Disrupted rich club organization of white matter networks in de novo Parkinson's disease with REM sleep behavior disorder

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Abstract

Introduction: Rapid eye movement (REM) sleep behavior disorder (RBD) is common in Parkinson's disease (PD) but the pathophysiological mechanism is still unclear in PD with RBD. The purpose was to explore the alterations of white matter network topology in de novo PD, with or without RBD.

Methods: In total, this study contained 153 de novo individuals with PD and 59 healthy controls recruited from the Parkinson's Progression Markers Initiative (PPMI) database. In such patients, 56 were probable RBD (PD-pRBD) and 97 were non-probable RBD (PD-npRBD) according to the RBD screening questionnaire (RBDSQ). All the recruited members had diffusion tensor imaging and complete neuropsychological assessments. The structural network of brain and organization of rich club were constructed based on deterministic fiber tracking at the individual level.

Results: Compared with PD-npRBD patients, the PD-pRBD patients showed diminished global efficiency and elevated shortest path length. It was found that both the PD-pRBD and PD-npRBD had common hubs including putamen, middle occipital gyrus, precuneus, besides, PD-pRBD mainly recruited additional hubs in the frontotemporal paralimbic regions. Furthermore, the PD-pRBD showed decreased rich-club connections in comparison to PD-npRBD. Additionally, the nodal shortest path length in the right superior frontal gyrus, orbital part (ORBsup.R) was positively correlated to RBDSQ scores in PD-pRBD patients($r=0.25$, $p=0.01$).

Conclusions: The results indicated the PD-pRBD patients showed disrupted topological organization of white matter in the whole-brain and rich-club connections which mainly located in frontotemporal paralimbic regions, thus partially helps to illustrate the pathological processes of RBD in PD patients.

Introduction

Patients with Parkinson's disease (PD) have many non-motor symptoms, and the rapid eye movement (REM) sleep behavior disorder (RBD) is one of the most common ones, which is suggested by dream-related motor behavior and accompanied by phasic tension electromyography during REM sleep(Gagnon et al. 2002; Sudarsky and Friedman 2006). Recently, a meta-analysis showed that RBD occurs in as much as 25% of new PD patients and the percentage elevates as the symptom progresses, with an overall prevalence of 42.3% in the PD population (Destrieux et al. 2010; Kalia and Lang 2015; Marion et al. 2008). In addition, there is growing evidence indicating the exhibition of RBD in PD patients is associated with poorer motor and non-motor symptoms, namely, smell disorders, constipation, visual hallucinations, cognitive impairment, depression, impulse control disorders(Agosta et al. 2015; Arnaldi et al. 2016). However, the potential neurologic mechanisms of RBD in such patients remain to be elucidated.

Dopaminergic denervation of the striatum is a common feature in PD(Kalia and Lang 2015). Idiopathic RBD (iRBD) may be induced by neuronal degeneration in brain regions regulating the tone of skeletal muscle during REM sleep, including the pontine nucleus, lateral dorsal tegmental nucleus and locus coeruleus(Sudarsky and Friedman 2006). However, only a subset of PD patients develops RBD and half of iRBD patients develop PD(Marion et al. 2008). Therefore, other potential factors are likely to play key roles in RBD pathogenesis in PD.

A handful of magnetic resonance researches have been conducted to explore the probable pathogenesis of PD with RBD. A longitudinal study compared the changes in the thickness of cortex and the volume of subcortex in PD cases with or without RBD. In comparison to the non-probable RBD (PD-npRBD) subset, the thinning rate of the left insula in the probable RBD (PD-pRBD) subset was significantly increased, and the volume of the left caudate nucleus, globus pallidus and amygdala decreased over time(Yoon and Monchi 2021). Some studies have suggested that the

neuropathological mechanism of PD with RBD may be related to abnormal spontaneous neuron activity patterns in cerebellum and visuomotor cortex, as well as enhanced connections between cerebellum and occipital and motor areas (Liu et al. 2021a). In addition, the differences in white matter microstructure in PD with RBD were explored by using diffusion tensor imaging(DTI), and it was shown that compared with PD-npRBD the fractional anisotropy(FA) of bilateral cingulate and left suboccipital tract was significantly reduced(Rahmani et al. 2016).

In contrast to approaches analyzing localized brain changes, lately, some new studies describe the human brain as a network model, and the structural and functional systems of the brain have the characteristics of complex networks. Graph theory is considered a good way to analyze such network. In graph theory, a network stands for a group of nodes or vertices and the edges or lines between them, and brain networks could be described quantitatively through multiple measurements (Bullmore and Sporns 2009; Sporns et al. 2005). Van and Power JD et al. (Power et al. 2013; van den Heuvel and Sporns 2011) demonstrated the existence of "rich club" formed by brain hubs of high-degree nodes. These nodes show a tendency to be more closely connected than those with lower degree values. Rich club provides significant information about the higher-level topology of brain networks.

In recent years, the white matter structural network connectome constructed by DTI has been increasingly applied in graph theory to reveal the alterations in the topological properties of brain structures, especially in PD patients(Li et al. 2017; Pereira et al. 2015). Several neuroimaging studies using DTI have shown that compared with health contrast (HC), PD patients had lower whole-brain clustering coefficient and lower global efficiency(Abbasi et al. 2018; Nigro et al. 2016). Liu et al (Liu et al. 2021b) revealed that in early PD patients, the rich club organization was disorganized and the connection strength between the peripheral regions was abnormal. However, it is still not clear whether PD-pRBD and PD-npRBD differ in brain white matter connectivity network.

To address this issue, this study focused on the alterations of structural network in the white matter of PD sufferers with or without RBD by using DTI. Based on the aforementioned clinical heterogeneity differences between PD-pRBD and PD-npRBD, it was hypothesized that the PD-pRBD could present convergent and divergent neural and anatomical abnormalities in the regions, which were correlated to the performance. These comparisons can probably contribute to clarify the common points and differences in neurobiological characteristics between PD-pRBD and PD-npRBD cases.

Methods

Participants and Clinical Evaluation

All MRI and clinical data were collected from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data), a multicenter longitudinal database of Parkinson's disease(Parkinson Progression Marker Initiative 2011). Each PPMI site was approved by its own ethical committee. All PPMI subjects provided written informed consents prior to participating in the program. The analysis procedure in this study was carried out basing on the approved PPMI guidelines.

PD cases included in the database were newly diagnosed and treatment-naïve and we only selected data from the baseline visits. Given that polysomnography was not currently available in the database, the presence of RBD in PD individuals was decided by RBD screening questionnaire (RBDSQ). The RBDSQ is highly sensitive and reasonably specific for RBD (Stiasny-Kolster et al. 2007). In the present study, PD patients with RBDSQ score ≥ 5 was defined as PD-pRBD, < 5 was defined as PD-npRBD(Kamps et al. 2019). HC with RBDSQ score ≥ 5 were excluded. Patients

with cognitive impairment (Montreal Cognitive Assessment (MoCA) score < 23) were also excluded (Nasreddine et al. 2005). Finally, 56 PD-pRBD patients, 97 PD-npRBD patients, and 59 HC were enrolled.

The neuropsychological performance of each participant was assessed using multiple cognitive and motor test scales, including the Hopkins Verbal Learning Test (HVLT), Montreal Cognitive Assessment (MoCA), Scales for Outcomes in Parkinson's disease- Autonomic (SCOPA-AUT), University of Pennsylvania Smell Identification Test (UPSIT) and Movement Disorder Society Unified Parkinson's Disease Rating Scale part three (MDS UPDRS-III).

Image acquisition

Non-contrast enhanced 3D volumetric T1-weighted MRI and DTI of these 212 subjects were acquired on 3T Siemens MRI scanners (Erlangen, Germany) using a MP-RAGE sequence at different centers. Acquisition parameters and detailed protocols were available on the PPMI website. The following indexes are included in the protocol: (1) DTI: 72 axial slices, echo time (TE) = 88ms, repetition time (TR) = 500ms-9,000ms, voxel size: $2.0 \times 2.0 \times 2.0 \text{ mm}^3$, acquisition matrix = 1044×1044 ; one diffusion-unweighted (b0) image and 64 diffusion-sensitive gradient directions at $b = 1,000 \text{ s/mm}^2$ images; (2) 3D-T1WI: TE = 2.98ms, TR = 2300ms, voxel size: $1.0 \times 1.0 \times 1.0 \text{ mm}^3$, acquisition matrix = 240×256 . Staff at each center were trained to ensure that data was collected in a standardized process. In subsequent data analysis, subjects with missing data were excluded.

DTI Preprocessing and Tractography

PANDA software (Cui et al. 2013) was used to preprocess DTI images, mainly including: First, the non-brain tissue was stripped off. Secondly, the eddy-current effect and mild head motion were corrected. Then the diffusion tensor (DT) matrix was calculated based on the voxel. Finally, the Fiber Assignment by Continuous Tracking (FACT) algorithm was applied to conduct deterministic tractography. If the curvature angle was greater than 45° or the voxel fractional anisotropy (FA) < 0.2, the trace was terminated.

Network Construction

The T1WI images of all individual subjects were first mapped to the corresponding $B = 0 \text{ s/mm}^2$ images to obtain jointly calibrated T1 images in the DTI space. Then the transformed T1 images were nonlinearly transformed into ICBM152 T1 template in Montreal Neuroscience Institute (MNI) space. According to automated anatomical labeling (AAL) atlas of MNI, the brain could be divided into ninety regions, which were nodes of the brain structural network (supplementary table 1). A 90×90 weighted matrix was obtained by taking the number of fibers (FN) in each pair of brain regions as the threshold value T. We set $T \geq 3$ to indicate the existence of fiber connections in brain regions, which was defined as 1; otherwise, it was defined as 0 (Shu et al. 2009), and then PANDA was used to establish the binary matrix of the whole brain network.

Graph analysis of network topology

Global and nodal properties

All network analyses were performed using the graph theory network analysis toolbox GREYNA (<https://www.nitrc.org/projects/gretna>) and the results were visualized by using the BrainNet Viewer toolbox (<http://www.nitrc.org/projects/bnv>).

The global properties of network include global efficiency (E_g), local efficiency (E_{loc}), cluster coefficient (C_p), shortest path length (L_p), and "small-world attribute" (σ) (Wang et al. 2020). E_g is considered as a significant parameter to estimate the transmission efficiency of global network. E_{loc} describes the network interconnection between nodes. C_p represents the average clustering coefficient of all nodes, mainly to measure the level of network interconnection. L_p refers to the average length of the shortest path between any two nodes in the network. A smaller L_p means a higher efficiency of network information transmission. The "small worldness" has a higher clustering coefficient and a smaller shortest path length, which ensures the transmission efficiency globally and locally. The study generated 1,000 random networks compared them with real ones to explore the subjects "small worldness". γ and λ respectively represent the ratios of C_p and L_p of real networks to that of random networks. σ is defined as the ratio of γ to λ . When $\gamma \gg 1$ and $\lambda \approx 1$, or $\sigma > 1$, the network was regarded as "small worldness" (Li et al. 2017).

The nodal properties of network include nodal efficiency (N_e), nodal shortest path length (N_{lp}), nodal cluster coefficient (N_{cp}), nodal degree centrality (D_c) and node betweenness (B_c). N_e refers to the efficiency of information transfer between node (i) and all other nodes in the network. N_{lp} refers to the shortest path from one node to all other nodes. N_{cp} refers to the density of connections between the neighbors of a node. D_c is defined as the number of edges shared by node (i) and other nodes in the network. B_c defines the fraction of the shortest path through node (i) (Wang et al. 2020).

Rich-club analysis

The central hub of global communication in the brain network described by rich club (van den Heuvel et al. 2012; van den Heuvel and Sporns 2011), stands for nodes with higher degrees within brain networks and nodes with a higher connection intensity (van den Heuvel and Sporns 2011). In this study, the group-averaged FN structural networks were constructed for the three groups separately. The weighted rich club coefficient $\phi_w(k)$, randomly rich club coefficient $\phi_{rand}(k)$, and normalized rich club coefficient $\phi_{norm}(k)$ for each group were calculated to describe rich club organization (van den Heuvel et al. 2012). The rich club regions refer to the node with the most consistent top 10% of the three groups (van den Heuvel et al. 2013). Three groups of connections were used to characterize the edge architecture of brain networks, which are: rich club connections (between rich club nodes), feeder connections (between rich and non-rich club nodes) and local connections (between non-rich club nodes) (van den Heuvel et al. 2012).

Statistical analysis

The demographic characteristics and clinical data were compared by using IBM SPSS 22 software among the three groups. Distribution-based Chi-square test was applied to compare qualitative data, and one-way ANOVA or Kruskal-Wallis H test was used for quantitative data. The significance level was $p < 0.05$. Significance values were adjusted by the Bonferroni correction for multiple tests. After controlling age, sex, and education years, one-way ANOVA was applied to compare differences in global and local attributes among the groups. For global parameters, $p < 0.05$ was considered significant; for nodal parameters, significance values were adjusted by the Bonferroni correction for multiple tests. Post hoc analysis was performed to further explore differences among the groups. At the same time, Bonferroni correction was also carried out. Comparison of rich club, feeder and local connection among groups was analyzed by one-way ANOVA and post hoc two-sample T test. All graph theory parameters were analyzed using GREYNA statistical model. At last, multiple linear regression analysis was applied to test the relationship between structural network parameters and RBDSQ scores in the PD-pRBD group.

Results

Demographic and clinical variables

No significant differences were found in age, gender and education level among the three subsets ($p>0.05$). There were no significant differences in HVLIT Immediate/Total Recall, HVLIT Discrimination Recognition, HVLIT Retention, MoCA, SCOPA-AUT, UPSIT and UPDRS-III between PD-pRBD and PD-npRBD patients ($p>0.05$). (Table 1).

Table 1
Characteristics of HC, PD-npRBD patients, and PD-pRBD patients

	HC(n=59)	PD-npRBD (n=97)	PD-pRBD (n=56)	<i>P</i> value	Post hoc analysis <i>P</i> value		
					HC vs PD- npRBD	HC vs PD- pRBD	PD- npRBD vs PD- pRBD
Age(years)	60.8(10.4)	61.1 (9.3)	62.2(9.9)	0.34(F)	0.98(t)	0.72(t)	0.75(t)
Gender(male%)	64.3%	63.9%	66.1%	0.74(χ^2)	0.88(χ^2)	0.71(χ^2)	0.79(χ^2)
Education(years)	16.06(3.45)	15.27(3.05)	15.36(2.89)	0.45(F)	0.25(t)	0.84(t)	0.51(t)
HVLIT Immediate/Total Recall	26.05(4.72)	25.29(5.34)	24.21(5.18)	0.08(H)	0.37(Z)	0.08(Z)	0.29(Z)
HVLIT Discrimination Recognition	9.61(3.67)	9.60(3.19)	8.95(3.42)	0.31(H)	0.98(Z)	0.31(Z)	0.27(Z)
HVLIT Retention	0.91(0.19)	0.88(0.18)	0.80(0.22)	0.28(F)	0.38(t)	0.27(t)	0.06(t)
MoCA	28.13(1.15)	27.84(1.94)	27.42(2.26)	0.09(F)	0.34(t)	0.09(t)	0.33(t)
SCOPA-AUT	6.20(3.04)	7.82(4.01)	10.14(5.78)	0.05(H)	0.26(Z)	0.05(Z)	0.41(Z)
UPSIT	24.89(10.06)	25.34(8.62)	25.83(9.48)	0.86(F)	0.96(t)	0.85(t)	0.95(t)
UPDRS-III	27.88(11.98)	28.09(10.96)	26.08(12.56)	0.57(H)	0.74(Z)	0.56(Z)	0.48(Z)
HC: healthy control group, PD-npRBD Parkinson's disease with no probably REM Sleep Behavior Disorder, PD-pRBD Parkinson's disease with probably REM Sleep Behavior Disorder; GDS: Geriatric Depression Scale; HVLIT: Hopkins Verbal Learning Test; MoCA: Montreal Cognitive Assessment; SCOPA-AUT: Scales for Outcomes in Parkinson's disease- Autonomic; UPSIT: University of Pennsylvania Smell ID Test; UPDRS-III: unified Parkinson's disease rating scale-third edition.							
F: one-way ANOVA test, t: two-tailed t test, χ^2 : Chi square 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 $p<0.05$.							

Global properties of network

No significant differences were found in the global properties of Cp and Eloc among HC, PD-npRBD and PD-pRBD groups, but they were found in Eg and Lp. Compared with the Hc group, PD-npRBD patients exhibited significantly increased Eg and decreased Lp in post-hoc analysis. However, in comparison to PD-npRBD, PD-pRBD patients exhibited significantly lower Eg but higher Lp ($p<0.05$). All groups showed that $\sigma > 1$ represented the small worldness property of WM connection network, and there is no statistical difference among the three groups (Fig. 1).

Nodal properties of network

Significant differences were confirmed in Ncp among the three groups. Compared with HC, the Ncp of PD-npRBD patients was all increased in the right superior occipital gyrus, left middle occipital gyrus, bilateral precuneus, bilateral putamen, bilateral superior temporal gyrus, and left middle temporal gyrus ($p < 0.05$, Bonferroni correction). However, there were no significant differences between PD-pRBD and PD-npRBD group, HC and PD-pRBD group (Table 2). Other nodal properties, such as Ne, Np, Dc and Bc, showed no significant difference within such groups.

Table 2
Among-group differences in the Nodal clustering coefficient (Ncp) in post hoc analysis

Nodes	Post hoc test (<i>P</i> value)			Nodal clustering coefficient difference
	HC vs PD-npRBD	HC vs PD-pRBD	PD-npRBD vs PD-pRBD	
ORBinf.R	0.014**	0.734*	0.864*	HC > PD-npRBD
MOG.R	0.037**	1.036*	0.974*	HC > PD-npRBD
SMG.L	0.016**	0.878	0.652*	HC > PD-npRBD
SMG.R	0.027**	0.985*	0.152*	HC > PD-npRBD
PCUN.R	0.021**	0.984*	0.656*	HC > PD-npRBD
PUT.L	0.041**	0.975*	0.541*	HC > PD-npRBD
THA.L	0.015**	0.462*	0.261*	HC > PD-npRBD
LING.R	0.026**	0.016*	0.076*	HC > PD-npRBD, PD-pRBD
IOG.R	0.017**	0.026*	0.084*	HC > PD-npRBD, PD-pRBD
FFG.R	0.021**	0.031*	0.090*	HC > PD-npRBD, PD-pRBD
FFG.L	0.023**	0.109*	0.021*	HC > PD-npRBD, PD-npRBD > PD-pRBD
PCL.R	0.098*	0.218*	0.011*	PD-npRBD > PD-pRBD
PAL.R	0.075*	0.721*	0.032*	PD-npRBD > PD-pRBD
The abbreviations of the 90 brain regions are given in supplementary materials (Online Resource).				
The significance threshold was set at $p < 0.05$.				
**post hoc Bonferroni test, * Bonferroni uncorrected.				

Rich-club analysis

It was illustrated the rich club organization found in the structural networks of HC, PD-npRBD and PD-pRBD groups. For the three groups, the normalized rich club coefficients $\varphi_{\text{norm}}^w(k) > 1$ over the range of degrees from $k = 1 - 15$ were found (Fig. 2). On contrast, there were no significant differences in $\varphi_{\text{norm}}^w(k)$ among the three groups ($p > 0.05$, Bonferroni-corrected).

The brain network hubs of the three groups were determined as the top 10% of the most connected region and the brain center region according to node degree. The following hubs were discovered in HC: left superior frontal gyrus,

medial orbital (ORBsupmed.L), right calcarine fissure and surrounding cortex (CAL.R), left temporal pole: superior temporal gyrus (TPOsup.L), right temporal pole: middle temporal gyrus (TPOmid.R), left middle occipital gyrus (MOG.L), bilateral precuneus (PCUN), bilateral putamen (PUT). The following hubs were present in PD-npRBD: bilateral temporal pole: superior temporal gyrus (TPOsup), left middle temporal gyrus (MTG.L), right superior occipital gyrus (SOG.R), left middle occipital gyrus (MOG.L), bilateral precuneus (PCUN), bilateral putamen (PUT). The following hubs were discovered in PD-pRBD: left insula (INS.L), right superior frontal gyrus, orbital part (ORBsup.R), left precentral gyrus (PreCG.L), right superior occipital gyrus (SOG.R), Middle occipital gyrus (MOG.L), bilateral precuneus (PCUN), bilateral putamen (PUT).

Among the three groups, 5 hub regions (3 association; 2 subcortical) were identical, including left middle occipital gyrus (MOG.L), bilateral precuneus (PCUN), bilateral putamen (PUT) (Fig. 3a-c, Table 3). The frontal and subcortical hub regions (left insula (INS.L), right superior frontal gyrus, orbital part (ORBsup.R), left precentral gyrus (PreCG.L)) of PD-RBD do not exist in PD-npRBD, whereas the temporal hubs (bilateral temporal pole: superior temporal gyrus (TPOsup), left middle temporal gyrus (MTG.L)) of PD-nRBD do not exist in PD-pRBD. Noticeably, these different hub regions were mainly located in the fronto-temporal paralimbic system. (Fig. 3d-f).

Table 3
Hubs characteristic of the HC, PD-npRBD and PD-pRBD groups

	Hub regions	Class	Degree
HC	ORBsupmed.L	Paralimbic	14
	CAL.R	Primary	19
	TPOsup.L	Paralimbic	14
	TPOmid.R	Paralimbic	16
	MOG.L	Association	15
	PCUN.L	Association	12
	PCUN.R	Association	18
	PUT.L	Subcortical	15
	PUT.R	Subcortical	12
PD-npRBD	TPOsup.R	Paralimbic	18
	TPOsup.L	Paralimbic	13
	MTG.L	Association	16
	SOG.R	Association	16
	MOG.L	Association	14
	PCUN.L	Association	11
	PCUN.R	Association	17
	PUT.L	Subcortical	14
	PUT.R	Subcortical	12
PD-pRBD	INS.L	Paralimbic	17
	ORBsup.R	Paralimbic	15
	PreCG.L	Primary	10
	SOG.R	Association	16
	MOG.L	Association	14
	PCUN.L	Association	12
	PCUN.R	Association	13
	PUT.L	Subcortical	11
	PUT.R	Subcortical	12
The regions in bold represent different hub regions between the PD-npRBD and PD-pRBD groups. The abbreviations of the 90 brain regions are given in supplementary materials (Online Resource).			

When describing the edge structure in the context of rich club organization, it was found that rich club connections ($p = 0.021$) increased in the PD-PRBD group compared with HC, while rich club connections ($p = 0.018$) decreased significantly in the PD-pRBD group compared with PD-npRBD group (permutation test, 10 000 times, Fig. 3C). There was no significant group effect being found in the feeder connection between rich and non-rich club regions ($p = 0.093$) and the local connection between non rich club regions ($p = 0.075$) (Fig. 4).

Correlation between graph parameters and clinical variables

Multiple linear regression analysis showed that no significant correlation was found between RBDSQ scores and global parameters. Nlp of the right superior frontal gyrus, orbital part (ORBsup.R) was positively associated with RBDSQ scores ($r=0.25$, $p=0.01$). $p < 0.05$ was considered as significant (Fig. 5).

Discussion

In this study, DTI and graph theory methods were applied to evaluate the topological properties of WM networks in de novo PD sufferers with probable RBD. The major findings are listed as below: 1) In global properties, compared with PD-npRBD patients, PD-pRBD patients exhibited diminished global efficiency and increased characteristic path length. 2) Nodes in putamen, middle occipital gyrus, precuneus were served as hubs in both two PD groups, and PD-pRBD exhibited additionally recruited hubs in fronto-temporal paralimbic regions. 3) Rich-club connections of brain networks diminished in PD-pRBD compared with PD-npRBD. 4) Nlp in ORBsup.R were positively correlated with RBDSQ scores in PD-pRBD patients. This study primarily reports topological structural brain connectome and rich club organization of WM networks in early-stage drug-naïve PD-pRBD.

In terms of global topological properties, different from PD-npRBD patients, PD-pRBD group exhibited significant decreased E_g and increased L_p of WM structural networks. E_g and L_p referred to the ability of communication between distributed nodes and thus reflected the global information transfer efficiency (Bullmore and Sporns 2012). The findings of decreased E_g and increased L_p may indicate that the inter-nodal organization of the whole brain was excessively destructed in PD-pRBD cases. Even though, the altered structural topological properties in PD with RBD were barely explored, former researches (Arnaldi et al. 2016) have indicated that PD with pRBD presenting more severe motor and non-motor symptoms than PD without pRBD, suggesting more severe and widespread neurodegeneration. It might indicate that normal topological network organization was impacted, namely, the separation and integration of brain networks was disrupted.

Our results confirmed that all three groups of brain networks demonstrate the presence of network hubs, comprising 5 identical hub regions (3 association; 2 subcortical): left middle occipital gyrus, bilateral putamen and precuneus. Most of them have already been reported as network hubs in human brain (Tomasi and Volkow 2011; van den Heuvel and Sporns 2011, 2013). Interestingly, the frontal and subcortical hub regions (left insula, right superior frontal gyrus, orbital part, left precentral gyrus,) of PD-pRBD do not exist in PD-npRBD, whereas the temporal hubs (bilateral temporal pole: superior temporal gyrus, left middle temporal gyrus) of PD-npRBD do not exist in PD-pRBD. Noticeably, these different hub regions were mainly located in the frontotemporal paralimbic system. Some earlier PET and fMRI studies have described a relative activation in limbic and paralimbic structures during REM sleep in comparison to NREM sleep and wakefulness (Braun et al. 1998; Nofzinger et al. 2002). Recently, a PET imaging study (Valli et al. 2021) suggested that the extra-striatal dopamine regions containing the prefrontal, temporal, and limbic regions are probably playing roles in the symptom progression of PD individuals with RBD. It was reported that compared with HC, PD-pRBD patients had lower availability of D2 receptors in these regions. Also, the study of Kotagal et al. (Kotagal et al. 2012) showed that compared with PD patients without RBD symptoms, subjects with

RBD symptoms exhibited decreased cholinergic innervation in the neocortical, limbic and thalamic cortex. In addition to molecular level, there are also some radiographic evidences that the paralimbic cortex may play a vital role in PD-pRBD. An MRI structure study of PD with RBD showed that, in comparison to the control group, inferior temporal cortex, supra-frontal bilaterally, and left rostral middle frontal cortices were extensively atrophied in PD patients, which suggested that RBD symptoms of PD patients appeared with significant paralimbic/limbic cortical changes(Pereira et al. 2019). In accordance with the previous studies, our results also revealed that the disruption of WT in the frontotemporal paralimbic regions may be associated with the neuropathological process of PD with RBD.

In this study, we discovered a decrease of rich-club connections in the PD-pRBD compared with PD-npRBD, while no significant differences of feeder connections and local connections were found between the two groups. It probably revealed that the rich-club connections among central hubs, which worked as high-cost and high-capacity backbone of global brain communication(Power et al. 2013; van den Heuvel et al. 2012), had higher tendency to be impaired in PD-pRBD patients. Structural networks in primary insomnia DTI studies have suggested that abnormal rich club connections, mainly in the limbic cortices and basal ganglia circuit network, were associated with primary insomnia severity(Wu et al. 2020). However, rich club organization in PD-pRBD has not been reported previously. In addition, Our results suggest an increase in rich club connections in PD-pRBD compared with HC,which may also be explained by a similar compensatory mechanism in early PD. Certainly, larger and longitudinal data would be required to verify this interpretation.

In the present study, positive correlation between RBDSQ scores and Nlp of ORBsup.R were detected in PD-pRBD. Nlp was an estimate parameter of transport and communication from one node to all other nodes. The orbitofrontal gyrus was part of the paralimbic system and a vital center for the processions of visual, spatial and emotional information. Three main connections of the orbitofrontal cortex were identified(Burks et al. 2018): one bundle to the thalamus and anterior cingulate gyrus, below the caudate nucleus, medial to the vertical fibers projected by the thalamus; One bundle to the brainstem, extending laterally to the caudate and medially to the internal capsule; And radiations to the parietal and occipital lobes, moving along with the inferior fronto-occipital fasciculus. A PET study(Bedard et al. 2019) showed that, in comparison to the healthy participants, significantly higher 18F-fluoroethoxybenzovesamicol uptakes were observed in patients with iRBD in orbitofrontal cortex. These findings suggested that white matter (WM) damages in the orbitofrontal domain linked to other brain regions might be involved in the pathophysiological process of PD-pRBD.

The study also had several limitations. First, we grouped PD using RBDSQ scores rather than polysomnography, which is the standard for diagnosis and quantitative description of RBD. However, RBDSQ score has high sensitivity and specificity for identifying RBD(Stiasny-Kolster et al. 2007). Second, a cross-sectional study with patients in the early stage of disease was conducted, which should be included in a longitudinal follow-up study thereafter to further explain the pathogenesis of PD-RBD. Third, we adopted the deterministic fiber tracking method to estimate the structural connectivity between regions, and the intersecting directions of multiple optical fibers cannot be determined. Therefore, in order to accurately measure the fiber trajectory, probabilistic tractography algorithm and diffusion spectral imaging technology will be used to solve these problems in the future. Fourth, other non-motor features may affect brain network structure were not considered, which should be taken into consideration as control variables in the future.

Conclusion

Taken as a whole, our study indicated the impaired global properties of network and diminished rich-club connections in PD-pRBD patients. Furthermore, we noticed that the white matter changes in frontotemporal hubs which mainly belong to the paralimbic regions are probably playing vital roles in the presence of PD-pRBD. Further longitudinal researches are required to check how and whether changes in white matter connectivity, including the exploration of the rich club properties, are associated with clinical progress in PD-pRBD individuals.

Declarations

Ethical approval The research was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to Participate The research was agreed to participate.

Consent to Publish The paper was agreed to be published.

Authors Contributions Amei Chen, Yuting Li, Zhaoxiu Wang, Xinhua Wei had made a substantial contribution to the conception and drafting and revising the article; Xiaofang Cheng, Ting Wang acquired the data; Dan Liang, Dandan Chen had made a substantial contribution to the analysis and interpretation of the data. All of the authors gave final approval of the version to be published.

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Competing Interests No conflicts of interest to declare.

Availability of data and materials The data and materials were available.

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Figures

Figure 1

One-way ANCOVA of global parameters among the three groups. Significant differences of global parameters of the structural network were detected among the three groups, performed by one-way ANCOVA, adjusting for age, gender and education years. $p < 0.05$ was set significant. Afterwards, two-sample t-test was employed to explore further differences. **Post hoc tests were corrected by Bonferroni correction with a significant different $p < 0.017$ ($0.05/3$). Eg: global efficiency; Lp: shortest path length; σ : small-world index.

Figure 2

The normalized rich club coefficient $\phi^w_{\text{norm}}(k)$ curves of the three groups were > 1 at the level of $k=1-15$ ($p < 0.05$, Bonferroni corrected). Different colored curves represent different groups of $\phi^w_{\text{norm}}(k)$. Black: HC; blue: PD-npRBD; red: D-pRBD. No significant difference in rich club organization was found among the three groups.

Figure 3

(a)-(c) Distribution of hub regions in HC, PD-npRBD and PD-pRBD groups. The first 10% degree nodes of each group were defined as hub regions using BrainNet View (NKLCNL, Beijing Normal University) for visualization. (d)-(f) Differences of hubs in the HC, PD-npRBD, PD-pRBD. Different colors represent the classification of functional areas of brain. Red: primary, purple: association, blue: paralimbic, yellow: subcortical. The size of the node reflects the value of the degree. The node abbreviations are shown in Table 3. L left hemisphere, R right hemisphere.

Figure 4

Comparison of group-averaged rich-club organization between HC, PD-npRBD and PD-pRBD groups. Edges across individual brain networks were divided into three distinct classes: rich club connections, feeder connections and local connections. Significant difference was shown in rich-club connections between HC, PD-npRBD and PD-pRBD groups, while no significant group effect was found in feeder connections and the local connections.

Figure 5

Correlation between significant topology properties and severity of RBD in PD-PRBD group. A positive correlation between Nlp of ORBsup.R and RBDSQ scores was found in PD-PRBD patients. $p < 0.05$ was set significant. The association was explored by multiple linear regression. $p < 0.05$ was set significant.

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