patients at 'OFF' state compared to healthy controls. Using graph theory, several studies (Fang et al. 2017; Tuovinen et al. 2018) showed decreased nodal degree centrality in PoCG in PD patients at 'OFF' state compared to controls. We also noticed different results from other studies (Hou et al. 2014; Wu et al. 2009a). Wu et al. (2009a) found decreased regional homogeneity (ReHo) in the SMA, and Hou et al. (2014) detected weakened ALFF in both the left PreCG and pre-SMA either in slow-4 (0.027–0.073 Hz) or slow-5 (0.01–0.027 Hz) frequency bands in PD patients at 'OFF' state compared to controls. The discrepancy may due to different patient samples or different methods. We assume that the alterations in the motor regions in this study may indicate sensory and motor functional abnormalities in PD patients.

We found decreased distant DC in several occipital regions, including the left lingual gyrus (LING) and left cuneus

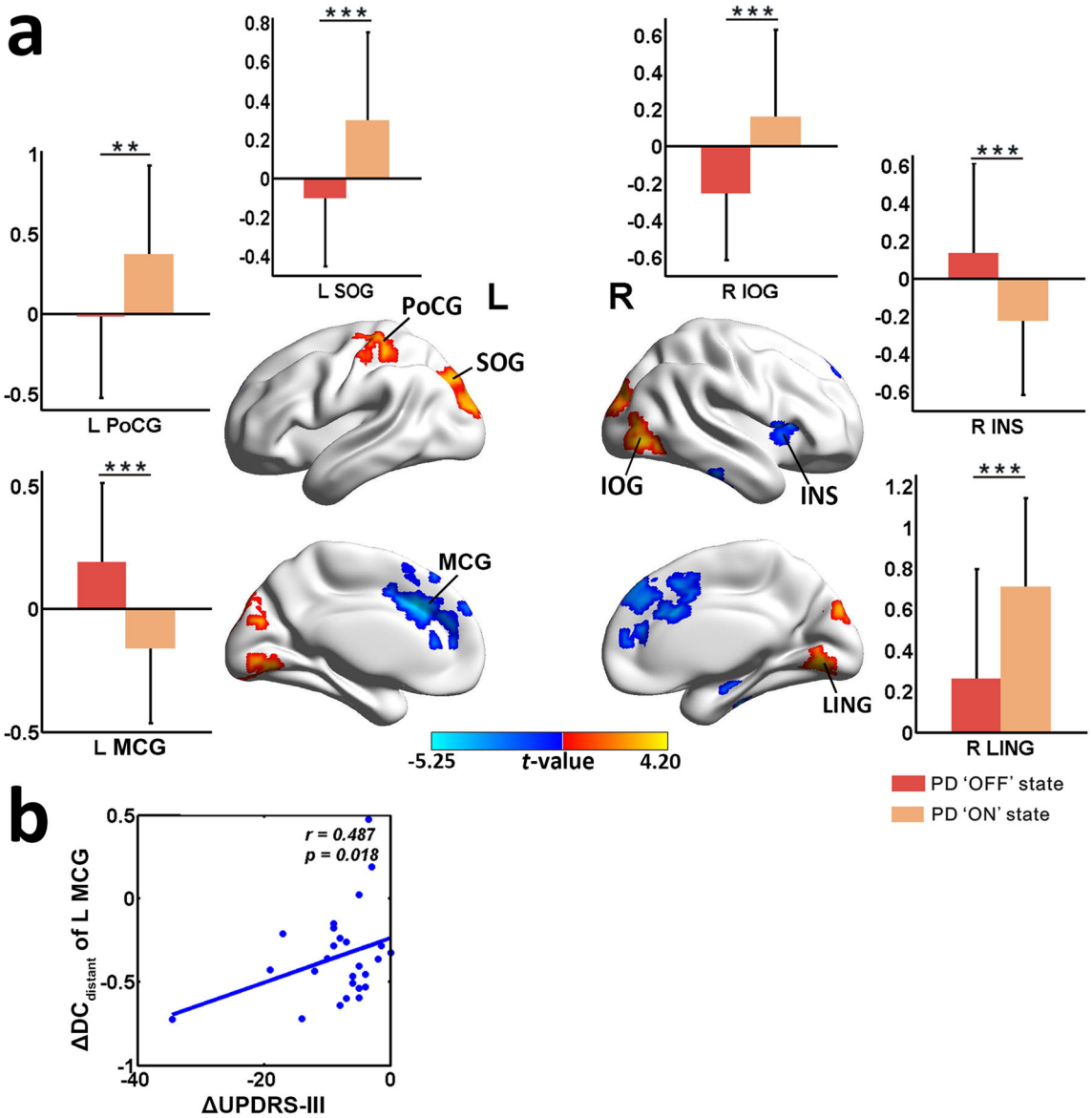

Fig. 3 Effects of levodopa therapy on distant degree centrality (DC) in the PD patients. **a** Clusters with a significant difference in distant DC in the PD patients at 'ON' state compared to 'OFF' state (voxel-wise $p < 0.001$, cluster level $p < 0.05$, Monte Carlo simulations). Warm (cold) color indicates significantly increased (decreased) distant DC in the PD patients at 'ON' state compared to 'OFF' state. The bar plots show distant DC values for these clusters. The bar height indicates the mean value and the error bar indicates the standard deviation for a given group. **b** Scatter plot showing the correlation between clinical difference and difference in distant DC. The plot shows a significant positive correlation between ΔUPDRS-III and $\Delta DC_{distant}$ in the left MCG in the PD patients. **, $p < 0.01$; ***, $p < 0.001$. PoCG, postcentral gyrus; SOG, superior occipital gyrus; MCG, median cingulate gyrus; IOG, inferior occipital gyrus; INS, insula; LING, lingual gyrus; L (R), left (right) hemisphere

(CUN), in the PD patients at 'OFF' state compared to the HC (Fig. 1, Table 2). This result is consistent with previous studies (Luo et al. 2015; Zhang et al. 2013). Zhang et al. (2013) acquired resting-state fMRI data of PD patients following overnight withdrawal from levodopa medication and healthy controls, performed analysis of ALFF in two different frequency bands, and showed that the PD patients had lower ALFF value in several occipital regions in the slow-4 band (0.027–0.073 Hz) compared to the controls. Similarly, Luo et al. (2015) analyzed ALFF and seed-based FC and showed that PD patients at 'OFF' state had decreased functional activity in the left occipital and lingual regions. It has been suggested that abnormal functional activity in occipital regions is related to cognitive dysfunction, particularly visual dysfunction in PD patients (Young et al. 2010; Meppelink et al. 2009), meanwhile, the impaired visual cognition has been reported in PD patients from mild to moderate stage (Uc et al. 2005), thus, our observation of changed distant DC in several occipital regions may be associated with cognitive deficits, especially, the abnormal processing of visual information in PD patients.

We also observed increased distant DC in frontal regions, including the left medial superior frontal gyrus (SFGmed) and

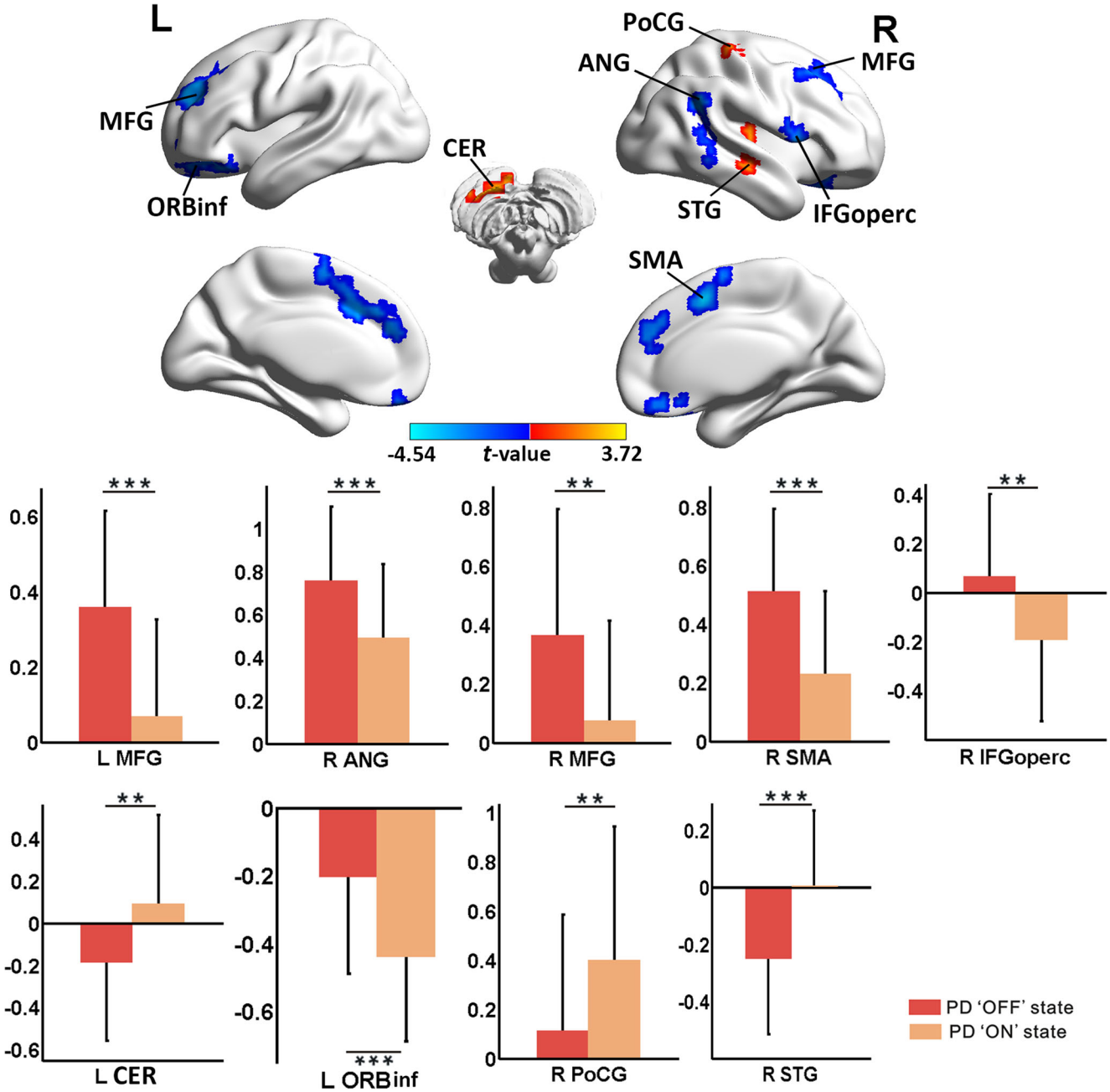

Fig. 4 Effects of levodopa therapy on local degree centrality (DC) in the PD patients. Clusters with a significant difference in local DC in the PD patients at 'ON' state compared to 'OFF' state were determined at the threshold of voxel-wise $p < 0.001$ and cluster level $p < 0.05$ (Monte Carlo simulations). Warm (cold) color indicates significantly increased (decreased) local DC in the PD patients at 'ON' state compared to 'OFF' state. The bar plots show local DC values for these clusters. The bar height indicates the mean value and the error bar indicates the standard deviation for a given group. **, $p < 0.01$; ***, $p < 0.001$. MFG, middle frontal gyrus; ORBinf, orbital part of inferior frontal gyrus; CER, cerebellum (lobule VII B); PoCG, postcentral gyrus; ANG, angular gyrus; STG, superior temporal gyrus; IFGoperc, opercular part of inferior frontal gyrus; SMA, supplementary motor area; L (R), left (right) hemisphere

right triangular part of inferior frontal gyrus (IFGtriang) in the PD patients at 'OFF' state compared to the HC (Fig. 1, Table 2). This result is in line with the study of Kwak et al. (2012), they compared ALFF between healthy controls and PD patients and found increased ALFF in the frontal regions in the PD patients at 'OFF' state compared to the controls. In contrast, other structural imaging studies (Zarei et al. 2013; Melzer et al. 2012; Jubault et al. 2011) found that there is a gradually gray matter (GM) loss in frontal and other brain regions from mild to severe stage in PD patients, and resting-state fMRI studies, using the measurement of ReHo (Wu et al. 2009a), ALFF (Skidmore et al. 2013) and graph

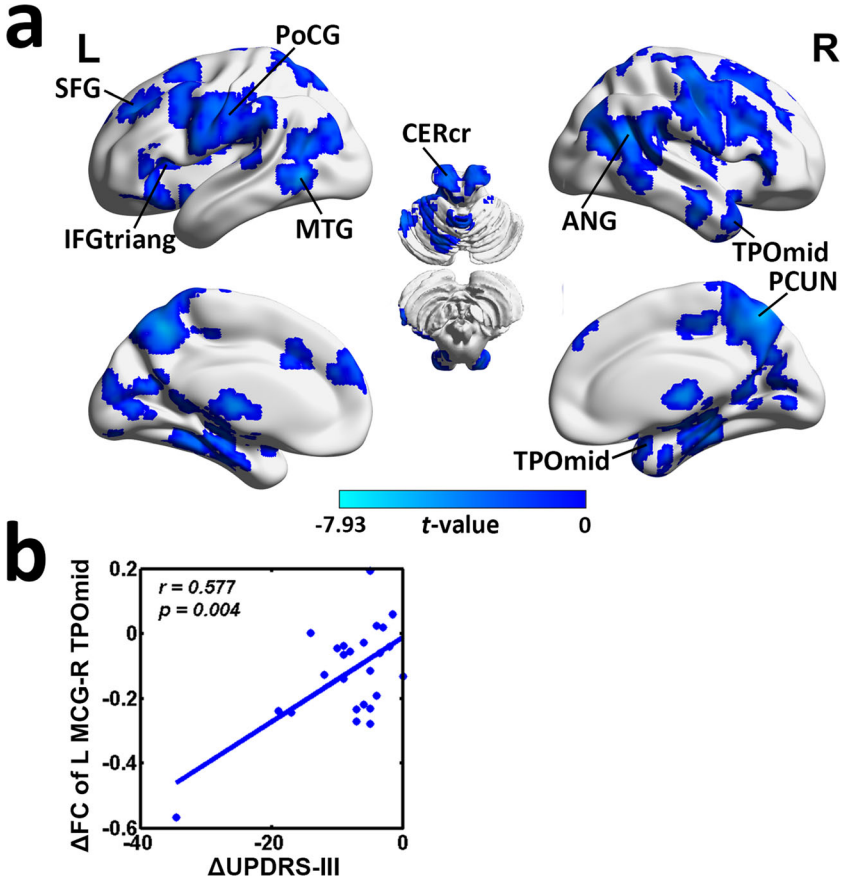

Fig. 5 Effects of levodopa therapy on seed-based functional connectivity (FC) in the PD patients. **a** Clusters with a significant difference in FC in the PD patients at 'ON' state compared to 'OFF' state (voxel-wise $p < 0.001$, cluster level $p < 0.05$, Monte Carlo simulations). Warm (cold) color indicates significantly increased (decreased) FC in the PD patients at 'ON' state compared to 'OFF' state. The bar plot shows FC values for these clusters. The bar height indicates the mean value and the error bar indicates the standard deviation in a given group. ***, $p < 0.001$. **b** Scatter plot showing the correlation between clinical difference and difference in FC. The plot shows a significant positive correlation between ΔUPDRS-III and ΔFC of the left MCG to right TPOmid in the PD patients. SFG, superior frontal gyrus; PoCG, postcentral gyrus; MTG, middle temporal gyrus; IFGtriang, triangular part of inferior frontal gyrus; ANG, angular gyrus; TPOmid, temporal pole of middle temporal gyrus; PCUN, precuneus; CERcr, cerebellum (crus I); MCG, median cingulate gyrus; L (R), left (right) hemisphere

Table 4 Brain clusters showing significantly altered functional connectivity (FC) in the PD patients at 'ON' state compared to 'OFF' state

Seed region	Location	Cluster size (voxels)	MNI coordinate (*x*, *y*, *z*)			*t*-value
L median cingulate gyrus	L triangular part of inferior frontal gyrus	366	−45	21	9	−4.26
	R temporal pole of middle temporal gyrus	511	30	18	−36	−4.35
	L cerebellum (crus I)	153	−54	−51	−30	−4.50
	L superior frontal gyrus	370	−19	36	30	−4.55
	L postcentral gyrus	1132	−48	−12	27	−4.82
	L middle temporal gyrus	438	−51	−60	0	−5.41
	R angular gyrus	2773	45	−54	24	−6.44
	R precuneus	3862	12	−60	51	−7.93

The coordinates correspond to the peak voxel location of *t*-value map in the MNI space. The *t*-value indicates a significant level of within-group difference in FC. Positive (negative) *t*-value means significantly increased (decreased) FC in the PD patients at 'ON' state compared to 'OFF' state. L (R), left (right) hemisphere

theory based analysis (Pereira et al. 2015), consistently showed decreased FC in frontal regions in PD patients at 'OFF' state, compared to controls.

Abnormal local DC in the PD patients at 'OFF' state

The current study observed increased local DC in temporal brain regions in the PD patients at 'OFF' state compared to the HC (Fig. 2, Table 3). Increased ALFF power in the slow-5 frequency band has been observed in temporal regions previously, including the left superior and inferior temporal gyrus, in PD patients at 'OFF' state relative to controls (Zhang et al. 2013). However, we also noticed different results from other resting-state fMRI studies (Dubbelink et al. 2013, 2014). Dubbelink et al. (2013) used magnetoencephalography and characterized whole-brain functional network with graph-theory based analysis, and found a reduction in nodal efficiency in temporal regions in PD patients. In their study, during brain imaging acquisition, patients were at the 'ON' medication state, therefore, the decreased functional activity in temporal regions in the PD patients was likely to be influenced by levodopa medication. Given pathogenesis of visual hallucinations in PD patients is related to the higher Lewy body in the temporal lobe (Kempster et al. 2010; Harding et al. 2002; Gallagher et al. 2011), we assume that the increased local DC in temporal brain regions detected here may be related to disruption in visual perception in PD patients.

We found decreased local DC in the bilateral insula (INS) in the PD patients at 'OFF' state compared to the HC (Fig. 2, Table 3). INS is acted as a central hub for processing information related to cognitive and mood states (Christopher et al. 2014a). Several previous studies also observed structural and functional abnormalities in the INS in PD patients. Shine et al. (2014) acquired MRI data from 22 PD patients while performing a task related to hallucinations identity, and found that the PD patients with impaired performance on the task had significantly decreased GM density in the bilateral INS. Christopher et al. (2014b) used positron emission tomography (PET) to study cortical D2 receptor availability among PD-MCI (PD patients with mild cognitive impairment), PD patients with normal cognitive function and controls, while the PD patients underwent overnight withdrawal from levodopa medication before PET scans, they found decreased dopaminergic D2 receptors in the INS in PD-MCI compared to other groups.

Effects of levodopa therapy on distant DC in the PD patients

We found that levodopa therapy increased the abnormally decreased distant DC in the left PoCG in the PD patients at 'ON' state, compared to 'OFF' state (Fig. 3a, Table 2). Levodopa-induced functional activity increase in PoCG has been reported before, in the study of Chen et al. (2015), the technique of arterial spin labeling (ASL) was used to measure cerebral blood flow (CBF) in PD patients, they found that levodopa increased CBF in motor network, including bilateral PoCG in the PD patients at 'ON' state compared to 'OFF' state. Gao et al. (2017) chose globus pallidus (GPi) as a region of interest (ROI) and revealed increased FC between GPi and left PoCG in PD patients at 'ON' state compared to 'OFF' state. In the current study, increased distant DC in the left PoCG may indicate the effects of levodopa therapy on sensory and motor functions in PD patients.

We also found that levodopa therapy increased the abnormally lower distant DC in multiple occipital regions, including the LING, in the PD patients at 'ON' state compared to 'OFF' state (Fig. 3a, Table 2). This finding is consistent with previous studies (Kwak et al. 2012; Chen et al. 2015). Kwak et al. (2012) acquired healthy controls and PD patients before and after taking a dose of 200 mg levodopa, compared ALFF with whole-brain analysis between groups, and found increased ALFF value in occipital gyrus in the PD patients at 'ON' state compared to 'OFF' state. Chen et al. (2015) used the technique of ASL, examined CBF changes in PD patients, and found that levodopa therapy increased CBF in occipital areas in the PD patients at 'ON' state compared to 'OFF' state. In contrast, other studies (Göttlich et al. 2013; Dubbelink et al. 2014) compared PD patients at 'ON' state to healthy controls. Dubbelink et al. (2014) examined FC in PD patients at 'ON' state and controls in a 3-year follow-up study, and demonstrated that the PD patients at 'ON' state showed decreased FC in occipital regions across the time, this change is associative with cognitive decline. Of note, the PD patients in these studies (Dubbelink et al. 2014; Göttlich et al. 2013) were at a relatively advanced disease stage, with average disease duration varied from 6.5 to 9.24 years, in contrast, the average disease duration is 3.47 years in our study, which may account for the discrepancy of the result.

We also observed that levodopa therapy decreased distant DC in the left median cingulate gyrus (MCG) in the PD patients at 'ON' state compared to 'OFF' state (Fig. 3a, Table 2), although we did not detect alteration in this brain regions in the PD patients at 'OFF' state. Decreased distant DC in the left MCG was related to improved UPDRS-III score in the PD patients at 'ON' state relative to 'OFF' state (Fig. 3b). The effects of levodopa on MCG in PD patients has been reported previously, Chen et al. (2015) used ASL and examined changes in CBF before and after levodopa therapy in PD patients, they found CBF changes in the left MCG was negatively correlated with improved bradykinesia subscore of UPDRS-III. Other studies (Hu et al. 2015; Dubbelink et al. 2014) also reported altered functional activity in MCG in PD patients, in these studies, PD patients at 'ON' medication state were compared to healthy controls. Hu et al. (2015) compared ALFF among depressed, non-depressed PD patients and healthy controls, and found increased ALFF in the left MCG in the depressed PD patients. As was suggested, the MCG plays an

important role in cognitive and affective processes (Bressler and Menon 2010; Vogt et al. 2003), but the current study observed that the decreased distant DC in MCG was associated with improved motor functions in the PD patients, further researches may be required to understand the underlying mechanisms of levodopa therapy in MCG in PD patients.

Effects of levodopa therapy on local DC in the PD patients

We found that levodopa therapy increased local DC in the left cerebellum, right PoCG and decreased local DC in the right SMA in the PD patients at 'ON' state compared to 'OFF' state (Fig. 4, Table 3). This result is consistent with the study of Kwak et al. (2012), they measured ALFF among healthy controls, PD patients at 'OFF' and 'ON' state, and found increased ALFF in cerebellum, decreased ALFF in SMA in the PD patients at 'ON' state compared to 'OFF' state. We also noticed different findings from other studies (Wu et al. 2009a, 2009b), Wu et al. (2009b) analyzed the connectivity degree of motor network in PD patients before and after levodopa therapy, and found that the PD patients at 'OFF' state had decreased FC in the SMA, and increased FC in the cerebellum, compared to the healthy controls, while levodopa therapy relatively normalized these FC patterns in the PD patients. The methodological differences may result in this discrepancy, first, different doses of levodopa have been used, Wu et al. (2009b) reported a dose of 200 mg levodopa, while the PD patients in our study received a dose of 400 mg levodopa. Second, we did not regress out the global signal in the preprocessing, while the study of Wu et al. did not give this information.

We also found decreased local DC in several frontal regions, including bilateral middle frontal gyri (MFG) in the PD patients at 'ON' state compared to 'OFF' state (Fig. 4, Table 3). Miller and Cohen (2001) reviewed that MFG is involved in performing a variety of high-level cognitive functions, such as working memory, abstract reasoning, decision making and attentional control. Our observation is in line with previous studies (Kwak et al. 2012; Tessitore et al. 2012a). Kwak et al. (2012) compared ALFF among healthy controls, PD patients at 'OFF' state and 'ON' state, and found decreased ALFF in MFG in the PD patients at 'ON' state compared to 'OFF' state. Tessitore et al. (2012a) evaluated resting-state brain networks of PD patients with and without freezing of gait (FOG), and found that the PD patients with FOG during levodopa medication showed decreased FC in the right MFG compared to healthy controls.

Effects of levodopa therapy on seed-based FC in the PD patients

The current study showed that compared to 'OFF' state, the PD patients at 'ON' state had decreased FC between the left MCG and several nodes of the default mode network (DMN) (Fig. 5a, Table 4). Particularly, decreased FC between the left MCG and right TOPmid was associated with improved UPDRS-III score in the PD patients at 'ON' state relative to 'OFF' state (Fig. 5b). Several previous studies (Hu et al. 2015; Tessitore et al. 2012b; Krajcovicova et al. 2012) have reported the effects of levodopa therapy on FC in DMN in PD patients. It should be noted that these studies compared PD patients at 'ON' state to healthy controls, but did not make a direct comparison between 'ON' and 'OFF' state in PD patient. Hu et al. (2015) found that compared to non-depressed PD patients at 'ON' state and healthy controls, the depressed PD patients had increased FC between the left MCG and several brain regions in the DMN. In contrast, Tessitore et al. (2012b) found decreased FC of DMN in cognitively unimpaired PD patients compared to healthy controls. However, Krajcovicova et al. (2012) found no significant difference between cognitively unimpaired PD patients at 'ON' state and healthy controls on FC of DMN. Given these controversies, the effects of levodopa therapy on DMN in PD patients needs to be further studied.

Limitations

Several limitations should be taken into consideration in the current study. First, we did not set up a placebo group due to ethics review in this study, which may induce several noise factors, such as the placebo effect. In the future, we need to include unmedicated PD patients as a matched placebo group to confirm the reliability of the result (Esposito et al. 2013). Second, we selected a correlation coefficient threshold $r_{ij} = 0.3$ to eliminate weak correlations possibly arising from noise, which may affect the generality of the result (Zuo et al. 2012). We will further investigate the robustness of our results to a broader range of thresholds criteria, such as calculation of the negative correlations. Third, we used the multiple comparison correction of uncorrected voxel-wise $p < 0.001$ together with a cluster size threshold to maintain a corrected threshold at the cluster level of 0.05. Although this correction has been used in many previous studies (Cha et al. 2016; Felger et al. 2016; Rice et al. 2016), it is not as conservative as FDR correction. We did not claim that the Type I (false positive) error was strongly controlled in this study. Fourth, we presented the results with and without GSR, and chose the results without GSR as the main results, although the discrepancy between the results with and without GSR have been consistently reported (Qing et al. 2015; Hayasaka 2013), two potential issues are still needed to address, i.e., whether the discrepancy observed can be reached by using other methods to correct for the GS, and whether the discrepancy can be found in other brain imaging parameters. Finally, we used real cortical distance with Euclidean distance (12 mm) to differentiate the distant and local DC, which may underestimate the true cortical distance (Sepulcre et al. 2010). The reason is that if two

nodes are located in two adjacent gyri, the Euclidean distance will be smaller than the true cortical distance.

Conclusion

The current study examined voxel-based distant and local DC as well as seed-based FC in PD patients before and after levodopa therapy. We found that levodopa therapy increased distant DC in the occipital and motor regions in the PD patients, but failed to normalize abnormal local DC in the PD patients. These results suggested that distant DC rather than local DC is more sensitive to levodopa therapy. We also detected decreased FC of the left median cingulate gyrus to brain regions in DMN in the PD patients after levodopa therapy. Our findings provided new evidence of the neural effects of levodopa therapy on the voxel-based whole-brain network in PD patients.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest All of the authors declare no conflicts of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

Achard, S., Salvador, R., Whitcher, B., Suckling, J., & Bullmore, E. (2006). A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. *Journal of Neuroscience, 26*(1), 63–72.

Anderson, J. S., Druzgal, T. J., Lopez-Larson, M., Jeong, E. K., Desai, K., & Yurgelun-Todd, D. (2011). Network anticorrelations, global regression, and phase-shifted soft tissue correction. *Human Brain Mapping, 32*(6), 919–934.

Bell, P. T., Gilat, M., O'Callaghan, C., Copland, D. A., Frank, M. J., Lewis, S. J., et al. (2015). Dopaminergic basis for impairments in functional connectivity across subdivisions of the striatum in Parkinson's disease. *Human Brain Mapping, 36*(4), 1278–1291.

Beucke, J. C., Sepulcre, J., Talukdar, T., Linnman, C., Zschenderlein, K., Endrass, T., et al. (2013). Abnormally high degree connectivity of the orbitofrontal cortex in obsessive-compulsive disorder. *JAMA Psychiatry, 70*(6), 619–629.

Birn, R. M., Diamond, J. B., Smith, M. A., & Bandettini, P. A. (2006). Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. *Neuroimage, 31*(4), 1536–1548.

Braak, H., Del Tredici, K., Rüb, U., De Vos, R. A., Steur, E. N. J., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging, 24*(2), 197–211.

Braak, H., Bohl, J. R., Müller, C. M., Rüb, U., de Vos, R. A., & Del Tredici, K. (2006). Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. *Movement Disorders, 21*(12), 2042–2051.

Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: emerging methods and principles. *Trends in Cognitive Sciences, 14*(6), 277–290.

Buccino, G., Vogt, S., Ritzl, A., Fink, G. R., Zilles, K., Freund, H.-J., et al. (2004). Neural circuits underlying imitation learning of hand actions: an event-related fMRI study. *Neuron, 42*(2), 323–334.

Buckner, R. L., Sepulcre, J., Talukdar, T., Krienen, F. M., Liu, H., Hedden, T., et al. (2009). Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *Journal of Neuroscience, 29*(6), 1860–1873.

Bullmore, E., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature Reviews. Neuroscience, 10*(3), 186–198.

Cardoso, E. F., Maia, F. M., Fregni, F., Myczkowski, M. L., Melo, L. M., Sato, J. R., et al. (2009). Depression in Parkinson's disease: convergence from voxel-based morphometry and functional magnetic resonance imaging in the limbic thalamus. *Neuroimage, 47*(2), 467–472.

Cha, J., Ide, J. S., Bowman, F. D., Simpson, H. B., Posner, J., & Steinglass, J. E. (2016). Abnormal reward circuitry in anorexia nervosa: A longitudinal, multimodal MRI study. *Human Brain Mapping, 37*(11), 3835–3846.

Chang, C., & Glover, G. H. (2009). Effects of model-based physiological noise correction on default mode network anti-correlations and correlations. *Neuroimage, 47*(4), 1448–1459.

Chen, Y., Pressman, P., Simuni, T., Parrish, T. B., & Gitelman, D. R. (2015). Effects of acute levodopa challenge on resting cerebral blood flow in Parkinson's Disease patients assessed using pseudo-continuous arterial spin labeling. *PeerJ, 3*, e1381.

Chéron, G., Dan, B., & Borenstein, S. (2000). Sensory and motor interfering influences on somatosensory evoked potentials. *Journal of Clinical Neurophysiology, 17*(3), 280–294.

Christopher, L., Koshimori, Y., Lang, A. E., Criaud, M., & Strafella, A. P. (2014a). Uncovering the role of the insula in non-motor symptoms of Parkinson's disease. *Brain, 137*(8), 2143–2154.

Christopher, L., Marras, C., Duff-Canning, S., Koshimori, Y., Chen, R., Boileau, I., et al. (2014b). Combined insular and striatal dopamine dysfunction are associated with executive deficits in Parkinson's disease with mild cognitive impairment. *Brain, 137*(2), 565–575.

Cohen, J. (1992). A power primer. *Psychological Bulletin, 112*(1), 155.

Contin, M., & Martinelli, P. (2010). Pharmacokinetics of levodopa. *Journal of Neurology, 257*(2), 253–261.

Di Martino, A., Zuo, X.-N., Kelly, C., Grzadzinski, R., Mennes, M., Schvarcz, A., et al. (2013). Shared and distinct intrinsic functional network centrality in autism and attention-deficit/hyperactivity disorder. *Biological Psychiatry, 74*(8), 623–632.

Diederich, N. J., Stebbins, G., Schiltz, C., & Goetz, C. G. (2014). Are patients with Parkinson's disease blind to blindsight? *Brain, 137*(6), 1838–1849.

Dubbelink, K. T. O., Hillebrand, A., Stoffers, D., Deijen, J. B., Twisk, J. W., Stam, C. J., et al. (2013). Disrupted brain network topology in

Parkinson's disease: a longitudinal magnetoencephalography study. *Brain, 137*(1), 197–207.

Dubbelink, K. T. O., Schoonheim, M. M., Deijen, J. B., Twisk, J. W., Barkhof, F., & Berendse, H. W. (2014). Functional connectivity and cognitive decline over 3 years in Parkinson disease. *Neurology, 83*(22), 2046–2053.

Esposito, F., Tessitore, A., Giordano, A., De Micco, R., Paccone, A., Conforti, R., et al. (2013). Rhythm-specific modulation of the sensorimotor network in drug-naive patients with Parkinson's disease by levodopa. *Brain, 136*(3), 710–725.

Fahn, S. (1999). Parkinson disease, the effect of levodopa, and the ELLDOPA trial. *Archives of Neurology, 56*(5), 529–535.

Fahn, S., & Elton, R. (1987). *Unified rating scale for Parkinson's disease*. (pp. 153–163): Macmillan, Florham Park, New York.

Fang, J., Chen, H., Cao, Z., Jiang, Y., Ma, L., Ma, H., et al. (2017). Impaired brain network architecture in newly diagnosed Parkinson's disease based on graph theoretical analysis. *Neuroscience Letters, 657*, 151–158.

Felger, J. C., Li, Z., Haroon, E., Woolwine, B. J., Jung, M. Y., Hu, X., et al. (2016). Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. *Molecular Psychiatry, 21*(10), 1358.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189–198.

Forno, L. S. (1981). Pathology of Parkinson's disease. In *Movement Disorders* (pp. 25–40): Elsevier.

Fox, M. D., Zhang, D., Snyder, A. Z., & Raichle, M. E. (2009). The global signal and observed anticorrelated resting state brain networks. *Journal of Neurophysiology, 101*(6), 3270–3283.

Gallagher, D. A., Parkkinen, L., O'sullivan, S. S., Spratt, A., Shah, A., Davey, C. C., et al. (2011). Testing an aetiological model of visual hallucinations in Parkinson's disease. *Brain, 134*(11), 3299–3309.

Gao, L. L., Zhang, J. R., Chan, P., & Wu, T. (2017). Levodopa Effect on Basal Ganglia Motor Circuit in Parkinson's Disease. *CNS Neuroscience & Therapeutics, 23*(1), 76–86.

Gibb, W., & Lees, A. (1988). The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry, 51*(6), 745–752.

Göttlich, M., Münte, T. F., Heldmann, M., Kasten, M., Hagenah, J., & Krämer, U. M. (2013). Altered resting state brain networks in Parkinson's disease. *PLoS One, 8*(10), e77336.

Group, P. S. (2004). Levodopa and the progression of Parkinson's disease. *New England Journal of Medicine, 351*(24), 2498–2508.

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C. J., Wedeen, V. J., et al. (2008). Mapping the structural core of human cerebral cortex. *PLoS Biology, 6*(7), e159.

Harding, A., Broe, G., & Halliday, G. (2002). Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. *Brain, 125*(2), 391–403.

Hayasaka, S. (2013). Functional connectivity networks with and without global signal correction. *Frontiers in Human Neuroscience, 7*, 880.

Helmich, R. C., Derikx, L. C., Bakker, M., Scheeringa, R., Bloem, B. R., & Toni, I. (2010). Spatial remapping of cortico-striatal connectivity in Parkinson's disease. *Cerebral Cortex, 20*(5), 1175–1186.

Hoehn, M. M., & Yahr, M. D. (1998). Parkinsonism: onset, progression, and mortality. *Neurology, 50*(2), 318–318.

Hou, Y., Wu, X., Hallett, M., Chan, P., & Wu, T. (2014). Frequency-dependent neural activity in Parkinson's disease. *Human Brain Mapping, 35*(12), 5815–5833.

Hu, X., Song, X., Li, E., Liu, J., Yuan, Y., Liu, W., et al. (2015). Altered resting-state brain activity and connectivity in depressed Parkinson's disease. *PLoS One, 10*(7), e0131133.

Jankovic, J. (2008). Parkinson's disease: clinical features and diagnosis. *Journal of Neurology, Neurosurgery and Psychiatry, 79*(4), 368–376.

Jenkins, I. H., Jahanshahi, M., Jueptner, M., Passingham, R. E., & Brooks, D. J. (2000). Self-initiated versus externally triggered movements: II. The effect of movement predictability on regional cerebral blood flow. *Brain, 123*(6), 1216–1228.

Jubault, T., Gagnon, J.-F., Karama, S., Ptito, A., Lafontaine, A.-L., Evans, A. C., et al. (2011). Patterns of cortical thickness and surface area in early Parkinson's disease. *Neuroimage, 55*(2), 462–467.

Kelly, C., de Zubicaray, G., Di Martino, A., Copland, D. A., Reiss, P. T., Klein, D. F., et al. (2009). L-dopa modulates functional connectivity in striatal cognitive and motor networks: a double-blind placebo-controlled study. *Journal of Neuroscience, 29*(22), 7364–7378.

Kempster, P. A., O'Sullivan, S. S., Holton, J. L., Revesz, T., & Lees, A. J. (2010). Relationships between age and late progression of Parkinson's disease: a clinico-pathological study. *Brain, 133*(6), 1755–1762.

Kish, S. J., Shannak, K., & Hornykiewicz, O. (1988). Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. *New England Journal of Medicine, 318*(14), 876–880.

Krajcovicova, L., Mikl, M., Marecek, R., & Rektorova, I. (2012). The default mode network integrity in patients with Parkinson's disease is levodopa equivalent dose-dependent. *Journal of Neural Transmission, 119*(4), 443–454.

Kurani, A. S., Seidler, R. D., Burciu, R. G., Comella, C. L., Corcos, D. M., Okun, M. S., et al. (2014). Subthalamic nucleus-sensorimotor cortex functional connectivity in de novo and moderate Parkinson's disease. *Neurobiology of Aging, 36*(1), 462–469.

Kwak, Y., Peltier, S., Bohnen, N., Müller, M., Dayalu, P., & Seidler, R. D. (2010). Altered resting state cortico-striatal connectivity in mild to moderate stage Parkinson's disease. *Frontiers in Systems Neuroscience, 4*, 143.

Kwak, Y., Peltier, S., Bohnen, N., Müller, M., Dayalu, P., & Seidler, R. D. (2012). L-DOPA changes spontaneous low-frequency BOLD signal oscillations in Parkinson's disease: a resting state fMRI study. *Frontiers in Systems Neuroscience, 6*, 52.

Ledberg, A., Åkerman, S., & Roland, P. E. (1998). Estimation of the probabilities of 3D clusters in functional brain images. *Neuroimage, 8*(2), 113–128.

Liu, W., Wei, D., Sun, J., Yang, J., Meng, J., Wang, L., et al. (2015). Abnormal Degree Centrality of Functional Hubs Associated with Negative Coping in Older Chinese Adults Who Lost Their Only Child. *Biological Psychology, 112*, 46–55.

Luo, C., Guo, X., Song, W., Chen, Q., Yang, J., Gong, Q., et al. (2015). The trajectory of disturbed resting-state cerebral function in Parkinson's disease at different Hoehn and Yahr stages. *Human Brain Mapping, 36*(8), 3104–3116.

Melzer, T. R., Watts, R., MacAskill, M. R., Pitcher, T. L., Livingston, L., Keenan, R. J., et al. (2012). Grey matter atrophy in cognitively impaired Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry, 83*(2), 188–194.

Meppelink, A. M., de Jong, B. M., Renken, R., Leenders, K. L., Cornelissen, F. W., & van Laar, T. (2009). Impaired visual processing preceding image recognition in Parkinson's disease patients with visual hallucinations. *Brain, 132*(11), 2980–2993.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience, 24*(1), 167–202.

Murphy, K., Birn, R. M., Handwerker, D. A., Jones, T. B., & Bandettini, P. A. (2009). The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? *Neuroimage, 44*(3), 893–905.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97–113.

Pereira, J. B., Aarsland, D., Ginestet, C. E., Lebedev, A. V., Wahlund, L. O., Simmons, A., et al. (2015). Aberrant cerebral network topology and mild cognitive impairment in early Parkinson's disease. *Human Brain Mapping, 36*(8), 2980–2995.

Qing, Z., Dong, Z., Li, S., Zang, Y., & Liu, D. (2015). Global signal regression has complex effects on regional homogeneity of resting state fMRI signal. *Magnetic Resonance Imaging, 33*(10), 1306–1313.

Rice, K., Moraczewski, D., & Redcay, E. (2016). Perceived live interaction modulates the developing social brain. *Social Cognitive and Affective Neuroscience, 11*(9), 1354–1362.

Roland, P. E., Larsen, B., Lassen, N. A., & Skinhoj, E. (1980). Supplementary motor area and other cortical areas in organization of voluntary movements in man. *Journal of Neurophysiology, 43*(1), 118–136.

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: uses and interpretations. *Neuroimage, 52*(3), 1059–1069.

Saad, Z. S., Gotts, S. J., Murphy, K., Chen, G., Jo, H. J., Martin, A., et al. (2012). Trouble at rest: how correlation patterns and group differences become distorted after global signal regression. *Brain Connectivity, 2*(1), 25–32.

Salat, D., & Tolosa, E. (2013). Levodopa in the treatment of Parkinson's disease: current status and new developments. *Journal of Parkinson's Disease, 3*(3), 255–269.

Schölvinck, M. L., Maier, A., Frank, Q. Y., Duyn, J. H., & Leopold, D. A. (2010). Neural basis of global resting-state fMRI activity. *Proceedings of the National Academy of Sciences of the United States of America, 107*(22), 10238–10243.

Sepulcre, J., Liu, H., Talukdar, T., Martincorena, I., Yeo, B. T., & Buckner, R. L. (2010). The organization of local and distant functional connectivity in the human brain. *PLoS Computational Biology, 6*(6), e1000808.

Shine, J. M., Halliday, G. M., Gilat, M., Matar, E., Bolitho, S. J., Carlos, M., et al. (2014). The role of dysfunctional attentional control networks in visual misperceptions in Parkinson's disease. *Human Brain Mapping, 35*(5), 2206–2219.

Skidmore, F., Yang, M., Baxter, L., Von Deneen, K., Collingwood, J., He, G., et al. (2013). Reliability analysis of the resting state can sensitively and specifically identify the presence of Parkinson disease. *Neuroimage, 75*, 249–261.

Takeuchi, H., Taki, Y., Nouchi, R., Sekiguchi, A., Hashizume, H., Sassa, Y., et al. (2015). Degree centrality and fractional amplitude of low-frequency oscillations associated with Stroop interference. *Neuroimage, 119*, 197–209.

Tanji, J., & Hoshi, E. (2001). Behavioral planning in the prefrontal cortex. *Current Opinion in Neurobiology, 11*(2), 164–170.

Tessitore, A., Amboni, M., Esposito, F., Russo, A., Picillo, M., Marcuccio, L., et al. (2012a). Resting-state brain connectivity in patients with Parkinson's disease and freezing of gait. *Parkinsonism & Related Disorders, 18*(6), 781–787.

Tessitore, A., Esposito, F., Vitale, C., Santangelo, G., Amboni, M., Russo, A., et al. (2012b). Default-mode network connectivity in cognitively unimpaired patients with Parkinson disease. *Neurology, 79*(23), 2226–2232.

Tomasi, D., & Volkow, N. D. (2010). Functional connectivity density mapping. *Proceedings of the National Academy of Sciences of the United States of America, 107*(21), 9885–9890.

Tuovinen, N., Seppi, K., de Pasquale, F., Müller, C., Nocker, M., Schocke, M., et al. (2018). The reorganization of functional architecture in the early-stages of Parkinson's disease. *Parkinsonism & Related Disorders*.

Uc, E., Rizzo, M., Anderson, S., Qian, S., Rodnitzky, R., & Dawson, J. (2005). Visual dysfunction in Parkinson disease without dementia. *Neurology, 65*(12), 1907–1913.

Vogt, B. A., Berger, G. R., & Derbyshire, S. W. (2003). Structural and functional dichotomy of human midcingulate cortex. *European Journal of Neuroscience, 18*(11), 3134–3144.

Wang, J. H., Zuo, X. N., Gohel, S., Milham, M. P., Biswal, B. B., & He, Y. (2011). Graph theoretical analysis of functional brain networks: test-retest evaluation on short-and long-term resting-state functional MRI data. *PLoS One, 6*(7), e21976.

Wang, L. F., Dai, Z. J., Peng, H. J., Tan, L. W., Ding, Y. Q., He, Z., et al. (2014). Overlapping and segregated resting-state functional connectivity in patients with major depressive disorder with and without childhood neglect. *Human Brain Mapping, 35*(4), 1154–1166.

Wang, L., Xia, M., Li, K., Zeng, Y., Su, Y., Dai, W., et al. (2015). The effects of antidepressant treatment on resting-state functional brain networks in patients with major depressive disorder. *Human Brain Mapping, 36*(2), 768–778.

Weissenbacher, A., Kasess, C., Gerstl, F., Lanzenberger, R., Moser, E., & Windischberger, C. (2009). Correlations and anticorrelations in resting-state functional connectivity MRI: a quantitative comparison of preprocessing strategies. *Neuroimage, 47*(4), 1408–1416.

Wu, T., & Hallett, M. (2005). A functional MRI study of automatic movements in patients with Parkinson's disease. *Brain, 128*(10), 2250–2259.

Wu, T., Long, X., Zang, Y., Wang, L., Hallett, M., Li, K., et al. (2009a). Regional homogeneity changes in patients with Parkinson's disease. *Human Brain Mapping, 30*(5), 1502–1510.

Wu, T., Wang, L., Chen, Y., Zhao, C., Li, K., & Chan, P. (2009b). Changes of functional connectivity of the motor network in the resting state in Parkinson's disease. *Neuroscience Letters, 460*(1), 6–10.

Wu, T., Long, X., Wang, L., Hallett, M., Zang, Y., Li, K., et al. (2011). Functional connectivity of cortical motor areas in the resting state in Parkinson's disease. *Human Brain Mapping, 32*(9), 1443–1457.

Wu, X., Zou, Q., Hu, J., Tang, W., Mao, Y., Gao, L., et al. (2015). Intrinsic functional connectivity patterns predict consciousness level and recovery outcome in acquired brain injury. *Journal of Neuroscience, 35*(37), 12932–12946.

Xie, C. l., Zhang, Y. Y., Wang, X. D., Chen, J., Chen, Y. H., Pa, J. L., et al. (2015). Levodopa alone compared with levodopa-sparing therapy as initial treatment for Parkinson's disease: a meta-analysis. *Neurological Sciences, 36*(8), 1319–1329.

Yan, C. G., & Zang, Y. F. (2010). DPARSF: a MATLAB toolbox for "pipeline" data analysis of resting-state fMRI. *Frontiers in Systems Neuroscience, 4*, 13.

Yan, C. G., Wang, X. D., Zuo, X. N., & Zang, Y. F. (2016). DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. *Neuroinformatics, 14*(3), 339.

Young, D. E., Wagenaar, R. C., Lin, C.-C., Chou, Y.-H., Davidsdottir, S., Saltzman, E., et al. (2010). Visuospatial perception and navigation in Parkinson's disease. *Vision Research, 50*(23), 2495–2504.

Zarei, M., Ibarretxe-Bilbao, N., Compta, Y., Hough, M., Junque, C., Bargallo, N., et al. (2013). Cortical thinning is associated with disease stages and dementia in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry, 84*(8), 875–882.

Zhang, J., Wei, L., Hu, X., Zhang, Y., Zhou, D., Li, C., et al. (2013). Specific frequency band of amplitude low-frequency fluctuation predicts Parkinson's disease. *Behavioural Brain Research, 252*, 18–23.

Zhang, J., Bi, W., Zhang, Y., Zhu, M., Zhang, Y., Feng, H., et al. (2015). Abnormal functional connectivity density in Parkinson's disease. *Behavioural Brain Research, 280*, 113–118.

Zuo, X. N., Ehmke, R., Mennes, M., Imperati, D., Castellanos, F. X., Sporns, O., et al. (2012). Network centrality in the human functional connectome. *Cerebral Cortex, 22*(8), 1862–1875.