Normalization effect of levodopa on hierarchical brain function in Parkinson’s disease

Short title: Levodopa-induced brain normalization of PD

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Abstract

Hierarchical brain organization, in which rich-club and diverse-club situates in core position, is critical for global information integration in human brain network. Parkinson’s disease (PD), a common movement disorder, has been conceptualized as a network disorder. Levodopa is an effective treatment for PD. Whether a functional divergence between hierarchical brain system under PD pathology, and how this divergence is regulated by immediate levodopa therapy, remains unknown. We constructed functional network in 61 PD patients and 89 normal controls, and graph theoretical analyses were applied to examine the neural mechanism of levodopa short response from the perspective of brain hierarchical configuration. The results revealed that: (1) PD patients exhibited disrupted function within rich-club organization, while the diverse-club remained preserved function, indicating a differentiated brain topology organization in PD; (2) along the rich-club derivate hierarchical system, PD patients showed impaired network properties within rich-club and feeder subnetwork, and decreased nodal degree centrality in rich-club and feeder nodes, along with increased nodal degree in peripheral nodes, suggesting the distinct functional patterns in different types of nodes; and (3) levodopa could normalize the abnormal network architecture of rich-club system. This study provides evidence for levodopa effects on hierarchical brain system with divergent function.
Author Summary

Many studies of brain network have revealed densely connected regions forming the rich-club and diverse-club, which occupy the central position of the hierarchical brain system. Here, we explore the hierarchical topology in Parkinson’s disease (PD) and investigate the neural effect of levodopa on it. We show that within the core position of hierarchical system, the function of diverse-club is preserved while the function of rich-club is impaired. Along the rich-club hierarchical system, the function of biologically costly rich-club and feeder subnetwork is disrupted, together with an increased function of peripheral nodes which could be normalized by levodopa. Our study provides the evidence of a disparity pattern between different levels of brain hierarchical system under PD pathology.
Introduction

Parkinson’s disease (PD) is a common neurodegenerative disorder characterized by hypo-dopaminergic neurotransmission within the nigrostriatal dopamine pathway (Braak et al., 2003; Lees, Hardy, & Revesz, 2009), leading to classic motor deficits (Kalia & Lang, 2015). Clinically, levodopa has become the most effective and widespread treatment for controlling PD symptoms (Cotzias, Van Woert, & Schiffer, 1967; Hauser, 2009). In recent years, network neuroscience approaches pointed that PD is a network-disconnection syndrome (Cronin-Golomb, 2010), and the network dysfunction could be represented by the functional abnormalities coupling various brain regions (Luo et al., 2015; Suo et al., 2017). And some preliminary exploration had demonstrated the normalization effect of dopaminergic drugs on PD functional brain architecture (Ballarini et al., 2018; Berman et al., 2016). However, brain function is not solely attributable to the properties of individual regions but rather emerges from the network organization of the brain as a whole (Sporns, 2011). Specifically, the human brain is a hierarchical system, in which different levels of brain region jointly preserve the overall brain function, but without much knowledge currently available. Therefore, although the dysfunction in PD connectome and the normalization effect of dopaminergic therapy on PD overall network measures have been indicated, whether there is a functional divergence between different levels of brain connectome under PD pathology, and how this divergence is regulated by immediate levodopa therapy, remains unknown.
To elucidate these questions, the first step was to characterize the brain hierarchical system. Network neuroscience revealed that there are a number of highly connected regions situated in the core position of brain network (Hagmann et al., 2008). As indexed by a high degree centrality or high participation, these brain regions play a central role in the overall network organization and have been identified as “brain hubs” (Sporns, Honey, & Kotter, 2007). Previous studies have demonstrated that some of these “brain hub” regions could generate a rich-club organization, in which these regions tend to be more densely connected among themselves than regions with a lower degree (van den Heuvel & Sporns, 2011). The rich-club is functionally valuable for global neural signaling and interregional brain communication, and providing information about network’s hierarchical ordering (van den Heuvel, Kahn, Goni, & Sporns, 2012). Meanwhile, a group of brain regions with a high participation coefficient showing diverse connectivity are also strongly inter-connected, forming the diverse-club, which allows for integrating information and coordinating connectivity between communities, enabling for the local modular processing (Bertolero, Yeo, & D’Esposito, 2017). Based on these highly functionally connected organizations, hierarchical brain system is depicted, which may contribute to the investigation of functional divergence of different brain levels in PD.

Next is how to transform these theories to practice. Neuroimaging analyses provide a powerful approach to map the brain network in vivo (Rubinov & Sporns, 2010). By employing the resting-state functional magnetic resonance imaging (rs-
fMRI), we could construct large-scale functional network, wherein brain regions serve as nodes and the interregional functional connectivity represents edges. Combining the graph theory approaches, researchers have successfully addressed the hierarchical brain system in several disease status (R. Li et al., 2016; Stellmann et al., 2017; Verhelst, Vander Linden, De Pauw, Vingerhoets, & Caeyenberghs, 2018). This hierarchical brain model provides an avenue to investigate the functional divergence of different levels in PD brain connectome, and by integrating with the immediate dopaminergic therapy, we could explore the neural effect of acute dopaminergic administration on various brain subsystems.

This study aimed to illustrate the neural mechanism of levodopa short response from the perspective of the brain hierarchical configuration. We hypothesized that PD patients would exhibit a disparity pattern between different levels of brain hierarchical system, and immediate levodopa supplementation would exert a flexible modulation effect on them.

**Materials and Methods**

**Participants**

All PD patients and normal controls signed informed consent forms in accordance with the approval of the Medical Ethic Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine.

A total of 61 PD patients and 89 normal controls were included in this study. The
diagnosis of PD was made by an experienced neurologist (B. Z.) according to UK Parkinson’s Disease Society Brain Bank criteria (Hughes, Daniel, Kilford, & Lees, 1992). Normal controls and PD patients with a history of other neurologic or psychiatric disorders, brain trauma, or general exclusion criteria for MRI scanning were excluded from this study. Demographic information, including age, sex, and education, was obtained from each participant. The neurologic assessments, including disease duration, Unified Parkinson's disease Rating Scale (UPDRS), and Hoehn-Yahr stage, were recorded from all PD patients in practically defined OFF-medication condition (>12 h after last dopaminergic medication). Additionally, motor symptoms were re-evaluated in an ON-medication condition defined as one hour following anti-parkinsonian treatment (one tablet of immediate release benserazide/levodopa 50/200 mg) immediately after initial clinical assessment and MRI scanning.

**MRI data acquisition and processing**

All participants were scanned on a 3.0 T MRI scanner (GE Health, Discovery 750) equipped with an 8-channel head coil. During MRI scanning, the head was stabilized using resting foam pads, and earplugs were provided to reduce the noise. Structural T1-weighted images were acquired using a fast spoiled gradient recalled sequence: repetition time (TR) = 7.336 ms; echo time (TE) = 3.036 ms; inversion time = 450 ms; flip angle (FA) = 11°; field of view (FOV) = 260 × 260 mm²; matrix = 256 × 256; slice thickness = 1.2 mm; 196 continuous sagittal slices. Rs-fMRI images were acquired
using a gradient recalled echo-echo planar imaging sequence: TR = 2000 ms; TE = 30 ms; FA = 77°; FOV = 240 × 240 mm²; matrix = 64 × 64; slice thickness = 4 mm; slice gap = 0 mm; 38 interleaved axial slices. After completing an initial rs-fMRI scanning session in the OFF-medications condition, PD patients were advised to uptake one tablet of benserazide/levodopa and re-scanned one hour afterward.

The rs-fMRI data processing was performed using fMRIPrep v1.5.9 (https://fmriprep.org/en/1.5.9/) (Esteban et al., 2019) with the default processing steps.

To summarize: each T1-weighted image was corrected for intensity non-uniformity and skull-stripped. Brain surfaces were reconstructed using recon-all from FreeSurfer software. Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c was performed through nonlinear registration, using brain-extracted versions of both the T1-weighted images and template. Brain tissue segmentation of cerebrospinal fluid, white matter and gray matter was performed on the brain-extracted T1-weighted images. Functional data was corrected for slice-timing, motion, and field distortion. This was followed by co-registration to the corresponding T1-weighted images using boundary-based registration with 9 degrees of freedom. All processed rs-fMRI data was denoised by fMRIDenoise (https://github.com/compneuro-ncu/fmridenoise) with the “24HMP8PhysSpikeReg” pipeline, including temporal bandpass filtering (0.008-0.08 Hz), detrending, and confound regression. The confound regression employed 24 head motion parameters (3 translations, 3 rotations, their temporal derivatives, and their quadratic term), 8 physiological noise parameters (mean
signals from white matter signal and cerebrospinal fluid, their temporal derivatives, and quadratic terms, and spike regressors based on framewise displacement (FD) and DVARS thresholds. After which, all functional data was resampled to 3mm isotropic and smoothed with a 5 mm FWHM Gaussian kernel, masked by gray matter.

**Network construction**

The functional network was constructed as in a previous study (Guan et al., 2019), where nodes represented brain regions and edges represented interregional functional connectivity between every pair of nodes. The anatomical automatic labeling (AAL) atlas with 90 regions of interest was used to generate network nodes. The mean time course of each node was extracted, and interregional resting-state functional connectivity was calculated based on the Pearson correlation between the time courses of each pair of nodes. To implement graph analyses relevant to functional network, negative correlations were omitted, and networks were thresholded at a connection sparsity that showing the best discrimination ability of PD patients and normal controls (see next section).

**Defining the connection sparsity for network analyses**

Since the human brain network shows the characteristic of sparsity, each functional network was thresholded by applying a set of sparsity from 0.1 to 0.5 with an interval of 0.02. We used network density to refer sparsity, which is defined as the ratio of the number of connections existing in the network to the maximum possible number of
connections (Liao, Vasilakos, & He, 2017). To implement the graph analyses in a specific sparse network, we employed support vector machine (SVM) to identify the specific sparsity for functional networks that was mostly discriminative and favorable for PD classification. We used the functional connectivity features of normal controls and PD patients in OFF-medication status to minimize the potential drug effects on the PD classification. To remove the redundant features, the functional connectivity features selected by two-sample t-test with p < 0.05 were applied in the SVM model using LIBSVM (https://www.csie.ntu.edu.tw/~cjlin/libsvm/) with default setting. Specifically, the hyper-parameter C of SVM was set to 1, and radial basis function (RBF) kernel was used. The raw functional connectivity features were scaled individual to range [-1, +1]. Leave-one-out cross-validation (LOOCV) scheme was used to evaluate the performance of the SVM classifier. For each sparsity across the range of 0.1 to 0.5 with an interval of 0.02, the same SVM procedure was performed. The sparsity with the highest accuracy for PD classification was used to perform the network analyses. Statistical significance of the highest classification accuracy was determined by permutation test, which involved repeating the classification procedure 1000 times with a different random permutation of the training group labels (F. Li et al., 2014). Moreover, we also validated the results within the connection sparsity range of 0.1-0.5 with an interval of 0.1. The results were shown in the Supplementary Materials (Table S9, Figure S1-S5).
**Network analyses**

The final functional network was thresholded by applying the sparsity with the best discriminative ability for PD classification. All network analyses were performed using Brain Connectivity Toolbox (BCT, [https://sites.google.com/site/bctnet/](https://sites.google.com/site/bctnet/)).

**Rich-club organization**

A brain network is thought to have a rich-club organization if nodes with a high degree are more densely and strongly interconnected than that would be expected by chance (van den Heuvel & Sporns, 2011). The presence of a rich-club organization was examined by calculating the weighted rich-club coefficient using BCT (Rubinov & Sporns, 2010). The weighted rich-club coefficient $\phi^w(k)$ across a range of degree $k$ of the individual brain network was computed and a detailed description was given in the Supplementary Materials. After the calculation of the weighted rich-club coefficient, the $\phi^w(k)$ was normalized by comparing it to the mean weighted rich-club coefficient of 1000 random networks. By definition, $\phi^w_{\text{norm}}(k) > 1$ for a range of $k$ was indicative of a rich club organization within a network.

**Rich-club nodes and subnetwork analyses**

The rich-club nodes definition was based on normal controls. To define the rich-club nodes, a group-averaged network within normal control group was computed as follows: first, from the set of individual group matrices, only connections that were
present in at least 60% of population of the group were selected for averages, while all other connections were set to 0. Then, the group-averaged matrix was computed by averaging only across the non-zero values of the individual subject matrices (R. Li et al., 2016). Based on the functional group-averaged network of normal controls, the rich-club regions were defined as the top 15% (n = 13) brain regions with the highest degree (R. Li et al., 2016; Yan et al., 2018).

Identification of the rich-club regions allowed for the categorization of the whole brain nodes of the connectome into three types: rich-club nodes, top 13 brain regions with the highest degree; feeder nodes, showing the connections with rich-club nodes; peripheral nodes, the remaining nodes except rich-club nodes and feeder nodes. Based on these three types of nodes, we categorized three types of subnetworks: rich-club subnetwork, subgraph with rich-club nodes and the edges linking members of the rich-club nodes; feeder subnetwork, subgraph with feeder nodes and the edges linking members of the feeder nodes; peripheral subnetwork, subgraph with peripheral nodes and the edges linking members of the peripheral nodes. These three types of nodes and the derived subnetworks based on normal controls were applied into PD group both in OFF- and ON-medication status.

The further subnetwork analyses focused on these three types of nodes and subnetworks. First, we evaluated the nodal properties for three types of nodes, which was defined by the sum of degree centrality of all nodes belonging to a specific node category. Then, we assessed the intra-subnetwork properties for each type of
subnetwork, including (1) network-based statistic (NBS, https://www.nitrc.org/projects/nbs/) analysis to identify the subnetwork difference between groups; (2) computation of the subnetwork connection strength, which was defined by the sum of all the weights of the connections within each type of subnetwork, respectively; (3) calculation of the global efficiency for each type of subnetwork. Finally, we further analyzed the inter-subnetwork interactions, including (1) interactions between rich-club subnetwork and feeder subnetwork, which were defined by the sum of all the weights of the connections linking the rich-club nodes and feeder nodes; (2) interactions between feeder subnetwork and peripheral subnetwork, which were defined by the sum of all the weights of the connections linking the feeder nodes and peripheral nodes.

**Diverse-club nodes and subnetwork analyses**

Except the rich-club organization, there is another set of nodes, which have edges diversely distributed across the network communities, forming a diverse-club in the human brain networks (Bertolero et al., 2017). The participation coefficient is an indicator of the diversity of each node’s connections across the network’s communities, where nodes with a high participation coefficient exhibit diverse connectivity and form the diverse-club. Similar to the rich-club nodes definition, the diverse-club regions were generated based on normal control groups. We firstly detected the community structure based on the group-averaged network. Then, based on the community structure, we
calculated the participation coefficient of each node. Similarly, we referred the high participation coefficient nodes (top 15%) as the diverse-club regions. The diverse-club nodes and the interconnections linking the member of diverse-club nodes comprised the diverse-club subnetwork, which were applied into PD groups. We calculated the connection strength and global efficient of this diverse-club subnetwork.

**Statistical analyses**

Statistical analyses of demographic and clinical data were performed using SPSS 19.0 statistical software. The one-sample Kolmogorov-Smirnov test was used to check the data normality. Differences in the age, sex distribution, and education between groups were compared with the unpaired t-tests, the Mann-Whitney U tests, and Pearson chi-squared test as appropriate. Wilcoxon signed-rank test was used to compare the difference of UPDRS motor scores between OFF-medication condition and ON-medication condition. Statistical significance was set at $p < 0.05$.

To check if a rich-club organization was present in the groups, one sample t-test was performed at each level of $k$ to examine whether the normalized rich-club coefficient $\phi^w_{\text{norm}}(k)$ statistically exceeded 1 in each group separately. False Discovery Rate (FDR) correction was applied to correct for multiple comparison across all examined levels of $k$. To determine the significance levels of altered connectivity networks in NBS analysis, a general linear model controlling age and sex as covariates at each edge independently was employed to test for group differences in subnetwork
connectivity. A threshold ($p = 0.05$) was used to form a set of suprathreshold edges (connections) among which any connected components and their size (number of edges) could be determined. The statistical significance of the size of each observed component was assessed with respect to an empirical null distribution of maximal component sizes obtained under the null hypothesis of random group membership (5000 permutations). Significant components in each subnetwork were determined at $p < 0.05$.

Group differences either in rich-club coefficient or other network properties between PD patients and normal controls were assessed using the permutation test (with 10000 permutations) with age and sex as covariates. Paired t-test or Wilcoxon signed-rank test was used appropriately to compare the network differences between patients in OFF-medication and ON-medication. Tests were two-tailed with a significance level of $p < 0.05$ and FDR correction (with $q < 0.05$) was applied to correct for multiple comparisons. Finally, the relationships between subnetwork properties or the clinical scores were examined via partial correlation analyses, taking age and sex into account.

Specifically, the relationships between subnetwork properties and motor symptoms in OFF- and ON-medication status, as well as the relationships between subnetwork changes and motor symptom improvement, were examined. Statistical significance was set at $p < 0.00185$ (Bonferroni corrected, 3 subnetworks $\times$ 3 properties $\times$ 3 kinds of relationship, 27 correlations in total, $p < 0.05/27 = 0.00185$). Regarding the relationships between network properties, statistical significance was set at $p < 0.0125$.
(Bonferroni corrected, 4 correlations in total: correlations between peripheral nodes degree and rich-club/feeder nodes degree in OFF-medication status, and correlations between peripheral nodes degree change rate and rich-club/feeder nodes degree improvement rate after levodopa administration).

In order to assess whether the results could be explained by motion, we additionally conducted permutation test with age, sex, and mean FD as covariates. Further, correlation analyses between motion parameters and network metrics both in normal control group and patients either in OFF or ON status were performed. Results were shown in Supplementary materials (Table S4, Table S5). The comparison results with mean FD as covariates between groups were similar with the main results, and further, there was no correlations between motion parameters and network metrics both in control group and PD patients either in OFF or ON status (FDR corrected), indicating that the network alterations were not explained by motion.

**Atlas-based validation on hierarchical topology**

Functional brain network is constructed by defining the synchronization of rs-fMRI signals between predefined brain regions, which could be potentially affected by the different brain parcellation (atlas) employed in the computations. To minimize the potential influence of brain atlas selection, we recruited a newly constructed brain atlas (200 parcellations) that was derived from rs-fMRI data and was in good agreement with certain architectonic and visuotopic boundaries.
Based on Schaefer et al., (2018) to validate our results. Based on this atlas, we replicated the same procedures to define different levels of brain hierarchical system and explored the neural substrate of immediate levodopa effect from the view of brain hierarchical configuration.

**Results**

**Demographic and clinical characteristics**

Demographic and clinical features of PD patients and normal controls were shown in Table 1. Age, sex distribution, or education was not significantly different between PD patients and normal controls. After levodopa administration, motor symptoms were significantly relieved in PD patients (p < 0.001).

**Table 1** demographic and clinical information

|                          | Normal controls | Parkinson's disease patients | p value |
|--------------------------|-----------------|------------------------------|---------|
| Age, mean (SD)           | 60.6 (7.0)      | 60.9 (8.8)                   | 0.805\textsuperscript{a} |
| Sex (M/F)                | 42/47           | 35/26                        | 0.220\textsuperscript{b} |
| Education, mean (SD)     | 8.5 (3.3)       | 8.1 (4.6)                    | 0.504\textsuperscript{c} |
| Disease duration, mean (SD) | -              | 4.7 (3.6)                   | -       |
| UPDRS-III (OFF/ON), mean (SD) | -              | 23.6 (15.0)/15.4 (12.5)     | < 0.001\textsuperscript{d} |
| Hoehn-Yahr stage, median (range) | -              | 2.5 (1-5)                   | -       |

\textsuperscript{a} Unpaired t-tests; \textsuperscript{b} Pearson chi-squared test; \textsuperscript{c} Mann-Whitney U tests; \textsuperscript{d} Wilcoxon signed-rank test.

**Connection sparsity for network analyses**

The final functional networks were thresholded at the sparsity of 0.2, in which the
discriminative ability for PD classification reached the highest accuracy of 88.7% (Table 2) and with highly significant at p = 0.001. Thus, all the following network analyses were performed based on the network sparsity of 0.2.

| Sparsity | Accuracy (%) | Sparsity | Accuracy (%) | Sparsity | Accuracy (%) |
|----------|--------------|----------|--------------|----------|--------------|
| 0.10     | 88           | 0.24     | 86           | 0.38     | 80           |
| 0.12     | 88           | 0.26     | 85.3         | 0.40     | 79.3         |
| 0.14     | 86.7         | 0.28     | 85.3         | 0.42     | 78           |
| 0.16     | 86           | 0.30     | 85.3         | 0.44     | 78.7         |
| 0.18     | 85.3         | 0.32     | 84.7         | 0.46     | 76           |
| 0.20     | 88.7         | 0.34     | 83.3         | 0.48     | 78           |
| 0.22     | 86.7         | 0.36     | 82           | 0.50     | 78           |

Rich-club organization

Figure 1 depicts the averaged rich-club coefficients and normalized rich-club coefficients for both groups. In the whole-brain network, rich-club coefficient was significantly lower in PD patients than normal controls in the range k = 12-15 (FDR corrected); after the levodopa administration, rich-club coefficient showed no difference between PD patients and normal controls. Compared with OFF-medication condition, patients in ON-medication condition showed increased rich-club coefficient in the range k = 13-15 (p < 0.05, uncorrected) (Figure 1A). Normalized rich-club coefficient increases as a function of degree (k) higher than 1 both in normal controls and PD patients in OFF- and ON-medication condition (Figure 1B), indicating a rich-club organization of the functional network in both groups. Comparisons of the normalized rich-club coefficient showed that PD patients either in OFF-medication
condition or ON-medication condition exhibited higher normalized rich-club coefficient than normal controls in a range $k$ ($k = 13-25$ for OFF-medication condition, $k = 10-23$ for ON-medication condition, FDR corrected). No difference was observed for normalized rich-club coefficient in PD patients between OFF-medication and ON-medication conditions.

**Figure 1** Rich-club organization of functional connectome. Group-averaged rich-club curve of weighted rich-club coefficient (A) and normalized weighted rich-club coefficient (B) for NC (red), PD-off (blue), and PD-on (yellow). The dash box indicates the differences between NC and PD patients (blue for PD-off, yellow for PD-on) after the FDR correction. * indicate the difference between PD-off and PD-on with $p < 0.05$. (C) Red nodes represent the functional rich-club regions. This figure is based on the functional group-averaged network in controls. The size of the red nodes indicates the degree centrality. (D) A simplified example of the three types of nodes: rich-club nodes (black nodes), feeder nodes (gray nodes), and peripheral nodes (light gray nodes).
types of nodes could form three classes of subnetworks. Dash lines indicate the
subnetwork interaction (dark blue represents the interactions between rich-club
subnetwork and feeder subnetwork; wathet blue shows the interactions between feeder
subnetwork and peripheral subnetwork). Abbreviation: NC, normal controls; PD-off,
PD patients in OFF-medication condition; PD-on, PD patients in ON-medication
condition; ORBinf.L, left orbital part of inferior frontal gyrus; PreCG.L, left precentral
gyrus; SMG.L, left supramarginal gyrus; SPG.L, left superior parietal gyrus; LING.L,
left lingual gyrus; MOG.L, left middle occipital gyrus; SOG.L, left superior occipital
gyrus; SMA.R, right supplementary motor area; ROL.R, right Rolandoic operculum;
FFG.R, right fusiform; SPG.R, right superior parietal gyrus; LING.R, right lingual
gyrus; SOG.R, right superior occipital gyrus; subnetwork Interaction-RF, interactions
between rich-club subnetwork and feeder subnetwork; subnetwork Interaction-FP,
interactions between feeder subnetwork and peripheral subnetwork.

Rich-club nodes

The rich-club nodes, selected on the basis of the group-averaged network, ranking
top 15% highest degree, included the following regions: left precentral gyrus, left
orbital part of inferior frontal gyrus, right Rolandoic operculum, right supplementary
motor area, bilateral lingual gyrus, bilateral superior occipital gyrus, left middle
occipital gyrus, right fusiform, bilateral superior parietal gyrus, and left supramarginal
gyrus (Figure 1C, red nodes).
Intra-subnetwork analyses

The results of Intra-subnetwork analyses were shown in Figure 2 and Table S1. First, in the comparison between normal controls and PD patients in OFF-medication condition, NBS analysis revealed a component showing significantly lower functional connectivity in PD patients in rich-club subnetwork (p = 0.008) and feeder subnetwork (p = 0.0002), respectively (Figure 2-column 1). Analyses of the intra-subnetwork connection strength showed that in OFF-medication condition, PD patients exhibited decreased functional connectivity strength in rich-club subnetwork (p = 0.0019) and feeder subnetwork (p < 0.001) when comparing with normal controls. There was no difference of connection strength in peripheral subnetwork between PD patients in OFF-medication condition and normal controls (p = 0.1205). After levodopa administration, there was no difference of connection strength between PD patients and normal controls both in three types of subnetwork (p = 0.1326, 0.0526, and 0.1390 for rich-club subnetwork, feeder subnetwork, and peripheral subnetwork, respectively). Compared with OFF-medication condition, PD patients in ON-medication condition showed increased connection strength in feeder subnetwork (p = 0.009) and decreased connection strength in peripheral subnetwork (p = 0.0383) (Figure 2-column 2, Table S1). These results indicated that levodopa administration could improve the disrupted functional connection strength in rich-club subnetwork and feeder subnetwork.

Regarding the global efficiency of subnetwork, compared with normal controls, PD patients in OFF-medication condition showed decreased global efficiency in rich-
club subnetwork and feeder subnetwork (both p < 0.001); PD patients in ON-medication condition showed decreased global efficiency in feeder subnetwork (p = 0.0061). Compared with OFF-medication condition, PD patients in ON-medication condition exhibited increased global efficiency in feeder subnetwork (p = 0.0203). No difference for global efficiency in peripheral subnetwork was observed between normal controls and PD patients either in OFF-medication condition or ON-medication condition (p = 0.48 and 0.0531, respectively) (Figure 2-column 3, Table S1). Similarly, levodopa administration relieved the damaged efficiency in rich-club subnetwork and feeder subnetwork.

**Figure 2** Comparisons of network properties for rich-club subnetwork (A), feeder subnetwork (B), and peripheral subnetwork (C). The blue nodes represent three types of nodes identified in this study. The edges concatenating nodes in (A) and (B) indicate
a significant component detected by network-based statistic (NBS) analysis in rich-club subnetwork and feeder subnetwork, respectively. ** indicate the differences corrected by FDR correction, * indicated the uncorrected differences with p < 0.05.

**Nodal property analyses**

For the analyses of nodal property, compared with normal controls, we found that PD patients in OFF-medication condition showed decreased nodal degree centrality in rich-club nodes and feeder nodes (p = 0.0075 and 0.0029, respectively), and increased degree centrality in peripheral nodes (p < 0.001); no difference was observed between patients in ON-medication condition and normal controls both in three types of nodes (p = 0.4188, 0.3745, and 0.3840 for rich-club nodes, feeder nodes, and peripheral nodes, respectively). Compared with OFF-medication condition, patients in ON-medication condition showed increased nodal degree centrality in rich-club nodes and feeder nodes (p = 0.0209 and 0.0257, respectively), which suggested a corrected effect of levodopa on rich-club nodes and feeder nodes; intriguingly, the degree centrality in peripheral nodes was decreased (p = 0.0130), which suggested a potentially compensatory effect of peripheral nodes on PD pathology (Figure 2-column 4, Table S1).

**Inter-subnetwork interaction**

We analyzed the interactions between subnetworks. We found that compared with normal controls, the interactions between rich-club subnetwork and feeder subnetwork
was decreased in PD patients in OFF-medication condition (p < 0.001), while PD patients in ON-medication condition and normal controls showed no difference in these interactions (p = 0.1687); directly compared with PD patients in OFF-medication condition, patients in ON-medication condition exhibited increased interactions between rich-club and feeder subnetwork (p = 0.0202) (Figure 3A, Table S2). For the interactions between feeder subnetwork and peripheral subnetwork, there was no difference between normal controls and patients either in OFF-medication condition or ON-medication condition (p = 0.3018 and 0.0893, respectively) (Figure 3B, Table S2).

Figure 3 Comparisons of subnetwork interaction between rich-club subnetwork and feeder subnetwork (A), and between feeder subnetwork and peripheral subnetwork (B). ** indicate the differences corrected by FDR correction.

Relationships among network properties and clinical scores

We did not find any relationships between subnetwork properties and motor symptom scores in PD patients either in OFF-medication condition or ON-medication condition, and there was no correlation between network changes and motor symptom improvements (Table S8). Interestingly, we found that, in OFF-medication condition,
the degree centrality of peripheral nodes was negatively correlated with degree centrality both of rich-club nodes and feeder nodes ($r = -0.840, p < 0.001$ and $r = -0.841, p < 0.001$, respectively, Figure 4A, B). After the levodopa administration, the change rate of degree in peripheral nodes (computed as $(\text{degree}_{\text{OFF}} - \text{degree}_{\text{ON}})/\text{degree}_{\text{OFF}}$) was positively correlated with the improvement rate of the degree both in rich-club nodes and feeder nodes (computed as $(\text{degree}_{\text{ON}} - \text{degree}_{\text{OFF}})/\text{degree}_{\text{OFF}}$) ($r = 0.821, p < 0.001$ and $r = 0.893, p < 0.001$, respectively, Figure 4C, D). These relationships between nodal degree centrality suggested that the peripheral nodes may serve as a positive role to compensate the disrupted function of core nodes (including rich-club nodes and feeder nodes).

**Figure 4** Correlations between network properties. Negative correlations between peripheral nodes degree and rich-club nodes degree (A) or feeder nodes degree (B) in OFF-medication condition. Positive correlations between the change rate of peripheral...
nodes degree and the improvement rate of rich-club nodes degree (C) and feeder nodes degree (D).

3 Diverse-club analyses

The diverse-club nodes, selected by the top 15% highest participation coefficient based on the group-averaged network, including the following regions: bilateral middle frontal gyrus, left opercular part of inferior frontal gyrus, left triangular part of inferior frontal gyrus, bilateral orbital part of inferior frontal gyrus, bilateral middle cingulum, right superior parietal gyrus, left inferior gyrus, bilateral supramarginal gyrus, and right angular (Figure 5A, red nodes).

Figure 5 Comparisons of diverse-club properties among groups. (A) Red nodes represent diverse-club regions in brain. (B) Connection strength and (C) global efficiency difference within diverse-club subnetwork were compared among groups.

Analyzing the connection strength and the global efficiency within the diverse club subnetwork, we found there was no difference between normal controls and PD patients either in OFF-medication condition or ON-medication condition (Figure 5B, C, Table S3), indicating a relatively reserved function of diverse-club in PD patients.
Robustness of normalization effect of levodopa on hierarchical brain organization in PD

We used the same network analysis procedures by employing another atlas to validate the main findings. First, both normal controls and PD patients in OFF- and ON-medication status showed a rich-club organization in their functional network, as the normalized rich-club coefficient higher than 1 across a range of degree (Figure S6). Second, we analyzed hierarchical brain organization along the rich-club core structure as previous procedures. We observed impaired function within rich-club and feeder subnetwork in PD patients with OFF-medication status, represented by decreased connection strength and global efficiency, as well as decreased nodal degree within rich-club and feeder subnetworks. Whereas, for peripheral subnetwork, PD patients in OFF-medication status showed increased connection strength and nodal degree. After levodopa administration, these abnormal network properties tend to reach a relatively normal state (Table S11). In summary, by recruiting a new brain atlas, we found similar hierarchical brain topography and levodopa normalize effect as the previous findings, verifying that these results were independent of the specific brain parcellations.

Discussion

In this study, we applied graph theory-based approach to analyze the topology organization of functional connectome in PD patients and the impact of dopaminergic therapy on its functional reorganization. The main findings were as follows: (1) PD
patients in OFF-medication condition showed impaired global network property for rich-club organization, while the diverse-club remained preserved function, indicating a differentiated brain topology organization in PD patients; (2) decreased nodal degree centrality in rich-club nodes and feeder nodes were observed in PD patients in OFF-medication condition, while the peripheral nodal degree showed an increase, suggesting the distinct functional patterns in different types of nodes; and (3) levodopa could exert a normalizing effect on abnormal network architecture of rich-club system.

Differentiated brain topology organization in PD patients

Rich-club organization is a property common to complex networks and is considered to be a basis for efficient global information transfer and complex neurological function in the brain (van den Heuvel et al., 2012; van den Heuvel & Sporns, 2011). In the present study, the functional brain networks of both normal controls and PD patients showed a rich-club organization, which meant that normal controls as well as PD patients both had a subset of highly connected nodes that were more interconnected than that would be expected by chance (van den Heuvel & Sporns, 2011). This finding was consistent with previous research reporting the existence of rich-club organization in PD patients (C. Li et al., 2017). Notwithstanding the presence of a rich-club organization, PD patients showed a significant reduction in rich-club interconnectivity compared with normal controls, which suggested that it was difficult for patients to maintain or repair this core subnetwork comprised by the rich-club nodes.
Previous studies had showed that the high degree nodes had higher blood flow, glucose metabolic rate, and longer connection distance than other nodes (Collin, Sporns, Mandl, & van den Heuvel, 2014; Tomasi, Wang, & Volkow, 2013). Their high topological centrality and high biological cost could make these nodes particularly vulnerable to pathogenic factors (Crossley et al., 2014). This phenomenon was strengthened by studies in different clinical populations, for example, in multiple sclerosis (Stellmann et al., 2017), schizophrenia (van den Heuvel et al., 2013), and epilepsy (R. Li et al., 2016). Our findings of disrupted interconnectivity among rich-club regions in line with the previous evidence and supported the proposal that the high-degree regions are generally more susceptible to the pathology of PD. Additionally, the existence of a rich-club organization has been proposed to underlie important network properties, such as global efficiency (Xu, Zhang, & Small, 2010). The topologically central role of the rich-club may indicate that pathological attack on pivotal regions will have an impact on the network’s global efficiency of information processing (Albert, Jeong, & Barabasi, 2000). Therefore, the reduced global efficiency of rich-club subnetwork suggests that the detected abnormalities may be partly due to impaired rich-club organization.

As opposed to the high connectivity that high degree nodes exhibited, nodes with a high participation coefficient exhibited diverse connectivity. These nodes are also highly interconnected and form a diverse-club (Bertolero et al., 2017). In the present study, in contrast with rich-club, the connection strength and global efficiency of diverse-club showed no disruption in PD, indicating a preserved function of diverse-
The diverse-club is another topology configuration of human brain network showing distinct roles in network communication differing from the rich-club. Specifically, the function of the rich-club may predominately be to maintain stability in the entire network via slow processing, potentially using its high degree to integrate information at slower time scales; while the diverse-club may act on shorter time scales (Bertolero et al., 2017; Gollo, Zalesky, Hutchison, van den Heuvel, & Breakspear, 2015). This different function of rich-club and diverse-club may underlie the observed phenomenon — impaired rich-club while the preserved diverse-club, indicating the topological dysfunction in PD has its intrinsic distinct pattern.

**Distinct functional pattern attributes to different levels of nodes**

Identification of rich-club nodes allows to class the whole-brain nodes into different levels, including rich-club nodes, feeder nodes, and peripheral nodes. Subsequently, the whole brain network could be subdivided into three subnetworks based on nodes classification. In the present study, we observed reduced connection strength and global efficiency within the rich-club and feeder subnetwork, whereas the properties within the peripheral subnetwork were unaffected, which suggested that PD is characterized by selective disruption in central nodes-related brain configuration. As mentioned before, the rich-club subnetwork and to a lesser extent the feeder network are biologically costly, making it harder to maintain or further develop and therefore are more likely to be affected in the pathological condition (Collin et al., 2014; Crossley...
et al., 2014). While the peripheral network might have a lower biological cost and therefore are less vulnerable and less affected in the same pathological burden (Verhelst et al., 2018). Therefore, our results underline the importance of subdividing the brain into subnetworks and uncovering differential effects of PD pathology on the hierarchical brain subnetworks’ properties.

Further, analyses of the nodal property reinforced the proposal of distinct functional pattern for different levels of nodes. A differential pattern of nodal degree centrality was observed in three levels of nodes. In particular, we found that PD patients in OFF-medication showed a decrease of nodal degree in rich-club nodes and feeder nodes together with an increase of nodal degree in peripheral nodes. These results suggested a likely divergence of nodal function in hierarchical network architecture. Since the rich-club nodes and to a lesser extent together with the feeder nodes are more likely to exhibit pathology (Crossley et al., 2014), the reduction of nodal degree in rich-club and feeder nodes may represent the direct pathologic influence. The increased degree centrality in peripheral nodes might reflect an attempt to restore or compensate reduced rich-club and feeder nodes degree. The human brain is an integrative network, brain nodes are working together to maintain the overall function of whole brain. Given that the vulnerability of topology central nodes under the pathologic condition, other nodes with a lower biological cost (e.g., peripheral nodes) may up-regulate their function to balance the overall communication within the whole brain (Crossley et al., 2014; Verhelst et al., 2018). Similar mechanism had been reported in patients with
traumatic brain injury (Verhelst et al., 2018), where the authors found the increased strength was confined to the local subnetwork and may compensate the reduced rich-club connectivity. Interestingly, the inverse associations between reduced degree centrality in rich-club nodes as well as feeder nodes and increased degree centrality in peripheral nodes were observed in the present study. Such relationship further theoretically supported the notion of compensation role of peripheral nodes. Taken together, analyses of nodal property as well as subnetwork property suggested a distinct functional pattern for different levels of nodes: disrupted function in topological central-related nodes accompanied with compensatory effect in topological peripheral nodes.

Since different network sparsity may influence the network analyses, we repeated the same network analyses over a range of network sparsity (0.1:0.1:0.5). As a result, over the range of sparsity thresholds, normalized rich-club coefficients of normal controls and PD patients either in OFF- or ON-medication status were more than 1, indicating the existence of the rich-club organization in both groups. Moreover, the findings of impaired function of rich-club and feeder subnetwork in PD-off status were consistently existing over the range of sparsity thresholds. The changes of peripheral subnetwork in PD patients with OFF-medication status were overall increased (e.g., increased peripheral nodes degree) along the range of sparsity thresholds, indicating a compensation role of peripheral subnetwork. While the specific metric (e.g., global efficiency) of peripheral subnetwork showed a decrement when the network was denser
(corresponding a higher sparsity, e.g., sparsity=0.4/0.5). The human brain network shows the ability to balance the cost and efficiency, the denser network often indicates higher wiring cost, which could result in a decrement of the network efficiency (Liao et al., 2017). In our study, we showed that the core hierarchical structures of the network were consistently impaired along a range of sparsity in PD patients, which was consistent with our main findings and may be resulted from the PD pathology regardless of the network density. Similar, the peripheral subnetwork with lower biological cost exhibited an overall compensation effect under the PD pathology, while the slight variation of the efficiency at higher density reflected the flexibility to dynamic balance the network cost (density) and the network efficiency, which further indicated the less vulnerable of peripheral subnetwork under the same pathological burden.

Levodopa modulates abnormal network architecture

To further investigate the effect of dopaminergic medication on the abnormal brain network, we compared the normal controls and PD patients in ON-medication. The improvement of decreased network properties in rich-club subnetwork and feeder subnetwork were observed after the levodopa administration. Furthermore, the direct comparisons of network properties between OFF- and ON-medication conditions yielded significant increment of network properties mainly in feeder subnetwork. These results implied that levodopa administration could improve the disrupted brain topology.

Previous studies investigated the effect of dopaminergic therapy on brain function
(Esposito et al., 2013; Gao, Zhang, Chan, & Wu, 2017; Zhong et al., 2019), and the results showed that levodopa had a significant impact on restoring the impaired functional connectivity of sensorimotor network, default-mode network, and basal ganglia motor circuit. The findings in this study were consistent with the previous results and indicated the restorative effects of levodopa on brain function. In addition, we found that levodopa could reduce the increased degree centrality of peripheral nodes in OFF-medication condition, making the brain organization reach a relatively normal state. Consistent with us, Berman et al. found that levodopa can reduce the local efficiency of specific subnetwork that showing significant increment in PD-OFF state (Berman et al., 2016), suggesting a normalization effect of levodopa on brain topology. Thus, these findings indicated that levodopa could modulate the abnormal brain architecture: not only can improve the impaired brain function but also could normalize the abnormally increased brain topology properties. Furthermore, a positive correlation between the change rate of peripheral nodes degree and the improvement rate of rich-club (and feeder) nodes degree was observed in this study, which reinforced the speculation of compensation role of peripheral nodes as we discussed above, and also suggested that levodopa could impart a flexible modulation effect on different parts of brain organization, making the whole brain reach a normal state.

Limitations

Several limitations of this study should be acknowledged. One major limitation
was that PD patients only took levodopa while without any placebo, and normal
controls were only scanned one time. Although we ensured all participants were in a
relatively stable state, the time effects may potentially influence the results. Both drug,
placebo, and time effects should be considered in the future studies to optimize the
experimental design. Second, there may be a long duration response for dopaminergic
drugs since we only withdrawing antiparkinsonian drugs at least 12 hours; even though,
this withdrawal time has been widely used to reflect PD-OFF status (Albanese et al.,
2001; Zach et al., 2020). Third, this study was a cross-sectional study including a
moderate sample size; further prospective and longitudinal studies with a larger sample
size are warranted to validate these findings and, importantly, to explore the
longitudinal alterations of the different types of nodes along the disease progression,
which is expected to give an in-depth understanding of the topology organization in PD
patients. Finally, PD patients in this study were under multiple antiparkinsonian
treatment, which may have a potential influence on the investigation of levodopa effect;
future studies including drug naïve PD patients could purify the effect of levodopa and
contribute to explore the levodopa induced brain alteration.

Conclusion

This study revealed differentiated brain organization in PD patients: the function
of rich-club organization was disrupted while the function of diverse-club remained
preserved. Furthermore, a functional divergency existed in PD hierarchical brain system,
characterized by disrupted function in topological central nodes along with the compensatory effect in topological peripheral nodes. Finally, dopaminergic therapy could modulate the brain architecture to make it reach a normal state.

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Author Summary

Many studies of brain network have revealed densely connected regions forming the rich-club and diverse-club, which occupy the central position of the hierarchical brain system. Here, we explore the hierarchical topology in Parkinson’s disease (PD) and investigate the neural effect of levodopa on it. We show that within the core position of hierarchical system, the function of diverse-club is preserved while the function of rich-club is impaired. Along the rich-club hierarchical system, the function of biologically costly rich-club and feeder subnetwork is disrupted, together with an increased function of peripheral nodes which could be normalized by levodopa. Our study provides the evidence of a disparity pattern between different levels of brain hierarchical system under PD pathology.
