



Changes of brain structural network connection in Parkinson's disease patients with mild cognitive dysfunction: a study based on diffusion tensor imaging

Wanyi Wang¹ · Mingjin Mei¹ · Yuyuan Gao¹ · Biao Huang² · Yihui Qiu¹ · Yuhu Zhang¹ · Limin Wang¹ · Jiehao Zhao¹ · Zhiheng Huang¹ · Lijuan Wang¹ · Kun Nie¹

Received: 5 August 2019 / Revised: 15 November 2019 / Accepted: 18 November 2019 / Published online: 2 December 2019

© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Introduction Previous studies have found that white matter (WM) alterations might be correlated in Parkinson's disease (PD) patients with cognitive impairment. This study aimed to investigate WM structural network connectome alterations in PD patients with mild cognitive impairment (PD-MCI) and assess the relationship between cognitive impairment and structural topological network changes in PD patients.

Methods All 31 healthy controls (HCs) and 71 PD patients (43 PD-NC and 28 PD-MCI) matched for age, sex and education underwent 3.0 T MRI and diffusion tensor imaging (DTI) scan. Graph theoretical analyses and network-based statistical (NBS) analyses were performed to identify the structural WM networks and subnetwork changes in PD-MCI.

Results PD-MCI patients showed significantly decreased global efficiency (E_{glob}) and increased shortest path length (L_p) compared with the HC group. Several nodal efficiencies showed significant differences in multiple brain regions among the three groups. The nodal efficiency of the orbitofrontal part was closely related to the overall cognitive ability and multiple sub-cognitive domains. Moreover, NBS analyses identified eight one-connect subnetworks, three two-connect subnetworks and two multi-connect subnetworks with reduced connectivity that characterizes the WM structural organization in PD-MCI patients. The two multi-connect subnetworks were located on the bilateral lobe, and both were centered on the orbitofrontal part.

Conclusions This study provided new evidence that PD with cognitive dysfunction is associated with WM structural alterations. The nodal efficiency and sub-network analyses focusing on the orbitofrontal part might provide new ideas to explore the physiological mechanism of PD-MCI.

Keywords Brain structural network connections · Network · Parkinson's disease · Mild cognitive dysfunction · Diffusion tensor imaging · Network-based statistics

Wanyi Wang and Mingjin Mei contributed equally to this work.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00415-019-09645-x>) contains supplementary material, which is available to authorized users.

✉ Lijuan Wang
wljgd68@163.com

✉ Kun Nie
nk20080911@126.com

¹ Department of Neurology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangdong Neuroscience Institute, No. 106 Zhongshan Er Road, Guangzhou 510080, Guangdong, China

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases, and it not only presents motor symptoms such as bradykinesia, rigidity and rest tremor, but also

² Department of Radiology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangdong Neuroscience Institute, No. 106 Zhongshan Er Road, Guangzhou 510080, China

non-motor symptoms such as constipation, depression and olfactory dysfunction. Cognitive impairment is another common non-motor symptom in patients with PD, which gradually deteriorates with the progression of the disease. Parkinson's disease with mild cognitive impairment (PD-MCI) is widely considered to be a risk factor and prodromal symptom of Parkinson's disease with dementia (PDD), which can seriously affect the quality of life, increasing disability and fatality of PD patients. PD-MCI was classified as different subtypes depending on the number of cognitive domains (language, memory, attention and working memory, executive function and visuospatial function) impairment. Studies have shown that different cognitive domain decline of PD-MCI patients might be associated with different motor phenotypes, severity and neuropathological alterations, affecting different quality of life and prognoses [1–4]. Early identification and detection of alterations in PD-MCI may prevent PDD in advance.

Previous studies have revealed alterations in white matter (WM) in PD patients that are correlated with cognitive impairment [5, 6]. Several other studies have explored the microstructure of white matter tissue through diffusion tensor imaging (DTI) technology. The results revealed that the white matter fiber in the frontal, temporal and bilateral cingulate bundles damage PD patients with cognitive impairment [7, 8]. However, these previous studies have focused only on isolated brain regions. The term “human connectome” was introduced to investigate and fully understand the complexity of brain structural network connections [8, 9]. Neuroimaging studies by using DTI have showed decreased whole-brain clustering coefficient and reduced global efficiency in PD patients when compared with healthy controls (HC) [10, 11]. Aarabi MH et al. by using network-based statistics (NBS) for the first time have shown significant reduction in the interconnecting fiber volume or average tract length in the cingulum, temporal lobe, frontal lobe, para-hippocampus, hippocampus, olfactory lobe and occipital lobe in PD patients [12]. According to a study conducted using NBS, decreased connectivity was observed in the two subnetworks in PD patients when compared to HCs, which involved the limbic system, basal ganglia and sensorimotor areas [11]. Disconnection in the above-mentioned areas might explain the motor (basal ganglia) as well as non-motor (e.g., limbic, olfactory) symptoms of PD. In summary, studies on brain structure and functional networks have shown the prevalence of brain disconnection in PD patients. However, few studies have analyzed the properties of brain structure network and subnetwork alterations associated with cognitive status in PD patients. This study aimed to identify WM structural network connectome alterations in PD-MCI patients and assess whether cognitive impairment is correlated with structural topological network changes in PD patients.

Materials and methods

Subject

All participants in this study were recruited from the Department of Neurology, Guangdong General Hospital (Guangzhou, China) between August 2014 and September 2017. 71 PD patients [43 PD-NC (normal cognition) and 28 PD-MCI] were diagnosed as having idiopathic PD independently by two neurologists according to The UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [13]. Since there was a lack of comprehensive scales with national norm at the beginning of the study, 28 patients were diagnosed as having PD-MCI according to the 2012 MDS proposed diagnostic criteria [14] in conjunction with our existing scales with at least 1.5 standard deviations (SDs) below normative scores on one or more cognitive domains. Besides, we recruited 31 healthy volunteers with no history of neurological disorders, or traumatic brain injuries in HC group. The age, education and gender of the HC group were comparable to those of the PD-NC and PD-MCI groups. This research protocol was approved by the Medical Ethics Committee of Guangdong General Hospital and informed consent was obtained from all participants.

Clinical assessment

The demographic data of all patients including general information such as age, gender, education level, height, weight and place of residence were collected. The clinical data included disease duration of PD, the United Parkinson's Disease Rating Scale-III (UPDRS-III) score [15], the modified Hoehn–Yahr (HY) score [16], and the Hamilton Anxiety Scale (HAMA) [17], Hamilton Depression Scale (HAMD) [18] and activities of daily living scale (ADL) [19].

Overall, the cognitive function status was assessed by the Mini-Mental State Examination (MMSE) score [20] in each participant. Montreal Cognitive Assessment (MoCA) [21] and five cognitive domains were further evaluated in PD patients. The test to assess five cognitive domains are as follows:

1. Executive function: verbal fluency test (VFT) [22, 23] and clock drawing test (CDT) [24].
2. Attention and working memory: symbol digit modalities test (SDMT) [23, 25] and digit span test (DST) [23].
3. Visuospatial function: block design test [23].
4. Memory: visual reproduction (VR) and logical memory [26].

5. Language: similarities test [23].

Image acquisition

MRI scan of all patients was performed by using a SIGNA EXCITE 3.0T MRI scanner (General Electric Company, USA). The specific parameters of the image are as follows: T1WI: repetition time (TR) = 580 ms; echo time (TE) = 18 ms; T2WI: TR = 5100 ms; TE = 130 ms; FLAIR: TR = 9600 ms; TE = 110 ms; matrix 320×192 , field of view (FOV) = $24 \text{ cm} \times 24 \text{ cm}$, layer thickness 5 mm, layer spacing 1 mm and a total of 25 layers. The DTI scan parameters were set as follows: TE = 76 ms; TR = 8000 ms; flip angle = 90° ; FOV = $256 \times 256 \text{ mm}^2$; slice thickness = 2.5 mm; voxel size = $2 \times 2 \times 3 \text{ mm}^3$; and NEX = 1. Images of 25 different nonlinear diffusion-weighted gradient directions ($b = 1000 \text{ s/mm}^2$) and non-diffusion-weighted gradient direction ($b = 0$) were collected, each gradient was scanned for 60 layers and a total of 1560 files were obtained. All data were saved in DICOM format.

Image (pre)processing

For image data, preprocessing was done by “Pipeline for Analyzing brain Diffusion images (PANDA)” software installed on Linux system and Matlab [27]. The specific preprocessing steps are as follows: (1) image conversion: the image data are required to be converted to NIFTI format before processing; (2) skull removal and cropping the gap: the brain tissues were extracted during head MRI; (3) correcting eddy current/motion; (4) calculating fractional anisotropy (FA) and mean diffusivity (MD); (5) network node definition: the brain region was divided by Automated Anatomical Labeling (AAL), which was used as the node of the network. In this way, the constructed network has 90 nodes. 3DT1-weighted image was registered to b0 image of DTI (non-diffusion-weighted gradient direction), and then further nonlinearly registered onto the MNI-ICBM152 template. After that, the inverse matrix of the transformed result was used to convert AAL atlas to DTI maps; (6) network edge definition: fiber tracking by using fiber assignment by continuous tracking (FACT) algorithm was performed. Tracking would be interrupted when the FA value was less than 0.2 or the tracking angle between two adjacent voxels was greater than 45° . When there were at least three fiber bundles between the two adjacent brain regions, it would be considered a connection (network edge).

Graph theory

All structural network properties were analyzed on the MATLAB-based GREYNA, a graph theoretical network analysis toolbox [28]. The global properties of the network,

hubs, and edge connections of the network were highlighted in this study.

Global properties of network

The global properties of the network included clustering coefficients (C_p), shortest path length (L_p), global efficiency (E_{glob}), local efficiency (E_{loc}) and “small worldness” (σ). C_p of the whole network represents the average clustering coefficients of all nodes, which are important indicators to measure the level of network interconnectivity. The average of the shortest path lengths between any two nodes in the network was defined as L_p . The shortest path length suggests higher efficiency of network information transmission. E_{glob} is also considered as an important parameter to estimate the global transmission efficiency of the network. Another important metric E_{loc} also illustrated the network interconnection among the nodes. The “small worldness” has high clustering coefficient and the shortest path length, ensuring transmission efficiency at both local and global levels. This study generated 1000 random networks that compared with real networks to explore “small worldness” in participants. γ and λ are separately defined as the ratio of real network’s C_p and L_p to the random network’s, and σ is defined as the ratio of γ to λ . When $\gamma = C_{\text{real}} \div C_{\text{random}} \gg 1$ and $\lambda = L_{\text{real}} \div L_{\text{random}} \approx 1$ or $\sigma = \gamma \div \lambda > 1$, we believe that the constructed network has a “small worldness” network.

Nodal efficiency and hubs

Nodal efficiency refers to the shortest path length between any node in the network and other nodes in the network. By comparing the differences in 90 nodes efficiency between groups, brain regions with impaired WM can be explored. Among these nodes, there are a number of specific nodes that interact with many other brain regions, which were defined as hubs. The hub plays an important role in maintaining network stability.

Two conditions should be met at the same time as a hub: (1) the degree of node [$D_{\text{nodal}(i)}$] should be greater than or equal to the average value plus SD of the network degree [$D_{\text{nodal}(i)} \geq D_{\text{mean}} + \text{SD}$]; and (2) the betweenness of node [$B_{\text{nodal}(i)}$] should be greater than or equal to the average value plus the SD of the network betweenness [$B_{\text{nodal}(i)} \geq B_{\text{mean}} + \text{SD}$].

Network-based statistical analysis

Network-based statistical analysis was used to analyze the number of WM fibers between the brain regions to explore the structural connectivity changes in patients with PD-MCI.

Statistical analysis

Statistical analysis of the clinical data was carried out using IBM SPSS 22. Continuous variables that conformed to the normal distribution were presented as mean \pm standard deviation, and the non-normally distributed continuous variables were expressed as median (interquartile range, IQR). Among the three groups, qualitative data were assessed by means of Chi square test based on the distribution, and quantitative variables were analyzed using one-way ANOVA test or Kruskal–Wallis H test. Significance values were adjusted by the Bonferroni correction for multiple tests. When comparing the PD-NC and PD-MCI groups, variables were analyzed with two-tailed t test or Mann–Whitney U test. To test whether cognitive impairment correlates with structural topological network changes in PD, Pearson correlation coefficient was performed to explore the correlation between node efficiency and overall cognitive function and five cognitive sub-domains. Statistical significance of WM fiber bundles connecting the brain regions between the PD-NC and PD-MCI groups was analyzed in two-sample t test on the MATLAB-based GREYNA. When the corrected value was $P < 0.05$, then a statistical difference existed. All the differences in the connections formed a differential subnetwork.

Result

Patients and clinical features

A total of 102 participants were enrolled (31 HC, 43 PD-NC and 28 PD-MCI). Demographic and clinical features are presented in Table 1. The analysis showed no significant differences among the three groups with respect to age, sex and education. However, the MMSE of the PD-MCI group was significantly worse than that of HCs and PD-NC (see Table 1). When PD-NC was compared with only PD-MCI, no statistically significant differences in HY stages, disease duration, UPDRS-III, ADL, HAMD and HAMA were observed. However, the scores of the five cognitive domains test in the PD-MCI group were statistically lower than those in the PD-NC group (see Table 1).

Global properties of network

The global properties of network showed no significant differences in C_p and E_{loc} , but observed in L_p and E_{glob} among PD-NC, PD-MCI and HC. When compared with the HC group, PD-MCI patients displayed significantly decreased E_{glob} and increased L_p in the post hoc analysis. Moreover, the brain networks of the three groups showed a “small

worldness” attribute ($\sigma > 1$), which showed a significant increase in the PD-MCI group when compared to the HC group in the post hoc analysis (see Table 1).

Nodal efficiency and hubs characteristics

Nodal efficiency

All nodal efficiencies of the WM network of the HC, PD-NC and PD-MCI groups were analyzed. If statistical differences among the three groups were observed, then a post hoc test was performed (see Table 2). The results showed significantly decreased nodal efficiency at the bilateral hippocampus, right fusiform gyrus, left caudate, right para-hippocampus, left posterior cingulate gyrus, left superior temporal gyrus, bilateral temporal pole (middle) and left inferior temporal in PD-NC patients when compared with HCs based on the AAL-90 atlas, while the brain regions exhibited significant reduction of nodal efficiency in the PD-MCI group in mainly the left rolandic operculum, right olfactory cortex, left amygdala, left putamen, right anterior cingulate and paracingulate gyri, left fusiform gyrus, right superior parietal gyrus, right hippocampus, right para-hippocampus, left posterior cingulate gyrus, left superior temporal gyrus, bilateral temporal pole (middle) and left inferior temporal when compared with the HC group. However, when compared with the PD-NC group, PD-MCI patients had significantly decreased nodal efficiency in the brain regions, which was distributed only at the left olfactory cortex and left superior frontal gyrus (medial orbital).

Hubs characteristics

The hubs of the brain network of the three groups were identified by node degree and node betweenness (HC, 17 hubs; PD-NC, 17 hubs; and PD-MCI, 19 hubs). Among them, 16 hubs were shared by three groups, mostly distributed in the bilateral cingulate gyrus (mainly the anterior cingulate and paracingulate gyri and median cingulate and paracingulate gyri), postcentral gyrus, precuneus, insula, striatum (caudate and putamen), left middle occipital gyrus and right hippocampus (see Table 3). Compared with the HC group, both PD-NC and PD-MCI groups had a decreased hub at the hippocampus on the left side, while one new hub was found at the angular gyrus in PD-NC and three were found at the right angular gyrus and bilateral precentral gyrus in PD-MCI patients (see Table 3, Fig. 1).

Correlation between nodal efficiency and cognitive function score

Except for visuospatial function, the regions with nodal efficiency showed significant correlation with the other four

Table 1 Demographical, clinical and neuropsychological characteristics and global properties of the different groups (HCs, PD-NC and PD-MCI)

	HCs (<i>n</i> = 31)	PD-NC (<i>n</i> = 43)	PD-MCI (<i>n</i> = 28)	<i>F</i> / χ^2 / <i>t</i> / <i>Z</i> / <i>H</i>	<i>P</i> value	Post hoc analysis		
						<i>P</i>	<i>P</i>	<i>P</i>
						HC vs PD-NC	HC vs PD-MCI	PD-NC vs PD-MCI
Age (years)	57.00 ± 10.63	60.19 ± 10.72	63.93 ± 10.88	<i>F</i> = 3.065	0.051	/	/	/
Sex (female/male)	15/16	20/23	15/13	χ^2 = 0.345	0.841	/	/	/
Education (years)	12.00 (7.00)	12.00 (6.00)	9.00 (6.00)	<i>H</i> = 3.531	0.171	/	/	/
MMSE	28.00 (3.00)	29.00 (2.00)	26.00 (5.00)	<i>H</i> = 33.14	< 0.001*	1.000	0.000	0.000
H–Y stages	/	2.00 (1.00)	2.50 (1.00)	<i>Z</i> = -1.870	0.061	/	/	/
Disease duration (months)	/	24.0 (24.00)	24.0 (26.00)	<i>Z</i> = -0.180	0.857	/	/	/
UPDRS-III	/	28.58 ± 10.68	30.83 ± 13.83	<i>t</i> = -0.771	0.443	/	/	/
ADL	/	14.00 (3.00)	15.00 (5.00)	<i>Z</i> = -1.225	0.220	/	/	/
HAMD	/	5.00 (6.00)	9.00 (11.00)	<i>Z</i> = -1.410	0.159	/	/	/
HAMA	/	4.00 (6.00)	6.00 (8.00)	<i>Z</i> = -0.272	0.786	/	/	/
MoCA	/	26.00 (5.00)	18.50 (8.00)	<i>Z</i> = -4.650	< 0.001*	/	/	/
Executive function								
CDT	/	3.00 (1.00)	2.00 (2.00)	<i>Z</i> = -2.694	0.007*	/	/	/
VFT	/	14.53 ± 3.44	12.07 ± 4.00	<i>t</i> = 2.765	0.007*	/	/	/
Attention and working memory								
DST	/	10.44 ± 2.14	8.68 ± 2.13	<i>t</i> = 3.400	0.001*	/	/	/
SDMT	/	8.00 (2.00)	5.50 (3.00)	<i>Z</i> = -4.222	< 0.001*	/	/	/
Visuospatial function								
Block design test	/	9.00 (3.00)	6.00 (5.00)	<i>Z</i> = -4.006	< 0.001*	/	/	/
Memory								
VR	/	10.00 (3.00)	5.00 (5.00)	<i>Z</i> = -5.325	< 0.001*	/	/	/
Understanding	/	5.00 (6.00)	4.00 (3.00)	<i>Z</i> = -2.018	0.044*	/	/	/
Language								
Similarities	/	10.12 ± 2.29	8.43 ± 2.19	<i>t</i> = 3.089	0.003*	/	/	/
Global properties								
<i>C_p</i>	0.526 (0.027)	0.530 (0.023)	0.528 (0.023)	<i>H</i> = 3.087	0.214	/	/	/
<i>E_{loc}</i>	0.735 (0.022)	0.735 (0.022)	0.733 (0.022)	<i>H</i> = 2.523	0.283	/	/	/
<i>L_p</i>	2.428 (0.115)	2.427 (0.131)	2.504 (0.132)	<i>H</i> = 9.510	0.009*	0.148	0.007	0.509
<i>E_{glob}</i>	0.412 (0.019)	0.405 (0.021)	0.399 (0.021)	<i>H</i> = 9.510	0.009*	0.148	0.007	0.509
γ	4.569 (0.461)	4.558 (0.515)	4.804 (0.428)	<i>H</i> = 10.183	0.006*	0.801	0.005	0.067
λ	1.194 (0.034)	1.207 (0.039)	1.207 (0.032)	<i>H</i> = 6.432	0.04*	0.099	0.066	1.000
σ	3.781 (0.311)	3.778 (0.349)	3.944 (0.333)	<i>H</i> = 6.761	0.034*	1.000	0.035	0.158

HC healthy control group, PD-NC Parkinson's disease with normal cognition, PD-MCI Parkinson's disease with mild cognitive impairment, UPDRS-III unified Parkinson's disease rating scale—third edition, ADL activities of daily living scale, HY stages the modified Hoehn–Yahr stage, HAMA Hamilton Anxiety Scale, HAMD Hamilton Depression Scale, MoCA Montreal Cognitive Assessment, VFT verbal fluency test, CDT clock drawing test, SDMT symbol digit modalities test, DST digit span test, VR visuospatial function, *C_p* clustering coefficients, *E_{loc}* local efficiency, *L_p* shortest path length, *E_{glob}* global efficiency, γ , λ , σ the “small worldness” attribute, *F* one-way ANOVA test, χ^2 Chi square test, *t* two-tailed *t* test, *Z* Mann–Whitney *U* test, *H* Kruskal–Wallis test. Significant values were adjusted by the Bonferroni correction for multiple tests

*The significance threshold was set at $P < 0.05$

Table 2 Among-group differences in the nodal efficiency in post hoc analysis

Nodes	Post hoc test (<i>P</i> value)			Nodal efficiency difference
	HCs vs PD-CN	HCs vs PD-MCI	PD-CN vs PD-MCI	
HIP_L	0.008*	0.073*	0.499*	HC > PD-CN
FFG_R	0.015*	0.074*	0.640*	HC > PD-CN
CAU_L	0.010*	0.087*	0.502*	HC > PD-CN
ROL_L	0.170*	0.005*	0.085*	HC > PD-MCI
OLF_R	0.187*	0.004*	0.062*	HC > PD-MCI
AMYG_L	0.051*	0.002*	0.157*	HC > PD-MCI
PUT_L	0.089*	0.003*	0.115*	HC > PD-MCI
ACG_R	0.076**	0.005**	0.689**	HC > PD-MCI
FFG_L	0.045**	0.019**	1.000**	HC > PD-MCI
SPG_R	0.309**	0.026**	0.654**	HC > PD-MCI
HIP_R	0.014*	0.025*	0.995*	HC > PD-CN, PD-MCI
PHG_R	0.038*	0.022*	0.646*	HC > PD-CN, PD-MCI
PCG_L	0.011*	0.017*	0.926*	HC > PD-CN, PD-MCI
STG_L	0.025*	0.002*	0.202*	HC > PD-CN, PD-MCI
TPOmid_L	0.021*	0.045*	0.930*	HC > PD-CN, PD-MCI
ITG_L	0.023*	0.021*	0.796*	HC > PD-CN, PD-MCI
TPOmid_R	0.037**	0.024**	1.000**	HC > PD-CN, PD-MCI
OLF_L	1.000**	0.015**	0.026**	HC, PD-CN > PD-MCI
ORBMed_L	0.647*	0.014*	0.026*	HC, PD-CN > PD-MCI
SFG_R	1.000**	0.053**	0.108**	NS
SPG_L	1.000**	0.050**	0.123**	NS
PUT_R	0.210**	0.052**	1.000**	NS
STG_R	0.086**	0.083**	1.000**	NS
MTG_L	0.158**	0.056**	1.000**	NS

The abbreviations of the 90 brain regions are given in supplementary materials (Online Resource). The significance threshold was set at $P < 0.05$. *R* (*L*) right (left) hemisphere

*Least significant difference (LSD) test, **post hoc Bonferroni test

cognitive function domains, as shown in Table 4 for detailed statistics.

Network-based statistical analysis

The results revealed that PD-MCI patients showed significant reduction of WM connectivity between several brain regions when compared with PD-NC patients. These differential connections constituted an aberrant subnetwork. Thus, eight one-connect subnetworks (Fig. 2a), three two-connect subnetworks (Fig. 2b) and two multi-connect subnetwork (Fig. 2c) were found to differ in comparison between PD-MCI and PD-NC patients.

Discussion

The purpose of our study is early detection of neuroimaging alterations in patients with PD-MCI. The global properties of the structural network showed significant decrease of E_{glob} and increase of L_p in PD-MCI patients.

Also, all patients in the three groups had “small worldness” attribute. In nodal efficiency analyses, compared with the HC group, the brain regions of the PD-NC and PD-MCI group with significantly reduced nodal efficiency were widely distributed, mainly in the hippocampus, parahippocampus, cingulate gyrus, temporal lobe, fusiform gyrus and amygdala. However, reduced nodal efficiency was distributed only at the left olfactory cortex and left superior frontal gyrus, and medial orbital in the PD-MCI group compared with PD-NC group. The correlation between nodal efficiency and cognitive function of PD patients was further analyzed. We found that the nodal efficiency in different brain regions was significantly associated with the different cognitive domains scores.

In the present study, differences in the two important multi-connect subnetworks were identified in the PD-MCI group when compared with PD-NC. Also, difference in the two important multi-connect subnetworks showed association with cognition. These two subnetworks are located on the bilateral lobe and both are centered on the orbitofrontal part.

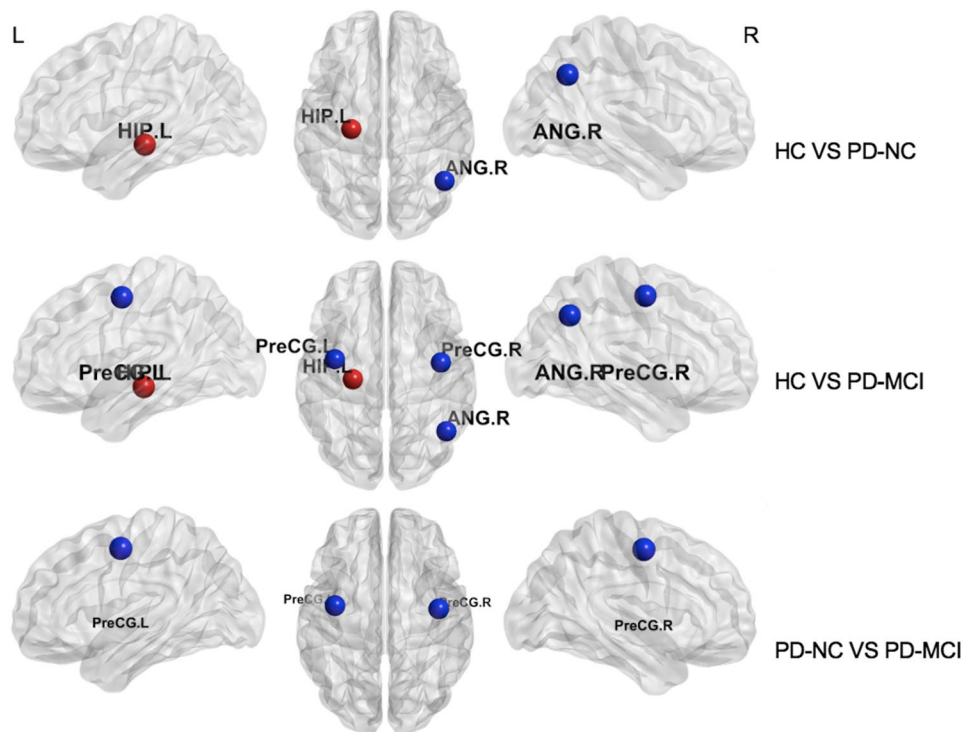
Table 3 Hubs characteristic of the HC, PD-NC and PD-MCI groups

Group	Region	Degree	Betweenness	Group	Region	Degree	Betweenness	Group	Region	Degree	Betweenness
HCs	INS_L	19	235.33	PD-NC	INS_L	18	254.10	PD-MCI	PreCG_L	13	107.81
	ACG_L	12	295.04		ACG_L	12	416.20		INS_L	17	250.15
	MCG_L	12	181.47		MCG_L	12	259.53		ACG_L	11	369.15
	HIP_L	12	231.65		MOG_L	13	143.83		MCG_L	12	278.68
	MOG_L	13	140.92		PoCG_L	13	154.64		MOG_L	12	146.58
	PoCG_L	13	124.33		PCUN_L	12	462.66		PoCG_L	13	134.68
	PCUN_L	12	468.70		CAU_L	11	192.61		PCUN_L	12	449.87
	CAU_L	12	280.72		PUT_L	20	365.98		CAU_L	12	342.70
	PUT_L	21	417.41		INS_R	19	340.35		PUT_L	18	324.88
	INS_R	20	314.56		ACG_R	11	215.09		PreCG_L	13	103.89
	ACG_R	12	236.34		MCG_R	11	191.30		INS_R	18	310.59
	MCG_R	12	204.83		HIP_R	11	146.01		ACG_R	11	198.83
	HIP_R	12	213.80		PoCG_R	12	115.09		MCG_R	12	286.50
	PoCG_R	13	113.03		ANG_R	11	106.97		HIP_R	11	169.70
	PCUN_R	14	484.07		PCUN_R	14	513.54		PoCG_R	13	126.34
	CAU_R	12	252.36		CAU_R	12	278.40		ANG_R	11	107.23
	PUT_R	20	292.26		PUT_R	18	279.25		PCUN_R	13	427.63
						CAU_R	12	406.92			
						PUT_R	18	281.74			

The abbreviations of the 90 brain regions are given in supplementary materials (Online Resource)

HCs healthy control group, PD-NC Parkinson’s disease with normal cognition, PD-MCI Parkinson’s disease with mild cognitive impairment

Fig. 1 Distribution differences of hubs in the HCs, PD-NC, PD-MCI groups. The abbreviations of the 90 brain regions are given in supplementary materials (Online Resource). The red dot represents the hub in the former group but not in the latter, and the blue node is the opposite. *L* left hemisphere, *R* right hemisphere



The above findings provide evidence that the efficiency of network information transmission was decreased with the decline of cognitive function of PD patients, which was

in line with the previous studies related to PD and Alzheimer’s disease (AD) [33–35]. Previous studies exploring brain structural networks in PD with DTI combined with

Table 4 Correlation between nodal efficiency and cognitive function status

Cognitive domains	Nodes	<i>r</i> value	<i>P</i> value
Overall cognitive function status	ORBMed_L	0.326	0.01
	ORBMed_R	0.302	0.01
	PUT_L	0.353	0.00
Executive function	ORBMed_L	0.304	0.01
Attention and working memory	ORBMed_L	0.304	0.01
	ORBMed_R	0.304	0.01
	ORBsup_R	0.304	0.01
	ORBmid_R_	0.334	0.00
	ORBinf_L	0.304	0.01
	OLF_L	0.304	0.01
	OLF_R	0.304	0.01
	REC_L	0.252	0.03
	ACG_L gyrus	0.429	0.00
	ACG_R	0.336	0.00
	AMYG_L	0.323	0.00
	MOG_L	0.333	0.01
	PUT_L_L	0.320	0.01
PUT_R	0.259	0.03	
Memory	ORBMed_L	0.307	0.01
	ORBMed_R	0.259	0.03
	PUT_L	0.242	0.04
	PUT_R	−0.254	0.03
Language	ROL_L	0.244	0.04

The abbreviations of the 90 brain regions are given in supplementary materials (Online Resource)

graph theory technology also have shown “small worldness” attribute in both the PD and HC groups [11, 36, 37], but none of them found a difference between groups. However, when compared with the HC group, the “small worldness” attribute was significantly increased in PD-MCI patients. A similar trend was observed in the structural and functional network studies [30, 33]. The explanations for these might be that low clustering coefficients in random networks were generated by the PD-MCI group, which in turn resulted in a larger γ value. Another reason might be that it was related to compensatory changes in the brain structure network in the PD-MCI group.

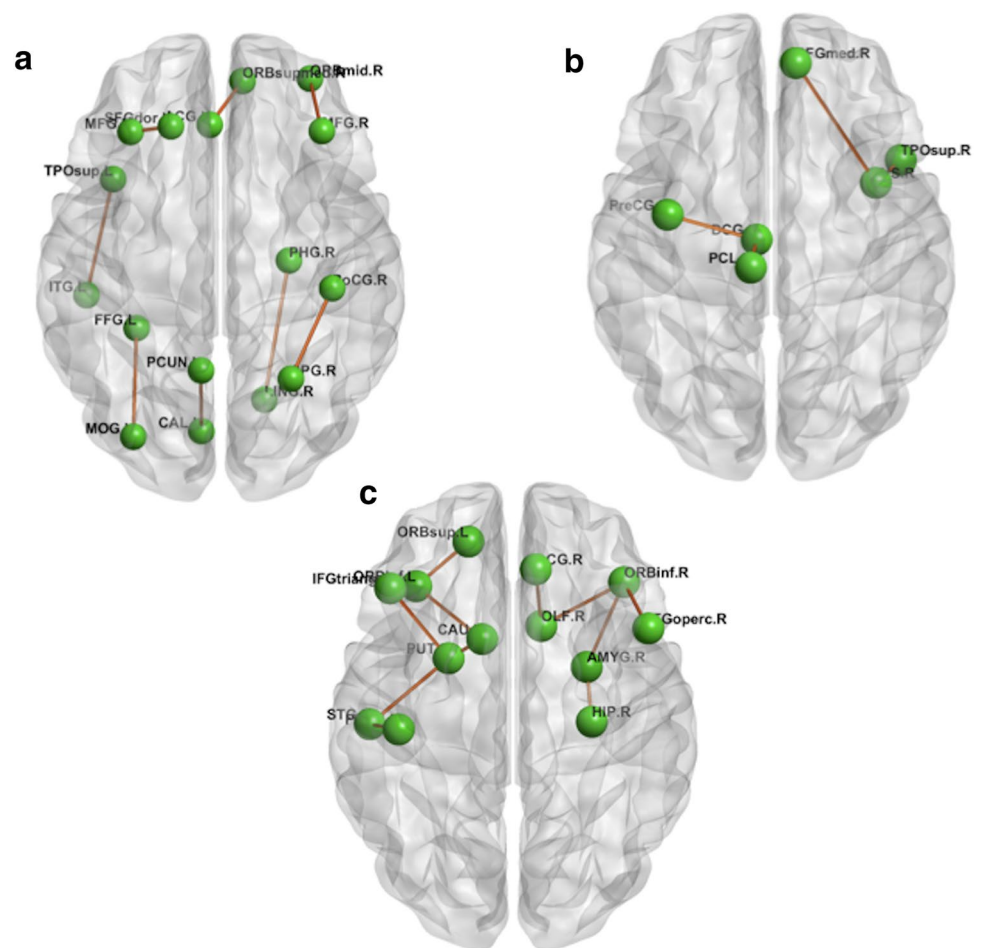
Previous DTI studies found WM integrity abnormalities in the corpus callosum, capsule, fornix, hippocampus and temporal, parietal and occipital cortices that might be specifically linked to the presence of cognitive impairment in PD [29, 38–41]. In the study conducted by Bledsoe et al., the anteriorly located DTI abnormalities were associated with the deficits of attention/working memory and executive function, while that of posteriorly located DTI abnormalities were associated with memory, visuospatial and executive function cognitive domains [29]. Another study showed that

WM integrity damages in the prefrontal areas were associated with executive function in PD patients [38]. According to the study by Zheng et al., the executive, language and attention functions were correlated with WM tracts in the frontal regions, while WM integrity in the anterior limb of the internal capsule and genu of the corpus callosum showed more correlation with executive function [39]. WM tract damages are widely distributed in association with decreased attention function [39]. The results of these studies are partially consistent with the findings of our study. For example, the regions with nodal efficiency were significantly correlated with attention and working memory scores that are widely distributed in the bilateral anterior cingulate, orbital part, olfactory cortex, basal ganglia and occipital gyrus, while no significant correlation was found between the visuospatial function and nodal efficiency. These findings further indicated that the limbic system damage may contribute to PD-MCI. Of note, in our study, the nodal efficiency in the orbitofrontal part showed a close relationship with the overall cognitive function and multiple sub-cognitive domains in our study, which was in line with the previous studies [38, 42]. These results suggested that WM in this part may act as a potential biomarker for structural changes in PD-MCI. Also, in hubs analysis, there are almost similar hub organizations in the three groups, but still there are differences in the distribution of hubs among the three groups at the left hippocampus, right angular gyrus and bilateral precentral gyrus. This subsequently explains that PD cognitive dysfunction might disrupt the structural network and reorganize the network’s hubs.

Burks et al. believed the orbitofrontal to be an important center for processing visual, spatial and emotional information because they identified three major connections of the orbitofrontal cortex [43]. They identified three major connections of the orbitofrontal cortex: a bundle to the thalamus and anterior cingulate gyrus that passes inferior to the caudate and medial to the vertical fibers of the thalamic projections; a bundle to the brainstem that travels from the lateral to the caudate and medial to the internal capsule; and radiations to the parietal and occipital lobes that travel with the inferior fronto-occipital fasciculus. As mentioned earlier, the orbitofrontal part showed a close relationship not only with the overall cognitive function, but also with multiple sub-cognitive domains. We therefore considered WM damages in the orbitofrontal domain linked to other brain regions showed close relation with the decline of PD cognitive function, and likely becomes a potential marker for early diagnosis of PD cognitive dysfunction in future.

However, our study has few limitations that can be explained from the following aspects. Firstly, our study diagnosed PD-MCI according to 2012 MDS proposed diagnostic criteria [14] combined with our existing scales. The main reason was that the Chinese version of the assessments

Fig. 2 Connection difference between the PD-MCI and PD-NC patients. The abbreviations of the 90 brain regions are given in supplementary materials (Online Resource). Green dots represent different brain regions; red lines indicate differential connections (edges). *L* left hemisphere, *R* right hemisphere



recommended by 2012 MDS-proposed diagnostic criteria had not been widely used in China, lacking norm comparison. Instead, we used the block design test, which is not very suitable since it requires motor responses. It may lead us to a negative result in studying the correlation between visuospatial function and nodal efficiency. Secondly, deterministic fiber tracking was performed to build a brain network, but there are two disadvantages. On one hand, DTI computation cannot judge the direction of multiple fibers when the fibers are crossing. The image collected from DTI only contains a part of the information about the dynamic process of diffusion of water molecules. Therefore, this cannot indicate inhomogeneity of a single voxel that contains multiple regions. Secondly, only damage of WM fibers connected between the brain regions can be inferred in NBS analysis, and the damage of WM in the brain region cannot be analyzed. This meant that we failed to understand WM damages in specific brain areas. In response to these deficiencies, future researches using some more detailed brain region atlas, such as the Human Brainnetome Atlas [44] and other finer divided multi-modal parcellation atlas should be conducted [45].

In conclusion, with the development of imaging technologies and the application of new analytical methods, the physiological mechanisms of cognitive impairment in PD patients can not only be understood, but also help to achieve early artificial intelligence diagnosis of PD cognitive dysfunction.

Funding The study funding was provided by the National Natural Science Foundation of China (No. 81501112, 81471654), Guangdong Natural Science Foundation (No. 2016A030310327), Key Program of Natural Science Foundation of Guangdong Province, China (No. 2017B030311015), Guangzhou Municipal People's Livelihood Science and Technology Project (No. 201803010085) and the Fundamental Research Funds for the Central Universities (2018MS27).

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval This research protocol was approved by the Medical Ethics Committee of Guangdong General Hospital and informed consent was obtained from all participants (No. GDREC2015195H). The research was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

References

- Goldman JG, Weis H, Stebbins G et al (2012) Clinical differences among mild cognitive impairment subtypes in Parkinson's disease. *Mov Disord* 27:1129–1136. <https://doi.org/10.1002/mds.25062>
- Domellof ME, Ekman U, Forsgren L, Elgh E (2015) Cognitive function in the early phase of Parkinson's disease, a five-year follow-up. *Acta Neurol Scand* 132:79–88. <https://doi.org/10.1111/ane.12375>
- Adler CH, Caviness JN, Sabbagh MN et al (2010) Heterogeneous neuropathological findings in Parkinson's disease with mild cognitive impairment. *Acta Neuropathol* 120:827–828
- Vasconcellos LFR, Pereira JS, Charchat-Fichman H et al (2019) Mild cognitive impairment in Parkinson's disease: characterization and impact on quality of life according to subtype. *Geriatr Gerontol Int* 19:497–502. <https://doi.org/10.1111/ggi.13649>
- Lee SJ, Kim JS, Yoo JY et al (2010) Influence of white matter hyperintensities on the cognition of patients with parkinson disease. *Alzheimer Dis Assoc Disord* 24:227–233. <https://doi.org/10.1097/WAD.0b013e3181d71a13>
- Kandiah N, Mak E, Ng A et al (2013) Cerebral white matter hyperintensity in Parkinson's disease: a major risk factor for mild cognitive impairment. *Park Relat Disord* 19:680–683. <https://doi.org/10.1016/j.parkreldis.2013.03.008>
- Matsui H, Nishinaka K, Oda M et al (2007) Dementia in Parkinson's disease: diffusion tensor imaging. *Acta Neurol Scand* 116:177–181. <https://doi.org/10.1111/j.1600-0404.2007.00838.x>
- Lichtman JW, Livet J, Sanes JR (2008) A technicolour approach to the connectome. *Nat Rev Neurosci* 9:417–422. <https://doi.org/10.1038/nrn2391>
- Sporns O, Tononi G, Kotter R (2005) The human connectome: a structural description of the human brain. *PLoS Comput Biol* 1:e42. <https://doi.org/10.1371/journal.pcbi.0010042>
- Abbasi N, Mohajer B, Abbasi S et al (2018) Relationship between cerebrospinal fluid biomarkers and structural brain network properties in Parkinson's disease. *Mov Disord* 33:431–439. <https://doi.org/10.1002/mds.27284>
- Nigro S, Riccelli R, Passamonti L et al (2016) Characterizing structural neural networks in de novo Parkinson disease patients using diffusion tensor imaging. *Hum Brain Mapp* 37:4500–4510. <https://doi.org/10.1002/hbm.23324>
- Aarabi MH, Kamalian A, Mohajer B et al (2015) A statistical approach in human brain connectome of Parkinson disease in elderly people using network based statistics. *Conf Proc IEEE Eng Med Biol Soc* 2015:4310–4313. <https://doi.org/10.1109/embc.2015.7319348>
- Gelb DJ, Oliver E, Gilman S (1999) Diagnostic criteria for Parkinson disease. *Arch Neurol* 56:33–39
- Litvan I, Goldman JG, Troster AI et al (2012) Diagnostic criteria for mild cognitive impairment in Parkinson's disease: movement disorder society task force guidelines. *Mov Disord* 27:349–356. <https://doi.org/10.1002/mds.24893>
- Fahn S, Elton R (1987) Recent developments in Parkinson's disease. *Macmillan Heal care Inf* 2:293–304
- Goetz CG, Poewe W, Rascol O et al (2004) Movement disorder society task force report on the Hoehn and Yahr staging scale: status and recommendations. *Mov Disord* 19:1020–1028. <https://doi.org/10.1002/mds.20213>
- Hamilton MAX (1959) The assessment of anxiety states by rating. *Br J Med Psychol* 32:50–55
- Hamilton M (1960) A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56–62. <https://doi.org/10.1136/jnnp.23.1.56>
- Lawton MP, Brody EM (1969) Assessment of older people: self-maintaining and instrumental activities of daily living. *The Gerontologist* 9:179–186. https://doi.org/10.1093/geront/9.3_Part_1.179
- Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12:189–198. [https://doi.org/10.1016/0022-3956\(75\)90026-6](https://doi.org/10.1016/0022-3956(75)90026-6)
- Nasreddine ZS, Phillips NA, Bedirian V et al (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 53:695–699. <https://doi.org/10.1111/j.1532-5415.2005.53221.x>
- Tombaugh TN, Kozak J, Rees L (1999) Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Arch Clin Neuropsychol* 14:167–177
- Gong Y et al (1989) Wechsler adult intelligence scale-revised in China Version. Hunan Med Coll Press, China
- Wang P, Shi L, Zhao Q et al (2014) Longitudinal changes in clock drawing test (CDT) performance before and after cognitive decline. *PLoS One* 9:1–9. <https://doi.org/10.1371/journal.pone.0097873>
- Smith A (1982) Manual for the symbol digit modalities test. Western Psychological Services, Los Angeles
- Gong Y et al (1989) Manual of Wechsler Memory Scale—Chinese Version. Hunan Med Coll Press, China
- Cui Z, Zhong S, Xu P et al (2013) PANDA: a pipeline toolbox for analyzing brain diffusion images. *Front Hum Neurosci* 7:42. <https://doi.org/10.3389/fnhum.2013.00042>
- Wang J, Wang X, Xia M et al (2015) GREYNA: a graph theoretical network analysis toolbox for imaging connectomics. *Front Hum Neurosci* 9:386. <https://doi.org/10.3389/fnhum.2015.00386>
- Bledsoe IO, Stebbins GT, Merkitich D, Goldman JG (2018) White matter abnormalities in the corpus callosum with cognitive impairment in Parkinson disease. *Neurology* 91:e2244–e2255. <https://doi.org/10.1212/wnl.0000000000006646>
- Baggio HC, Sala-Llonch R, Segura B et al (2014) Functional brain networks and cognitive deficits in Parkinson's disease. *Hum Brain Mapp* 35:4620–4634. <https://doi.org/10.1002/hbm.22499>
- Baggio HC, Segura B, Sala-Llonch R et al (2015) Cognitive impairment and resting-state network connectivity in Parkinson's disease. *Hum Brain Mapp* 36:199–212. <https://doi.org/10.1002/hbm.22622>
- Lopes R, Delmaire C, Defebvre L et al (2017) Cognitive phenotypes in parkinson's disease differ in terms of brain-network organization and connectivity. *Hum Brain Mapp* 38:1604–1621. <https://doi.org/10.1002/hbm.23474>
- Pereira JB, Aarsland D, Ginestet CE et al (2015) Aberrant cerebral network topology and mild cognitive impairment in early Parkinson's disease. *Hum Brain Mapp* 36:2980–2995. <https://doi.org/10.1002/hbm.22822>
- Yao Z, Zhang Y, Lin L et al (2010) Abnormal cortical networks in mild cognitive impairment and Alzheimer's disease. *PLoS Comput Biol* 6:e1001006. <https://doi.org/10.1371/journal.pcbi.1001006>
- He Y, Chen Z, Evans A (2008) Structural insights into aberrant topological patterns of large-scale cortical networks in Alzheimer's disease. *J Neurosci* 28:4756–4766. <https://doi.org/10.1523/jneurosci.0141-08.2008>
- Li C, Huang B, Zhang R et al (2017) Impaired topological architecture of brain structural networks in idiopathic Parkinson's disease: a DTI study. *Brain Imaging Behav* 11:113–128. <https://doi.org/10.1007/s11682-015-9501-6>
- Wen MC, Xu Z, Lu Z et al (2017) Microstructural network alterations of olfactory dysfunction in newly diagnosed Parkinson's disease. *Sci Rep* 7:12559. <https://doi.org/10.1038/s41598-017-12947-7>
- Auning E, Kjaervik VK, Selnes P et al (2014) White matter integrity and cognition in Parkinson's disease: a cross-sectional study. *BMJ Open* 4:e003976. <https://doi.org/10.1136/bmjopen-2013-003976>

39. Zheng Z, Shemmassian S, Wijekoon C et al (2014) DTI correlates of distinct cognitive impairments in Parkinson's disease. *Hum Brain Mapp* 35:1325–1333. <https://doi.org/10.1002/hbm.22256>
40. Deng B, Zhang Y, Wang L et al (2013) Diffusion tensor imaging reveals white matter changes associated with cognitive status in patients with Parkinson's disease. *Am J Alzheimers Dis Other Demen* 28:154–164. <https://doi.org/10.1177/1533317512470207>
41. Chen B, Fan GG, Liu H, Wang S (2015) Changes in anatomical and functional connectivity of Parkinson's disease patients according to cognitive status. *Eur J Radiol* 84:1318–1324. <https://doi.org/10.1016/j.ejrad.2015.04.014>
42. Koshimori Y, Segura B, Christopher L et al (2015) Imaging changes associated with cognitive abnormalities in Parkinson's disease. *Brain Struct Funct* 220:2249–2261. <https://doi.org/10.1007/s00429-014-0785-x>
43. Burks JD, Conner AK, Bonney PA et al (2018) Anatomy and white matter connections of the orbitofrontal gyrus. *J Neurosurg* 128:1865–1872. <https://doi.org/10.3171/2017.3.JNS162070>
44. Fan L, Li H, Zhuo J et al (2016) The Human Brainnetome Atlas: a new brain atlas based on connective architecture. *Cereb Cortex* 26:3508–3526. <https://doi.org/10.1093/cercor/bhw157>
45. Glasser MF, Coalson TS, Robinson EC et al (2016) A multi-modal parcellation of human cerebral cortex. *Nature* 536:171–178. <https://doi.org/10.1038/nature18933>