The Functional and Structural Changes of the Brain in Parkinson's Disease Patients with Mild Cognitive Impairment

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Abstract

Background: Parkinson's disease (PD) is often associated with cognitive impairment. However, the neural mechanism of cognitive impairment is not clear. The present study investigated the functional and anatomic changes in PD patients with mild cognitive impairment (MCI) and their correlations with cognitive functions by the application of combined functional and structural analysis.

Methods: T1-weighted magnetic resonance imaging (MRI) and resting-state functional MRI data were acquired from 23 PD patients with MCI (PD-MCI), 23 PD patients with normal cognitive function (PD-NCI), and 23 matched healthy controls (HC). The structural imaging data was analyzed by voxel-based morphometry (VBM) and surfaced-based morphometry (SBM) methods to assess the changes of gray matter density and cortical thickness, respectively. And the amplitude of low-frequency fluctuations (ALFF) analysis using resting-state functional imaging data to measure the spontaneous changes of brain activity. Their Correlations with neuropsychological assessments (e.g., Montreal cognitive assessment, MOCA; Mini-mental state examination, MMSE) were also examined.

Results: Compared to the HC group, the PD-MCI patient group showed both decreased ALFF in the occipital regions (i.e., left middle occipital gyrus) and parietal regions (i.e., left precuneus) and increased ALFF in the right inferior frontal gyrus and bilateral hippocampus. Also, the PD-MCI patient group showed reduced gray matter density in the right inferior frontal gyrus and middle frontal gyrus. Cortical thinning in the left middle temporal gyrus and right superior temporal gyrus was found in the PD_MCI patient group relative to the control group. Furthermore, ALFF of the right hippocampus and gray matter density of right frontal gyrus was correlated with cognitive impairment (e.g., MOCA), respectively. Cortical thickness of right superior temporal gyrus was also associated with cognitive deficit (e.g., MMSE).

Conclusion: MCI in PD is associated with widespread brain functional and structural alternations. The combination of functional and structural abnormalities may be related to subtle cognitive impairment in PD.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that is characterized by using the progressive loss of dopaminergic neurons in the substantia nigra [1]. The typical clinical hallmarks of PD are motor dysfunction such as tremor, rigidity, and postural instability[2]. In addition to the typical motor symptoms, PD patients often develop non-motor symptoms (e.g., cognitive abnormalities)[3]. Cognitive impairment is a significant non-motor feature of PD, which can frequently occur in the disease even prior to the diagnosis of the disease [4]. Patients with PD experiencing mild cognitive impairment (MCI) are at a higher risk of developing dementia than cognitively intact PD patients[5]. However, the underlying pathophysiological mechanisms of cognitive impairments in PD are not entirely understood.

Of interest, resting-state functional magnetic resonance imaging (rs-fMRI) as a promising method has shown the ability to explore the functional activity in distributed brain networks in a reliable way and

characterize the pathological basis of PD [6, 7]. Recently, Amplitude of low-frequency fluctuations (ALFF), a proxy for neural activity magnitude during rest, has been suggested to be sensitive marker in PD [8, 9]. Many studies have found extensive disturbances of ALFF in PD [10, 11]. To be illustrated, Compared with the cognitively normal PD patients (PD-NCI), PD patients with mild cognitive impairment (PD-MCI) exhibited increased ALFF in the right inferior parietal cortex and left posterior cerebellum and decreased ALFF in the posterior cingulate and bilateral putamen [12]. In addition, both decreased ALFF values have been observed in the right superior temporal gyrus and increased ALFF values have been also found in the left superior frontal gyrus in the PD-MCI patient group compared to healthy control (HC) group [13]. These results suggest that mild cognitive impairments in PD_ is associated with abnormal spontaneous brain activity in the cortical and subcortical regions.

Furthermore, T1 weighted magnetic resonance imaging (MRI) provides a tool to measure structural changes that are related to morphological alternation of gray matter in PD. By using voxel-based morphometry (VBM) analyses, Several MRI studies have investigated the morphometric of gray matter and its correlation with specific cognitive impairment in PD patients. For instance, Gao and colleagues reported that PD-MCI patients had gray matter atrophy in the left middle frontal gyrus, left superior temporal gyrus, and right inferior temporal gyrus in comparison with PD_NCI [14]. Chen et al. also found abnormalities of gray matter atrophy in left inferior gyrus, right medial temporal gyrus, and hippocampus in PD-MCI group were related with cognitive impairment-by the VBM analysis [15]. These studies point out several important gray matter structures (e.g., prefrontal and temporal cortex) involving in cognitive impairment in PD patients.

But both ALFF and VBM analyses may be not enough to detect early cortical changes in PD_MCI patients. Surface-based morphometry such as cortical thickness can provide more sensitive measurement to identify regional gray matter changes associated with PD. In a small sample, Biundo et al. reported significant decreased cortical thickness in the right parietal-frontal regions and left temporal-occipital regions in PD_MCI patients compared with PD_ NCI patients [16]. Studying a bigger sample, Pereira et al. found reduced cortical thickness in the parietal and temporal regions in the PD_MCI group in comparison with PD non-MCI patients [17].

Investigation of brain functional and structural abnormalities that is related to PD_MCI is very important not only for the management and treatment of PD but also the further understanding of neuronal and pathophysiological mechanisms in PD development. Therefore, the present study aimed to investigate the anatomical and functional changes of brain and their associations with cognitive impairment in PD_MCI patients using a combined application of structural (e.g., VBM and cortical thickness) and functional (e.g., ALFF) analysis, and provide further understanding for the underlying pathophysiological mechanism of cognitive dysfunction in PD.

2. Method

2.1 Participants

Twenty-three right-handed patients who were clinically diagnosed as PD-MCI and 23 right-handed patients who were diagnosed as PD-NCI, were recruited from Department of Neurology at the Sunshine Union Hospital, Weifang (from January 12, 2018 to December 20, 2019). The diagnosis of PD was clinically determined according to the UK Parkinson's Disease Brain Bank criteria [18]. PD-NCI patients exhibit no impairment on cognitive abilities or do not take cognitive dysfunction on any perception, and PD-MCI patients met the as following criteria: a decrease in cognitive abilities observed by a clinician or reported by patients; cognitive impairments can be distinguished by cognitive rating scales, but related dementia do not reach clinical criteria [19]; the cognitive deficits are not attributable to age or other certain systemic diseases. Exclusion criteria were: brain lesion contraindication on MRI; sever concomitant diseases that might influence brain metabolic alterations; history of current psychiatric illness. All diagnosis was managed by at least two professional neurologists. Twenty-three gender- and age- and education-matched healthy participants from the community served as the controls.

2.2 Neurological and neuropsychological

The Unified Parkinson's Disease Rating Scale (UPDRS_III) was used to measure the severity of motor symptoms in the PD patients in the "ON" state, and Hoehn and Lahr (H&Y) scale was used to evaluate disease stage of PD patients [20]. general cognitive assessments were executed by using the Mini-Mental Status Examination (MMSE) [21] and Montreal Cognitive Assessment (MoCA) [4], which evaluated memory and executive functions in the patient groups. Clinical and demographic details of all participants are showed in Table 1.

2.3 Imaging data acquisition

Data were acquired with a Siemens Magnetom TIM Trio 3.0 T scanner (Siemens, Munich, Germany). The examination was performed in darkness. Earplugs and foam pads were used to reduce noise and head motion. Participants were required to move as little as possible and close their eyes and relax but not fall asleep. Three-dimensional axial) T1-weighted MPRAG (magnetization-prepared rapid gradient echo) magnetic resonance images were collected with the following parameters: TR=2530 ms; TE =3.42 ms; FOV = 256× 256cm; flip angle = 15°; matrix = 256× 256; 176 single-shot interleaved slices with no gap; thickness = 1.1 mm. resting-state functional MRI data were collected using a gradient echo-planar imaging (EPI) sequence (TR=2000 ms, thickness =3 mm, flip angle = 90°, FOV=24 cm × 24 cm, TE=60 ms, 34 axial slices, 3 mm thickness without gap matrix=64 × 64, containing 160 volumes).

2.4 Anatomic data analysis

The anatomical images were processed and analyzed using the CAT12 toolbox implemented in Statistical Parametric Mapping (SPM12; www.fil.ion.ucl.ac.uk/spm). CAT12 provides processing pipelines for both voxel-based morphometry (VBM) as well as surface-based morphometry (SBM) including cortical thickness, allowing us to perform all analyses with this software package. For the steps of processing and analysis, the parameters used default settings met the standard protocol (<http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf>). This tool has been previously used and

validated in morphometric studies in PD [22, 23] and other neurodegenerative diseases [24]. A two-step quality assurance was also included by processing: first, all images were inspected for artifacts (prior to preprocessing) visually; secondly, statistical quality control was performed for overall image quality and inter-subject homogeneity as included in the CAT12 toolbox after segmentation.

The analysis of cortical thickness based on the same for extraction of the cortical surface implemented in CAT 12 was performed. The cortical thickness was estimated using a projection-based distance measure. The vertex-wise cortical thickness measures were resampled and smoothed by a 12 mm full width at half-maximum (FWHM) standard Gaussian kernel.

For VBM analysis, the anatomical images were normalized to a standard template by DARTEL approach and then segmented into three voxel classes: gray matter, white matter, and cerebrospinal fluid using partial volume segmentation with MAP approach. Then the regional gray matter density differences were tested using modulated normalized gray matter maps. The abstracted GM maps were smoothed utilizing a 8 mm FWHM kernel and used for further analysis.

2.5 Functional data analysis

Resting-state functional data was preprocessing by Data Processing Assistant for Resting-state fMRI toolkit[25]. The first 10 volumes of the functional imaging were discarded for the MRI signal equilibrium and the adaptation of the participants to the scanning circumstance. The remaining 150 volumes were then corrected for the intra-volume acquisition time delay between slices for inter-volume geometrical displacement due to head motion. No participants were excluded under a criterion of head displacement of > 2.5 mm or angular rotation of $> 2.5^\circ$ in any direction. Afterward, individual T1-weighted images were coregistered to the mean realigned functional images using a linear transformation. Finally, functional images were spatially normalized into the Montreal Neurological Institute (MNI) template and smoothed with a 6 mm FWHM standard Gaussian kernel.

The ALFF calculation was executed by the Resting-State fMRI Data Analysis Toolkit (<http://restfmri.net/forum/REST>). Briefly, for a given voxel, fast Fourier transform was used to convert the time domain to the frequency domain. The mean square root of the power spectrum was computed and averaged throughout 0.01 Hz to 0.08 Hz at all voxels. The resulting ALFF was converted into z-scores by subtracting the mean and dividing by the global standard deviation for standardization purposes. And reducing the global effects of variability across participants

2.4 Statistical analysis

Statistical analyses of anatomical imaging data were performed in the CAT12 SPM12 statistical module using a two-sample t-test to each of both morphometric measures (gray matter density with VBM and cortical thickness with SBM). Using age, gender, and educational years as covariates (and for VBM analyses, additionally, total intracranial volume, TIV). The group differences of statistical thresholds were set at $P < 0.05$ with FDR correction for multiple comparisons.

For the ALFF difference of between-group, a two-sample t-test was also performed with age, gender, educational years, head motion, and gray matter volume as variables between each pair of the three groups. Voxel-level intensity threshold of $P < 0.01$ with a minimum cluster size of 50 contiguous voxels was used to correct for multiple comparisons using the Random Gaussian field (GRF) theory.

Demographic and clinical data analysis was performed by SPSS 20 Statistics software package (IBM Corporation, New York, EUA). T-tests were used to test differences between groups, and Pearson correlation was used to calculate the relationship between imaging and clinical data.

3. Results

3.1 Clinical and demographical examining of participants

The clinical and demographic profiles of all the participants are exhibited in Table 1. There was no significant difference among the three groups in gender, age, educational years, and disease duration. Moreover, no significant differences in UPDRS-III score and H & Y stage scores were found between the PD_MCI and PD_NCI subtypes. However, the PD_MCI patients had significantly lower MOCA and MMSE scores than PD_NCI and HC group, in concert with the clinical diagnosis of each subtype.

Table 1 Demographic and clinical characteristics of PD_MCI, PD_NCI, and HC groups.

	PD_MCI	PD_NCI	HC	F/ χ^2	P-values
n (female, male)	23(11,12)	23(9,14)	23(13,10)	1.39	>0.05
Age (years)	64.30	63.65	62.04	2.27	>0.05
Education years	6.65	7.43	7.39	1.90	>0.05
Duration (months)	6.30	6.95		1.03	>0.05
MMSE	26.39	29.65		20.36	<0.001
MOCA	24.13	27.43	28.65	68.11	<0.001
UPDRS-III	28.31	25.62	-		
H&Y Stage (1,2)	1.5 $\pm$ 0.5	1.3 $\pm$ 0.5		0.81	

Note: PD, Parkinson's disease; PD-NCI, Parkinson's disease with normal cognition; PD-MCI, Parkinson's disease with mild cognitive impairment; HC, healthy control. UPDRS, Unified Parkinson's Disease rating scale; H&Y, Hoehn and Yahr; MoCA, Montreal cognitive assessment. MMSE, mini mental state examines.

3.2 Comparisons of ALFF values between groups

Compared with the HC, the PD_MCI group exhibited ALFF decreases in the occipital regions (i.e., left middle occipital gyrus) and parietal regions (i.e., left precuneus), whereas ALFF increases in the right

inferior frontal gyrus and bilateral hippocampus (Table 2 and Figure 1A). The PD_NCI group showed decreased ALFF in the left putamen compared to the HC (Table 2 and Figure 1B). Besides, the PD_MCI group displayed increased ALFF in the left superior parietal gyrus relative to the PD_NCI (Table 2 and Figure 1C) group.

Table 2 ALFF differences between groups.

	Brain regions	Coordinate			T	Voxels
		x	y	z		
PD-MCI vs. HC	L Middle Occipital Gyrus	-30	-69	24	-5.131	57
	L Precuneus	-6	-48	21	-5.499	132
	R Inferior Frontal Gyrus	24	-24	21	5.281	94
	L Hippocampus	-36	-24	-15	4.145	56
	R Hippocampus	24	-42	-3	3.53	169
PD-NCI vs. HC	L Putamen	-27	-3	3	-4.412	184
PD-MCI vs. PD-NCI	L Superior Parietal Gyrus	-12	-66	57	5.56	96

–Figure 1–

3.3 Comparison of VBM between groups

VBM analysis showed that PD_MCI patients had reduced gray matter density in the right inferior frontal gyrus and middle frontal gyrus, while PD-NCI patients had increased gray matter density in the bilateral putamen compared with HCs. In addition, PD-MCI patients, when compared with PD-NCI patients, had reduced gray matter density in the right insula and right cerebellum (and Table 3 and Figure 2).

Table 3 Difference of gray matter density between groups

Comparisons	Brain regions	Coordinate			T	Voxels
		x	y	z		
PD-MCI vs. HC	R Middle Frontal Gyrus	39	54	11	-4.35	83
	R Inferior Frontal Gyrus	51	24	6	-4.27	186
PD-NCI vs. HC	R Putman	33	-11	-5	4.37	389
	L Putman	-33	-15	-5	3.76	57
PD-MCI vs. PD-CNI	R Insula	35	-11	-3	-4.54	176
	R Cerebellum	30	-65	-42	-3.74	121

3.4 Comparison of cortical thickness between groups

Cortical thickness analysis revealed cortical thinning in the left middle temporal gyrus and right superior temporal gyrus for patients in the PD-MCI group compared to patients the HC group, while for patients in the PD-NCI group had cortical thinning in the left cuneus. In addition, compared to the PD_NCI patient group, the PD-MCI patient group showed cortical thinning in the left precuneus.

Table 4 Areas with a reduced cortical thickness on the gray matter between groups

Comparisons	Brain regions	Coordinate			T	Voxels
		x	y	z		
PD-MCI vs. HC	L Middle Temporal Gyrus	-4	-89	19	-4.74	177
	R Superior Temporal Gyrus	6	-85	-26	-5.34	379
PD-NCI vs HC	L Cuneus	-9	-90	24	-3.51	278
PD-MCI vs PD-NCI.	L Precuneus	-5	-66	40	-3.93	79

3.4 Correlation analysis

In the PD_MCI patient group, there was a negative association between the ALFF value of the right hippocampus and with cognitive function-higher MOCA score ($r=-0.562$, $P=0.005$) (Figure 4A). A similar correlation was found in the PD_MCI patient group: a larger gray matter density of the right middle frontal gyrus was associated with a higher MOCA score ($r=0.415$, $P=0.049$)(Figure 4B). A negative association between the cortical thickness of the right superior temporal gyrus and higher MMSE score was also found in PD_MCI patients as a group ($r=-0.495$, $P=0.016$)(Figure 4C).

4. Discussion

The present study investigated the structural and functional changes of the brain in PD_MCI patients. The ALFF analysis showed that there was increased ALFF in the prefrontal cortex (e.g., inferior frontal gyrus) and hippocampus and decreased ALFF in the parietal (e.g., precuneus) and occipital cortex (e.g., middle occipital gyrus) in the PD_MCI group compared with the control group. Besides, the PD_MCI patients showed brain atrophy (e.g., reduced gray matter density and cortical thinning) in the prefrontal and temporal regions was found in the PD_MCI patients relative to the controls. And these abnormal structural and functional changes were associated with cognitive impairments in PD_MCI patients.

ALFF is physiologically meaningful for assessing the spontaneous neuronal activity of the brain[26, 27]. The present study found that the PD-MCI patient group showed enhanced spontaneous brain activity (i.e.,

hyperactivity) in the right inferior frontal gyrus and bilateral hippocampus. Some researchers have reported treatment (i.e., rivastigmine) can normalize neural activity in PD_MCI patients. Spontaneous brain activity deficit in the left inferior frontal gyrus was restored in the PD patient after treatment [28]. Specially, the non-treatment PD-MCI group also exhibited increased ALFF in the inferior frontal gyrus [29]. And the increased activity in the inferior frontal gyrus was also found in the PD_MCI patients during performing a planning set-shifts task[30]. The increased ALFF emerged in the bilateral hippocampus was also found in the PD patients compared with the controls [8]. The hippocampus plays an essential role in memory and cognition[31]. With regarding cognitive domains, the regional ALFF in the right hippocampus was negatively correlated with general cognitive functions as measured by MOCA in the PD_MCI patient group, which may indicate that more cognitive deficit induced higher neural activity in this region. Then increased spontaneous activity in the inferior frontal gyrus and hippocampus may reflect an adaptive compensatory effect in response to modest cognitive impairment in PD patients with MCI.

Reduced ALFF was also found in the occipital cortex (i.e., middle occipital gyrus) and parietal cortex (i.e., precuneus) in the PD_MCI group. This finding was also consistent with the previous studies that identify spontaneous neural activity in PD patients by resting-state MRI[32, 33]. More emerging evidence also indicates the occipital and parietal cortex are crucial involvement in the pathophysiology of PD. For instance, a recent PET study has found that both the PD-MCI group and PD_NCI groups had reduced glucose metabolism in the occipital and parietal regions relative to controls[34]. Moreover, a longitudinal study over two years using PET has reported a decline in learning-related activation in parietal and occipital areas at the follow-up in PD patients. Hence decreased spontaneous activity in occipital and parietal regions may be related with the PD development.

VBM showed a more localized gray matter loss in the prefrontal cortex, which were parallel with previous studies that specifically characterized PD patients with MCI[35-37]. The prefrontal regions involve in visual processing, attention, memory, other cognitive functions[38-40], and their gray matter changes were related to declines in cognition. So it is not hard to find out a correlation between gray matter atrophy (e.g., the middle frontal gyrus) and neuropsychological deficits (e.g., MOCA) in PD_MCI patient group. In addition, a multicentral PD cohort study has reported that PD patients with MCI have cortical thinning in the temporal and parietal cortical regions [17]. The present study also supported the finding that there were reduced cortical thickness in the middle temporal gyrus and superior temporal gyrus in the PD_MCI patients compared with the controls.

Lesion research suggests that the temporal lobe is critical for cognitive functions such as memory and execution[41]. A functional MRI study found that PD patients with MCI showed temporal lobe (e.g., middle temporal gyrus) hypoactivation during cognitive tasks relative to the controls [42]. Pereira et al have found that cognitive performance was associated with temporoparietal thinning in PD patients with MCI [17]. Consistent with these findings, the cortical thickness of the temporal lobe (e.g., superior temporal gyrus) correlated with cognitive impairment (e.g., MMSE) in PD_MCI patients was observed in the present study and suggested that cortical thinning was also related to cognitive changes in PD.

In conclusion, the present study found that PD_MCI patients showed the functional and structural alternations in the prefrontal, and temporooccipital regions relative to controls, and these alternations were significantly correlated with cognitive impairments. These results suggested that cognitive impairment in PD is most likely due to a combination of both functional (e.g., hypoactivity) and structural (e.g., cortical atrophy) abnormalities.

Declarations

Authors' contributions

JBj prepared the first draft of the manuscript. All authors (JBj, ZT, CTJ, WZ, and CX) were involved in the conceptualization of this work, interpretation of study findings, substantive review of manuscript drafts, and approval of the final manuscript for submission.

Availability of data and materials

The datasets used during the study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Weifang Medical University Ethics Committee approved this study. Written informed consent was obtained from all the study participants.

Competing interests

The authors declare that they have no competing interest.

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Figures

Figure 1

Differences in ALFF among PD_MCI, PD_NCI, and HC groups. (A), Differences in ALFF between PD_MCI and HC; (B) Differences in ALFF between PD_NCI and HC; (C) Differences in ALFF between PD_MCI and PD_NCI. All the multiple comparisons were performed with GRF correction (cluster level <0.05 , voxel-level <0.05 , size >50). For details of the significant regions, see Table 2.

Figure 2

VBM difference between PD_MCI vs. the controls (A), PD_NCI vs. the controls (B), and PD_MCI vs. PD_NCI(C).

Figure 3

Regions of significant cortical thinning. A) show areas with atrophy in PD_MCI vs. HC; B) show area with cortical thinning in PD_NCI vs. HC; C) show areas reduced cortical thickness in PD_MCI vs. PD_NCI .

Figure 4

Scatter plots of correlation between ALFF values of the right hippocampus and MOCA score (A), gray matter density of right middle frontal gyrus and MOCA score (B), cortical thickness of right superior temporal gyrus and MMSE score (C). HIP, hippocampus; MFG, middle frontal gyrus; STG, superior temporal gyrus.