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ORIGINAL RESEARCH

Functional Connectivity in Parkinson's Disease Patients with Mild Cognitive Impairment

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Objective: To explore the alteration of pattens of anatomical and functional connectivity (FC) of posterior cingulate cortex (PCC) in Parkinson's disease (PD) patients with cognitive dysfunction and the relationship between the connection strengths and cognitive state.

Methods: We prospectively enrolled 20 PD patients with mild cognitive impairment (PD-MCI), 13 PD patients with normal cognition (PD-NC) and 13 healthy controls (HCs). By collecting, preprocessing and FC analyzing resting-state functional magnetic resonance imaging (rs-fMRI) data, we extracted default mode network (DMN) patterns, compared the differences in DMN between the three groups and the analyzed the correlation between FC value with the commonly used neuropsychological testing.

Results: The PD-MCI showed significant worse performances in general cognition, and PD-NC and HCs showed comparable performances of cognitive function. Cognitive-related differences in DMN were detected in the bilateral precuneus (BPcu). Compared with the HCs, PD-NC and PD-MCI showed significantly decreased FC within BPcu (both $P < 0.001$). For PD-MCI, the rho of the Fisher's Z-transformed FC (zFC) value within BPcu with the TMTA, DSST and CFT-20min were 0.50, 0.66 and 0.47, respectively. For PD-NC, the rho of the zFC value within BPcu with the MMSE was 0.58.

Discussion: BPcu was the cognitive-related region in DMN. As cognition declines, FC within BPcu weakens. For PD-MCI, the higher the FC values within BPcu were likely to be related to the better the performances of TMTA, DSST and CFT-20 min DR, which needs to be further confirmed by large-sample studies.

Keywords: Parkinson's disease, mild cognitive impairment, resting-state functional magnetic resonance imaging, functional connectivity

Introduction

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder, decreasing the quality of life and placing serious social and economic burdens.[1] In China, the prevalence of PD is 1700 per 100,000 in individuals older than 65 years, which is similar to the rate reported in developed countries.[2,3] PD is usually characterized by motor symptoms that the main clinical manifestations are bradykinesia, rest tremor present, muscular rigidity and postural instability[4] but may lead to mild cognitive impairment and dementia. Evidence implicates that patients with PD are six times more likely to develop dementia than healthy people.[5] PD with mild cognitive impairment (PD-MCI) has attracted much attention in recent years.

The pathogenesis and pathogenesis of PD-MCI are not yet fully understood. In recent years, researchers have conducted in-depth studies on the pathogenesis and clinical features of PD-MCI. Among them, the research progress of imaging,

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especially magnetic resonance imaging (MRI) has shown potential significance for early screening and early diagnosis of PD-MCI.

MRI is one of the most widely used methods studying PD-MCI in recent years. Studies have shown that MRI technology provides a new evidence for early detection of PD-MCI. Current imaging techniques mainly include anatomical structure MRI imaging region-of-interest (ROI), voxel-based morphometry (VBM), cortical thickness analysis, white matter imaging technology, magnetic resonance diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI) and perfusion imaging technology. At present, there are few reports on the application of resting state fMRI (rs-fMRI) technology to study PD-MCI.

In order to investigate the cognitive-related changes of gray matter structure and function in PD patients, this study using rs-fMRI to assess the pattens of anatomical and functional connectivity (FC) damage in PD patients with normal cognition (PD-NC) and PD-MCI. Furthermore, we analyze the relationship between the connection strengths and cognitive state.

Materials and Methods

Participants

Twenty PD-MCI, 13 PD-NC and 13 healthy controls (HCs) were employed in the present study through newspaper advertisements. All subjects underwent clinical evaluations and MRI scans. One PD-MCI and one PD-NC were excluded from the imaging analysis because of the excessive motion artifacts. The study was approved by the Research Ethics Committee of the Affiliated Jiangyin People's Hospital of Southeast University Medical College and written informed consent was obtained from all participants.

Clinical Evaluation

Each subject underwent comprehensive clinical evaluations, including the demographic information, history of past illness and neuropsychological testing. Mini-Mental State Examination (MMSE) was used to assess the general cognition. The neuropsychological battery mainly comprised of Auditory Verbal Learning Test-20-min delayed recall (AVLT-20min DR), the Rey-Osterrieth Complex Figure Test (CFT-20min DR), Trail Making Test (TMT)-A and B, Verbal Fluency Test (VFT), Digital Symbol Substitution Test (DSST) and Clock Drawing Test (CDT) were used to evaluate the episodic memory, visuospatial function, information processing speed and executive function.

Inclusion and Exclusion Criteria

The diagnosis of PD was made following the 2016 Chinese diagnostic criteria for PD.[6]

The diagnosis of MCI was made following the recommendations of Petersen et al[7] and others:[8,9] (a) subjective memory impairment corroborated by the subject and an informant; (b) objective memory performance documented by an AVLT-20min DR score less than or equal to 1.5 SD of age- and education-adjusted norms (cut-off of ≤4 correct responses on 12 items for patients with ≥8 years of education); (c) MMSE score of 24 or lower; (d) Clinical Dementia Rating (CDR) of 0.5; (e) no or minimal impairment in activities of daily living; (f) absence of dementia or insufficient dementia to meet the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Alzheimer's criteria. In addition, the controls were required to have a CDR of 0, an MMSE score ≥26, and an AVLT-20min DR score ≥4 for subjects with 8 or more years of education.

Participants were excluded from the study if they had a history of dementia and mental illness, severe heart, liver, and kidney dysfunction, malignant tumors and endocrine and metabolic diseases, left-handed, cerebrovascular disease, trauma, progressive ascending paralysis confirmed, multiple system atrophy, and cortical basal ganglia disease.

MRI Data Acquisition

The subjects were scanned using a General Electric 1.5 Tesla scanner (General Electric Medical Systems, USA) with a homogeneous birdcage head coil (16 channels). Subjects lay supine with the head snugly fixed by a belt and foam pads to minimize head motion. Conventional axial fast relaxation fast spin echo sequence T2 weighted anatomic MR images were obtained to rule out major white matter changes, cerebral infarction or other lesions: repetition time (TR) = 3500 ms; echo time (TE) = 103 ms; flip angle (FA) = 90°; acquisition matrix = 320×192; field of view (FOV) = 240×240 mm; thickness = 6.0 mm; gap = 0 mm; no. of excitations (NEX) = 2.0. High-resolution T1-weighted axial images covering the whole brain were acquired using a 3D spoiled gradient echo sequence as follows: TR = 9.9 ms; TE = 2.1 ms; FA =

15°; acquisition matrix = 256×192; FOV = 240 mm×240 mm^2; thickness = 2.0 mm; gap = 0 mm. The functional scans (T2* weighted images) involved the acquisition of 30 contiguous axial slices using a GRE-EPI pulse sequence: TR = 3,000 ms; TE = 40 ms; FA = 90°; acquisition matrix = 64×64; FOV = 240×240 mm; thickness = 4.0 mm; gap = 0 mm and 3.75×3.75 mm^2 inplane resolution parallel to the anterior commissure–posterior commissure line. This acquisition sequence generated 142 volumes in 7 min and 6 s. All subjects have eyes closed during scanning.

MRI Data Preprocessing

The preprocessing was performed by using Data Processing Assistant for Resting-State fMRI (DPARSF) (Yan & Zang, 2010, http://www.restfmri.net), which is based on Statistical Parametric Mapping (SPM5) (http://www.fil.ion.ucl.ac.uk/spm) and Resting-State fMRI Data Analysis Toolkit (REST, Song et al, 2011. http://www.restfmri.net). Data analyses of groups were conducted with SPM5 toolkit (http://www.fil.ion.ucl.ac.uk/spm). The first eight volumes of the scanning session were discarded to allow for T1 equilibration effects. The remaining images were corrected for timing differences and motion effects. No translation or rotation parameters of head motion in any given data set exceeded ±3 mm or ±3. The resulting images were spatially normalised into the SPM5 Montreal Neurological Institute echo-planar imaging template using the default settings and resampling to 3 × 3×3 mm3 voxels, and smoothed with a Gaussian kernel of 6 × 6×6 mm. Then, the linear trend of time courses was removed and the resulting fMRI data were band-pass filtered (0.01 <f < 0.08 Hz).

FC Analysis

The posterior cingulate cortex (PCC) hub [coordinate in the MNI space: −2, −45, 34] was selected to generate a 6-mm radius spherical seed region,[10,11] followed by coregistration to the functional data. Individual time courses were extracted based on the coregistered seed region. Furthermore, voxel-wise cross-correlation (CC) values between the seed region and the whole brain were calculated. A Fisher's Z-transformation was then applied to improve the normality of the CC values. Finally, the individual default mode network (DMN) patterns were obtained. Additionally, the mean time series of global, white matter, cerebrospinal fluid signals and head motion parameters were introduced as covariates of no interest.

Voxelwise-Based Grey Matter Volume Correction

To explore the FC changes that cannot be attributed to anatomical difference, the voxel's likelihood of containing grey matter was introduced as nuisance variables. Firstly, VBM was used to explore grey matter volume maps of every subject. These maps were transformed into the same standard space as the rs-fMRI images using affine linear registration. Further, the resampled data were smoothed as the corresponding functional data (8 mm). Finally, the resulting voxelwise grey matter volume maps were input as covariates in the analysis of functional data. The voxelwise-based grey matter volume correction was used for each subject.[12]

Statistical Analysis

Demographic and Neuropsychological Data

One-way analysis of variance (ANOVA) was used for normally distributed data. Kruskal Wallis tests followed by Dunn-Bonferroni post hoc were performed as the neuropsychological data were not normally distributed ($P < 0.05$ for Kolmogorov–Smirnov test). The χ^2 tests were performed for gender. The SPSS 22.0 software was used and the statistical significance was set at $P < 0.05$.

Group-Level Analyses of the DMN

Within groups: to determine the patterns of DMN in each of three groups, the spatial maps of DMN IC in each group were submitted to a random-effect analysis using one-sample *t*-tests. The thresholds were set at a corrected $P < 0.001$, determined by Monte Carlo simulation for multiple comparison (single voxel P value = 0.001, a minimum cluster size of 6156 mm3, FWHM = 6 mm; http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf).

Between groups: ANOVA was performed to explore the different DMN patterns among HCs, PD-NC and PD-MCI. The effects of age, gender and education were corrected.[13,14] The statistical thresholds were set at an AlphaSim-corrected $P < 0.001$ as determined by Monte Carlo simulation (single voxel P value = 0.001, a minimum cluster size of 6156 mm3, FWHM = 6 mm; http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf). The regions survived the Monte Carlo simulations were taken as ROIs, and the Fisher's Z-transformed FC (zFC) strengths for each subject were extracted for further analysis.

Characteristic of Disease-Related Difference in DMN

Post hoc tests were performed to explore the different DMN patterns of regions with disease-related changes

Table 1 Demographic and Neuropsychological Data for HCs, PD with Normal Cognition and PD with MCI

	PD with MCI (n = 20)	PD with Normal Cognition (n = 13)	HC (n = 13)	P (KW)
Age (years)	72.6±6.1	70.4±6.4	70.2±7.1	0.233
Gender (M/F)	12/8	7/6	4/9	0.247
Education (years)	11.7±3.3	12.2±3.9	12.1±3.5	0.688
MMSE	26.9±3.1***	28.5±1.5	28.8±1.4	<0.001
AVLT-20min DR	2.9±1.2***	6.9±1.1	7.7±1.5	<0.001
CFT-20min DR	13.3±4.9***	17.5±4.5	19.2±4.9	<0.001
CDT	8.0±2.1*	9.2±1.4	8.9±1.0	0.037
DSST	33.8±7.8***	41.2±8.8	40.3±10.7	<0.001
TMT-A (second)	75.8±14.5*	63.6±19.8	66.2±20.1	0.019
VFT	17.1±4.1***	19.9±4.4	21.1±5.2	<0.001
TMT-B (second)	210.9±70.1***	197.1±72.1	187.3±74.1	<0.001

Notes: Data was represented as mean±SD. Kruskal Wallis tests followed by Dunn-Bonferroni post hoc were performed as the neuropsychological data were not normally distributed ($P < 0.05$ for Kolmogorov–Smirnov test). The χ^2 tests were performed for gender. *Indicates a statistical difference compared with HC. *Indicate P < 0.05 and ***Indicate P < 0.001.

Abbreviations: MMSE, Mini-Mental State examination; AVLT-20, Auditory Verbal Learning Test-20-minute delayed recall; CFT20, Rey-Osterrieth Complex Figure Test-20-minute delayed recall; CDT, Clock Drawing Test; DSST, Digital Symbol Substitution Test; TMT-A, Trail Making Test-A; VFT, Verbal Fluency Test; TMT-B, Trail Making Test-B.

among three groups. ANOVA analyses followed by the least-significant difference (LSD) analyses were utilized. To explore the cognitive significances of the disease-related changes in DMN, the Spearman correlation analyses were performed between the zFC strengths and the neuropsychological performances. The SPSS 22.0 software was used and the statistical significance was set at P < 0.05.

Results

Demographic and Cognitive Data

As shown in Table 1, the PD-MCI showed significant worse performances in general cognition (ie, MMSE), episodic memory (ie, AVLT-20min DR and CFT-20min DR), visuospatial function (ie, CDT), information processing speed (ie, DSST and TMT-A) and executive function (ie, TMT-B and VFT, all P < 0.05). Furthermore, the PD-NC and HCs showed comparable performances of cognitive function (all P > 0.05). It should be noted that there were no significant differences with regard to demographic data among the three groups (all P > 0.05).

Identification of Disease-Related Differences in DMN

As illustrated by the one-sample *t*-test, the DMN patterns for each group were obtained by using PCC seed-based FC analysis (shown in Figure 1).

As shown by one-way ANOVA, the disease-related differences in DMN were detected in the bilateral precuneus (BPcu) (shown in Table 2 and Figure 2). It should be noted that the region mentioned above was taken as ROI.

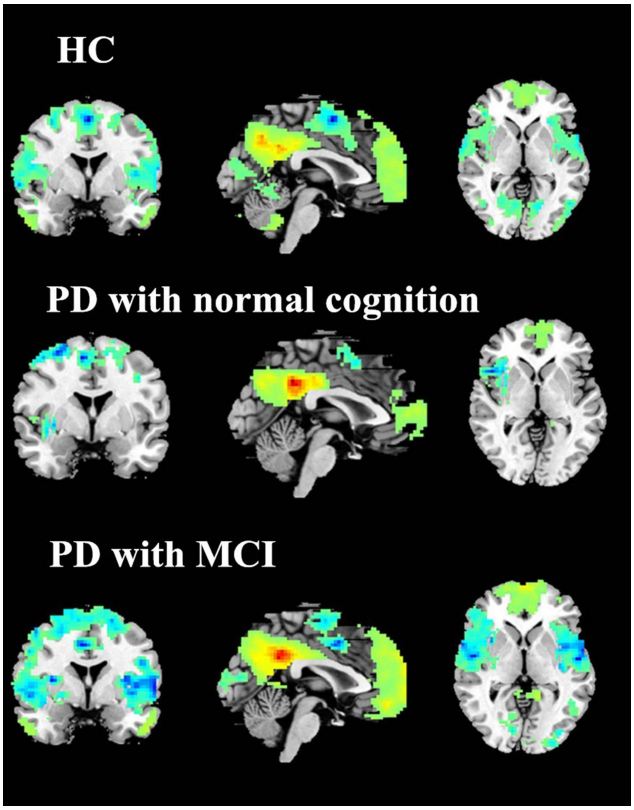

Figure 1 Whole-brain voxelwise pattern of the default mode network in each group. The DMN pattern for each group was obtained by using PCC (MNI coordinate: −2, −45, 34, radius = 6 mm) seed-based functional activity analysis. The random-effects one-sample *t*-test was performed and threshold was set at a corrected P < 0.01, determined by Monte Carlo simulation.

Table 2 Descriptions of Disease-Related Differences in DMN Revealed by One-Way ANOVA

Brain Region	Peak MNI Coordiates x, y, z (mm)	Peak F value	Cluster Size (mm^3)
Bilateral Precuneus	−9, −63, 51	12.4	6615

Notes: All the regions survived the Monte Carlo Stimulations, and the thresholds were set as voxel-wise $P < 0.01$, cluster sizes larger than 6156 mm^3.

Group-Level Differences and Behavioral Significance of the Genotype-by-Disease Interaction in DMN

Among the three groups, significant FC differences were detected within the BPcu (F = 10.7, P < 0.001). The LSD analysis indicated that compared to PD-NC and PD-MCI, the HCs showed significantly increased FC within BPcu (both P < 0.001). Further, there was also significant difference regarding the FC within BPcu between the two PD groups (P < 0.001, shown in Figure 3).

As illustrated in Figure 4, for PD-MCI, the higher the FC values within BPcu were related to the better the performances information processing speed (ie, shorter time consumed of TMTA, rho = −0.50, P = 0.033, and higher scores of DSST, rho = −0.66, P = 0.003) and episodic memory (ie, higher scores of CFT-20 min DR, rho = 0.47, P = 0.047). Similar associations were also detected between the FC within BPcu and performances of MMSE (rho = 0.58, P = 0.046) for PD-NC.

Discussion

The primary objective of this study was to explore the difference of pattens of anatomical and FC in HCs, PD, and PD-MCI and the relationship between the connection strengths and cognitive state. We found that in PD patients, brain network associated with the cognitive dysfunction was BPcu, and the FC within BPcu significantly decreased in PD-NC and PD-MCI. Furthermore, higher connectivity strength was associated with a faster information processing speed (TMTA, DSST), a better episodic memory (CFT-20 min DR) and a better general cognition (MMSE).

Rs-fMRI is a promising approach that measures naturally occurring low-frequency fluctuations in blood oxygenation level-dependent (BOLD) signals reflecting physiologically meaningful changes of spontaneous neural activity in the resting-state networks (RSNs) to investigate neuropsychiatric disorders.[15] It avoids demanding task performance and can easily obtain relatively stable results.[16] Rs-fMRI is widely used in Alzheimer's disease

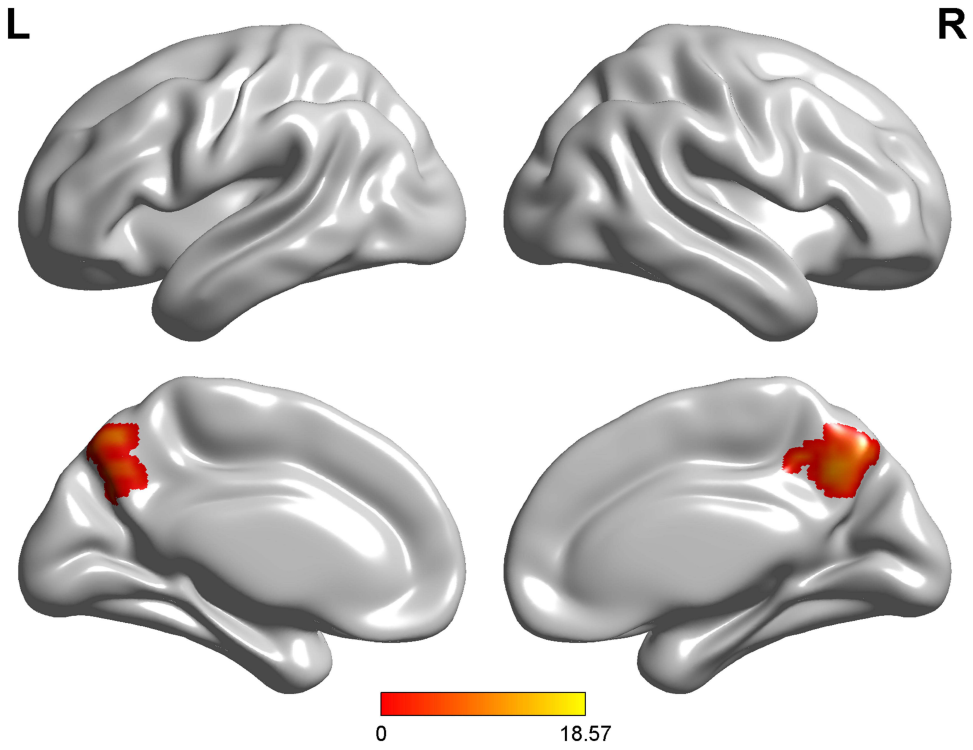

Figure 2 One-way ANOVA of DMN functional connectivity. Thresholds were set at a corrected P < 0.01, determined by Monte Carlo simulation.

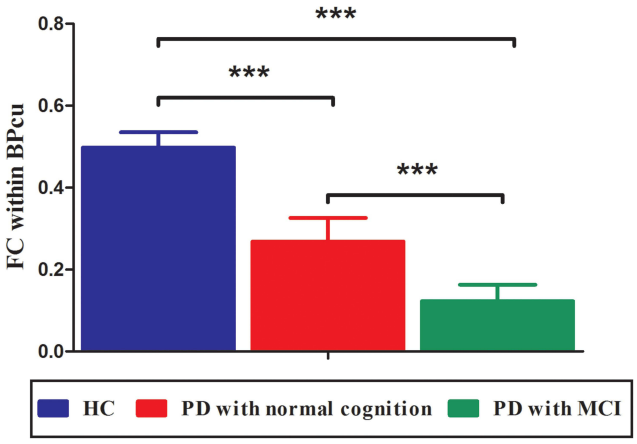

Figure 3 Group-level differences of the disease-related differences in DMN. Compared to PD patients with normal cognition and PD patients with MCI, the HCs showed significantly increased FC within BPcu. Further, there was also significant difference regarding the FC within BPcu between the two PD groups. ***Indicate P < 0.001.

(AD),[17] other dementias[18] and mood disorders.[15] Mounting studies have identified a wide array of brain regions that exhibit group-wise differences between HCs and neuropsychiatric disorders.[15] Over the last decades, rs-fMRI has been carried out to investigate the FC changes in patients with PD.[19–22] However, there is still a need for understanding the exact relationship between the function and brain regions and the relationship between the connection strengths and cognitive state.

DMN is the most popular target in RSNs, including a midline core (including the anterior medial prefrontal cortex (aMPFC) and PCC) and two subsystems (the dorsal medial prefrontal cortex (DMPFC) subsystem and the medial temporal lobe (MTL) subsystem).[23] DMN is thought to be involved in advanced cognitive functions. Early study has observed DMN dysfunction in PD patients.[24] Wolters et al[25] observed that cognitive impairment in PD was correlated with reduced FC in networks involved in cognition, especially in the DMN. Studies suggested that the precuneus was implicated in high-level cognitive functions, including self-related processing, episodic memory, and aspects of consciousness.[26–28] Our

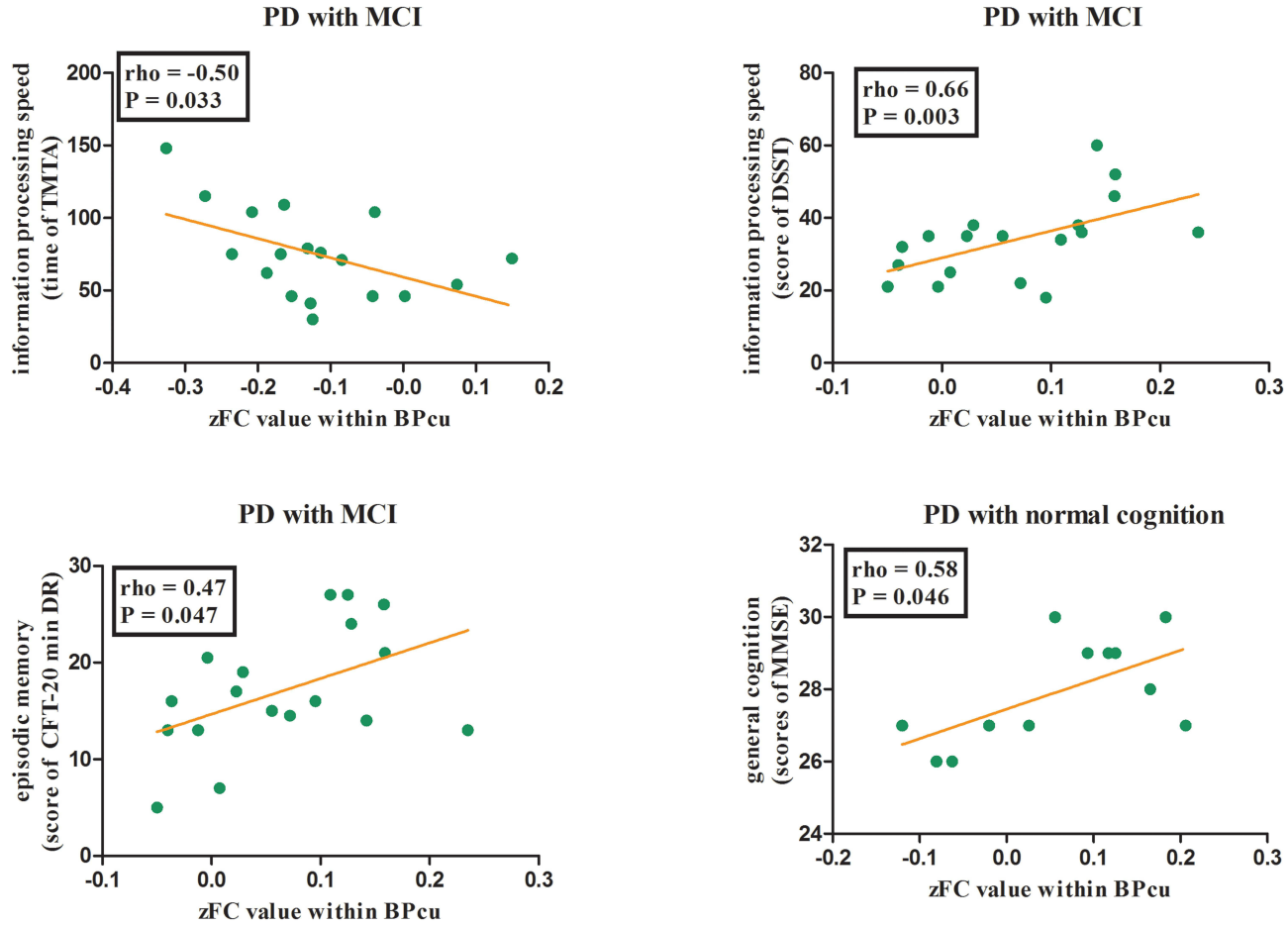

Figure 4 Behavior significances of the regions with disease-related differences in DMN. For PD patients with MCI, the higher FC within BPcu were related to better performances of TMTA, DSST and CFT-20 min DR. For PD patients with normal cognition, the FC within BPcu were associated with scores of MMSE.

study found that BPcu was the cognitive-related region in DMN.

There is significant clinical heterogeneity in cognitive impairment in PD29. The prevalence of PD-MCI was 25%[29] and with the development of the disease, the cumulative prevalence of PD with dementia (PDD) gradually increases.[18] The frequency and severity of PD induced cognitive decline emphasise the need to approach this impairment as a symptom that requires separate attention. However, the mechanism of PDD is not clear yet. It is urgently needed to find biomarkers or identify the risk factors or signal of PDD in early stage for improving the prognosis of the disease.[30] The PD-NC and HCs in our study showed comparable performances of cognitive function, but the FC within the cognitive-related region in the brain – BPcu in PD-NC was significantly declined compared to HCs, which might be an early signal of cognitive damage. Díez-Cirarda et al[19] included 26 HCs, 12 PD-NC and 23 PD-MCI and found that PD-MCI group dynamic FC deteriorated but did not been observed in PD-NC.

The cognitive impairment of PD patients is mainly manifested in visual space, attention, executive function, and memory, but these clinical manifestations are not diagnostic specific. Similar with the report, PD-MCI in our study showed significant worse performances in general cognition. For PD-MCI, the higher the FC values within BPcu were related to better performances information processing speed (ie, shorter time consumed of TMTA and higher scores of DSST) and episodic memory (ie, higher scores of CFT-20 min DR). Similar associations were also detected between the FC within BPcu and performances of MMSE for PD-NC.

There are some limitations in this study. First, this is a single center study with a limited number of patients. Second, all PD patients from this study were on medication and we cannot rule out the possibility that the drugs may have impacted the rs-fMRI. Third, MoCA scale for the global cognitive function assessment would be better while we did not collect relevant data. Four, we used 1.5T MRI, which is less sensitive than 3.0T. Lastly, the use of the outcomes needs to be further validated in additional populations.

Conclusions

In conclusion, BPcu was the cognitive-related region in DMN. As cognition declines, FC within BPcu weakens. For PD-MCI, the higher the FC values within BPcu were likely to be related to the better the performances of TMTA, DSST and CFT-20 min DR, which needs to be further confirmed by large-sample studies.

Statement of Ethics

The study complied with the declaration of Helsinki and was approved by the medical ethics committee of the Affiliated Jiangyin People's Hospital of Southeast University Medical College. Written consent was obtained from all participants.

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Disclosure

The authors have no conflicts of interest to declare.

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