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Decreased resting-state functional connectivity and brain network abnormalities in the prefrontal cortex of elderly patients with Parkinson's disease accompanied by depressive symptoms

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Abstract: This study aimed to explore the brain network characteristics in elderly patients with Parkinson's disease (PD) with depressive symptoms. Thirty elderly PD patients with depressive symptoms (PD-D) and 26 matched PD patients without depressive symptoms (PD-NOD) were recruited based on HAMD-24 with a cut-off of 7. The resting-state functional connectivity (RSFC) was conducted by 53-channel functional near-infrared spectroscopy (fNIRS). There were no statistically significant differences in MMSE scores, disease duration, Hoehn-Yahr stage, daily levodopa equivalent dose, and MDS-UPDRS III between the two groups. However, compared to the PD-NOD group, the PD-D group showed significantly higher MDS-UPDRS II, HAMA-14, and HAMD-24. The interhemispheric FC strength and the FC strength between the left dorsolateral prefrontal cortex (DLPFC-L) and the left frontal polar area (FPA-L) was significantly lower in the PD-D group (FDR $p < 0.05$). As for graph theoretic metrics, the PD-D group had significantly lower degree centrality (aDc) and node efficiency (aNe) in the DLPFC-L and the FPA-L (FDR, $p < 0.05$), as well as decreased global efficiency (aEg). Pearson correlation analysis indicated moderate negative correlations between HAMD-24 scores and the interhemispheric FC strength, FC between DLPFC-L and FPA-L, aEg, aDc in FPA-L, aNe in DLPFC-L and FPA-L. In conclusion, PD-D patients show decreased integration and efficiency in their brain networks. Furthermore, RSFC between DLPFC-L and FPA-L regions is negatively correlated with depressive symptoms. These findings propose that targeting DLPFC-L and FPA-L regions *via* non-invasive brain stimulation may be a potential intervention for alleviating depressive symptoms in elderly PD patients.

***Keywords*:** Parkinson's disease, depressive symptoms, functional near-infrared spectroscopy, functional connectivity, prefrontal lobe

Introduction

Parkinson's disease (PD) is a common chronic, progressive, and neurodegenerative disorder, which is common in the middle-aged and elderly groups and characterized by motor dysfunction and various non-motor symptoms. The pathological process of PD primarily involves dopamine deficiency in the substantia nigra striatum and abnormalities in other neurotransmitter systems, such as noradrenergic, serotonergic, and cholinergic systems (*1*). Depressive symptoms represent a common and heterogeneous non-motor manifestation in the prodromal and diagnosed stages of PD, particularly occurring frequently in the early and late phases of PD (*2*). The reported prevalence of depression in PD varies widely (*3*), ranging from 2.7% to over 90% (*4*), because of differences in survey methods, inconsistent diagnostic criteria for depressive symptom, and diverse assessment scales. A systematic review and meta-analysis reported that the subtypes of depressive disorders in PD patients were similar to those with other diseases, including major depressive disorder (MDD) and non-major depressive disorders (mild and persistent depressive disorders). They found a global frequency of depressive disorders of 30.7% and MDD of 14.0% (*5*). Studies suggest that depressive symptoms have a greater impact on patients' quality of life than severe motor symptoms (*6*). Depressive symptoms are associated with increased disability (such as dementia), rapid progression of motor symptoms, and increased

mortality (*7*). Early assessment and intervention for depressive symptoms can prevent patients from sliding into MDD or experiencing relapses after depression treatment, ultimately improving their quality of life. However, the depressive symptoms of PD are often underestimated and inadequately treated in clinical practice, which is partly due to the overlap of some symptoms in PD patients with depressive symptoms (such as psychomotor retardation, reduced facial expression, insomnia, decreased appetite, anhedonia, fatigue) (*8*), the insidious nature of symptoms, lack of active reporting symptoms, cognitive impairment hindering cooperation with examinations, and the absence of objective biomarkers (*9*).

The pathophysiology and etiological mechanisms of depression in PD is multifactorial and complex, primarily associated with underlying neurodegenerative processes, in particular dysfunction in neurotransmitter systems and disturbances of striato-thalamic-prefrontal, cortico-limbic, mediotemporal-limbic networks; other hypothesized mechanisms include neuroinflammation, neuroimmune imbalance, stress hormones, neurotrophic factors, and toxic or metabolic factors (*10*). The advancement of brain imaging technology and the development of graph theory offer possibilities to explore potential mechanisms of PD with depressive symptoms. A wide range of brain regions and networks have been proven involved in the occurrence and development of depression in PD. Still, there is no unified conclusion, and more research is needed to investigate changes in brain anatomical structures and functional networks during the dynamic progression of the disease. Functional near-infrared spectroscopy (fNIRS) is a non-invasive, ecologically valid, and cost-effective neuroimaging technique. The wavelength of near-infrared light ranges from 650 to 950 nm and fNIRS travel several centimeters through the scalp and skull. fNIRS is able to measure changes in cortical oxyhemoglobin (HbO_2) and deoxyhemoglobin concentrations in real time because of the differences in optical properties of brain tissues (*e.g.*, absorption and scattering coefficients) (*11*). While fMRI has been often used in previous studies to measure metabolic activities in the brains of PD patients, fNIRS, with its higher temporal resolution than fMRI, has been widely employed in clinical studies of various chronic neurological and psychiatric disorders (*12*).

Functional connectivity (FC) is essentially an "unmodelled" description of the joint state of multiple brain elements (*e.g.*, neurons, regions) (*13*), providing a time-dependent representation of the activation patterns of anatomically separated brain regions (*14*). Resting-state functional connectivity (RSFC) manifests as slow spontaneous oscillations during quiet rest or sleep (*15*). Compared to task-related data, resting-state data can effectively eliminate individual differences when performing specific tasks. Therefore, this study collected data on the hemodynamic changes in the frontal lobe cortex of elderly Chinese PD patients during the resting state and compared the differences in FC and brain networks between patients with and without depressive symptoms.

Materials and Methods

Subject

In this study, primary PD patients were recruited from October 2022 to June 2023 from outpatients of the Department of Neurology of Xinhua Hospital, Shanghai Jiao Tong University School of Medicine (XH-SJTUSM). The study followed the Declaration of Helsinki and was reviewed and approved by the Ethical Review Committee of XH-SJTUSM (approval no.: XHEC-C-2022-134-1). All patients made their own decision to participate in this study and gave verbal consent after being fully informed of the potential benefits and risks of participating in the study.

Inclusion criteria were as follows: *i*) Chinese residents aged 60 to 80 years, *ii*) met the Chinese diagnostic criteria (2016 version), currently undergoing dopaminergic medication for at least one month with a favorable response, *iii*) without any apparent cognitive impairment (Mini-mental State Examination scale [MMSE] cu-toff values: illiterate > 17, elementary school > 20, junior high school and above > 24), and *iv*) right-handed.

Exclusion criteria included: *i*) history of deep brain stimulation surgery, *ii*) severe mental illness, *iii*) combined with severe diseases affecting the heart, brain, kidneys, *etc.*, and *iv*) suffered from a major negative life event (*e.g.*, bereavement) within one year.

Clinical assessment

All patients were examined in a practically defined "ON" state by healthcare professionals specializing in PD. General Demographic and Disease Information including gender, age, years of education, the onset of motor symptoms, and usage of anti-Parkinsonian medications were collected.

The Hoehn-Yahr (H-Y) stage and Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part II and III scores were used to evaluate the disease severity. H-Y stage is a single-item assessment to evaluate the symptoms and severity of PD, which ranges from 0 (no symptoms) to stage 5 (complete dependence on a wheelchair or bedridden without assistance). MDS-UPDRS II and MDS-UPDRS III consist of 13 and 18 items respectively, and evaluate the impact of motor symptoms on daily life and motor function respectively, with scores ranging from 0 to 4 for each item. Higher scores of MDS-UPDRS indicate more severe motor symptoms in PD patients. The MMSE was a 30-item questionnaire to assess the cognitive function

of each subject based on their cultural background. The Hamilton Anxiety Rating Scale (HAMA-14) was used to assess the anxiety state of each subject. The Hamilton Depression Rating Scale (HAMD-24) was used to evaluate depression severity, and all patients with a score of at least 8 points were considered depressive.

fNIRS signal acquisition of resting state

In a resting state, patients sit on a chair in a quiet, temperature-appropriate room. Patients were asked to stay awake, not to speak, and not to think about anything as much as possible. A 53-channel BS-7000 fNIRS system (Wuhan Znion Technology Co., Wuhan, China) was used to monitor the hemodynamic oxygenation changes in the cerebral cortices. A helmet with 16 light-emitting probes and 16 optical receivers covered the patients' prefrontal and temporal lobes. Distribution of near-infrared sensors followed the international 10-20 system, with the lowest channel positioned at Fp1-Fp2.

The region is divided into the bilateral Pre-Motor and Supplementary Motor Cortex (PreM and SMC) (Channel 1,4,10,40,47,52), Broca's area (Broca) (Channel 2,3,5,7 ,8,13,44,46,49,50,51,53), dorsolateral prefrontal cortex (DLPFC) (Channel 6,11,14,17,18,20,31,32,34,39,42,4 5), frontal eye fields (FEF) (Channel 12,24,26,38) and frontopolar area (FPA) (Channel 9,15,16,19,21,22,23,2 7,30,33,35,36,37,41,43,48) according to the Brodmann areas (BA) (Figure 1). The fNIRS data collection lasted for 6 min for each subject.

Data processing and statistical analysis

Descriptive and analytical statistics were conducted using SPSS 25.0. Statistical descriptions of measurement data were expressed as mean, standard deviation, median, and quartiles; statistical descriptions of count data were expressed as frequency, percentage, rate, and constitutive ratio. Continuous data were analyzed using *t*-tests, and categorical data were analyzed using the χ^2 test to compare differences in FC and brain network topological properties between PD with depressive symptoms (PD-D, HAMD-24 scores ≥ 8) group and PD without depressive symptoms (PD-NOD, HAMD-24 scores ≤ 7) group. Pearson correlation analysis was employed for a two-sided test to examine the correlation between RSFC and self-reported depressive symptoms. Statistical significance was set at $p < 0.05$.

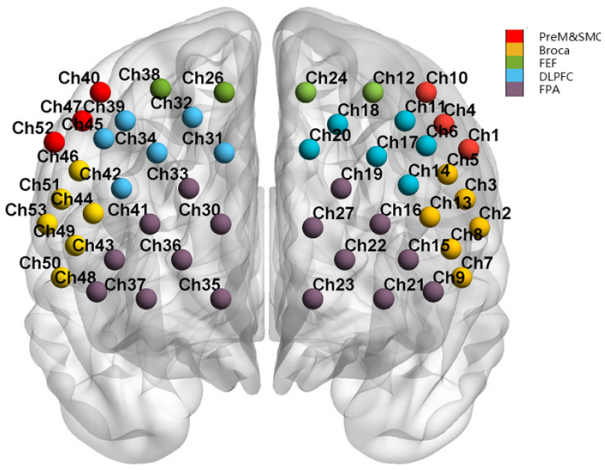

Figure 1. The arrangement of channels of the 53-channel near-infrared spectroscopy system according to Brodmann's map of the cortex. Ch, channel; PreM & SMC, Pre-Motor and Supplementary Motor Cortex; Broca, Broca's area; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; FPA, frontopolar area.

The data processing and statistical analysis for fNIRS in this experiment were primarily conducted in the Matlab (2014b) environment. The brain network analysis of all fNIRS data was performed using the Homer2_UI, NIRS-SPM, and GRETNA2.0 toolkits, and visualized by NIRS_KIT and BrainNet Viewer.

Preprocessing of fNIRS data involved converting raw data into hemoglobin concentration data. The first and last 10 seconds of resting-state data were discarded to obtain stable signals. The raw data were then converted to the .nirs format, and bad channels were removed based on the coefficient of variation value. Homer2 was used for preprocessing, converting raw intensity data to optical density (OD) data. Motion artifacts were identified by using a moving time window with a time window of 0.5 seconds and a standard deviation threshold of 20 for each channel, and were calibrated and removed; and then low-pass filtering (0.1Hz) was used to eliminate physiological noise (*e.g.*, heart, respiration and blood pressure fluctuations), and finally, the OD was converted to HbO_2 concentration.

In this study, each of the 10 brain regions was defined as a node, corresponding to a measurement channel. Functional connectivity matrices were obtained by calculating Pearson correlation coefficients (*r* values) of the time series for each channel. Fisher's r-to-z transformation was then applied to convert the obtained *r* values to z scores, creating a 50 × 50 correlation matrix. RSFC graphs specific to each group were generated using single-sample *t*-tests. RSFC strength between ROIs in the PD-D and PD-NOD groups was compared using two-sample *t*-tests.

In this study, the overall and local topological properties of prefrontal resting-state brain networks were calculated within the level of threshold 0.4 to 0.65 and step size 0.05.

The overall topological properties: *i*) Small-world parameters (Sigma), clustering coefficient (Cp), and shortest path length (Lp). Sigma value > 1 is considered to be a small-world property of the network. The Cp measures the likelihood its neighborhoods are connected to each other. The Lp quantifies the mean distance or routing efficiency between this node and all the other nodes in the network. *ii*) Network efficiency parameters, including global efficiency (Eg) and local

efficiency (Eloc), both of which measure the network's ability to transmit information at the global and local levels, respectively; the higher the value, the faster the transmission speed.

The local topological parameters include five node indicators: *i*) the nodal degree centrality (Dc) for a given node reflects its information communication ability in the functional network; *ii*) the betweenness centrality (Bc) for a given node characterizes its effect on information flow between other nodes, and regions with higher Bc have a role of hub for the network; *iii*) the node efficiency (Ne) refers to the efficiency of parallel information transfer of network nodes, and regions with high Ne has a higher efficiency in communicating with other brain regions; *iv*) the nodal local efficiency (NLe) is a measure of functional segregation, higher NLe suggest a higher degree of interconnectedness in local networks consisting of direct neighbors of the region; *v*) the nodal clustering coefficient (NCp) measures the extent to which nodes tend to cluster together. The area under the curve (AUC) is a scalar that is highly sensitive to the topology of brain disease anomalies and does not depend on the selection of a specific threshold, so we calculated the AUC of each network metric as the final metric; this study included the AUC of Sigma(aSigma), the AUC of Cp(aCp), the AUC of Lp(aLp), the AUC of Eg(aEg), the AUC of Eloc(aEloc), the AUC of Dc(aDc), the AUC of Bc(aBc), the AUC of Ne(aNe), the AUC of NLe(aNLe), the AUC of NCp (aNCp) as the final indicators. The false discovery rate (FDR) was utilized to correct for multiple comparisons.

Results

A total of 83 elderly primary PD patients were recruited in the neurology outpatient clinic, and 64 patients' data of resting-state fNIRS were collected after initial screening.. One patient with drowsiness, one patient with cough, and six patients with bad channels in the data collection were deleted. A total of 56 patients' data were analyzed.

Demographic and clinical characteristics

The age of the patients ranged from 60 to 79 (69.39 ± 4.58) years and 30 (53.6%) were male. A comparison of demographic and clinical characteristics between the two groups is shown in Table 1. There was no significant difference in gender, age, education years, MMSE score, course of PD disease, H-Y stage, daily levodopa equivalent dose (LEDD), and MDS-UPDRS III score between the PD-D group and PD-NOD group (all $p > 0.05$). The MDS-UPDRS II (14.07 ± 8.78 *vs.* 9.04 ± 4.26), HAMA (14.07 ± 7.99 *vs*. 3.96 ± 3.16) and HAMD (17.43 ± 7.69 *vs.* 3.58 ± 2.45) scores of PD-D group were higher than those in the PD-NOD group (all $p < 0.05$).

Functional connectivity

fNIRS quantified the strength of the interaction of HbO_2 signals between the various brain regions covered by the channel. There was a significant difference in the RSFC matrix between the two groups of patients (Figure 2).

Interhemispheric FC strength of patients in the PD-D group is lower than that of the PD-NOD group and the difference was significant (0.19 ± 0.26 *vs.* 0.39 ± 0.33, $p = 0.015$); the FC strength of the DLPFC-L and FPA-L (0.19 ± 0.24 *vs*. 0.50 ± 0.26) is lower than that of the PD-NOD group and the difference was significant (FDR, $p < 0.001$) (Figure 3). There was no statistically significant difference in FC strength between the other brain regions of the two groups.

Pearson correlation analysis found a significant negative correlation between interhemispheric FC strength and HAMD scores ($r = -0.327$, $p = 0.014$); and a significant negative correlation between the FC strength of DLPFC-L and FPA-L, and the HAMD scores ($r = -0.458$, $p < 0.001$).

Table 1. Comparison of demographic and clinical characteristics of patients in the PD-D and PD-NOD groups

Variable	Total ($n = 56$)	PD-D ($n = 30$)	PD-NOD ($n = 26$)	t/χ^2-value	p value
Male (%)[a]	30 (53.6%)	14 (46.7%)	16 (61.5%)	1.239	0.266
Age (y)[b]	69.39 ± 4.56	69.20 ± 5.11	69.62 ± 3.96	-0.336	0.738
Years of education (y)[b]	10.29 ± 2.10	10.6 ± 2.22	9.92 ± 1.94	1.206	0.233
MMSE scores[b]	27.64 ± 2.02	27.4 ± 2.36	27.92 ± 1.55	-0.965	0.339
Disease duration (y)[b]	5.35 ± 4.76	5.96 ± 4.0	4.64 ± 5.51	1.039	0.303
H-Y stage[a]	2 (2,3)	2 (2,3)	2 (2,2)	4.151	0.246
LEED (mg/day)[b]	484.19 ± 268.61	536.97 ± 314.77	423.29 ± 191.33	1.656	0.104
MDS-UPDRS II scores[b]	11.73 ± 7.44	14.07 ± 8.78	9.04 ± 4.26	2.659	0.010
MDS-UPDRS III scores[b]	26.52 ± 13.68	29.27 ± 14.74	23.35 ± 11.85	1.639	0.107
HAMA scores[b]	9.38 ± 8.0	14.07 ± 7.99	3.96 ± 3.16	6.379	< 0.001
HAMD scores[b]	11.0 ± 9.09	17.43 ± 7.69	3.58 ± 2.45	9.336	< 0.001

Note: [a]Data were performed for group differences with the chi-squared test. [b]Data were performed for group differences with *t*-test. PD-D, Parkinson's disease with depressive symptoms; PD-NOD, Parkinson's disease without depressive symptoms; MMSE, Mini-mental State Examination scale; H-Y stage, Hoehn-Yahr stage; LEDD, levodopa equivalent daily dosage; MDS-UPDRS II, Movement Disorder Society Unified Parkinson's Disease Rating Scale part II; MDS-UPDRS III, Movement Disorder Society Unified Parkinson's Disease Rating Scale part III; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale.

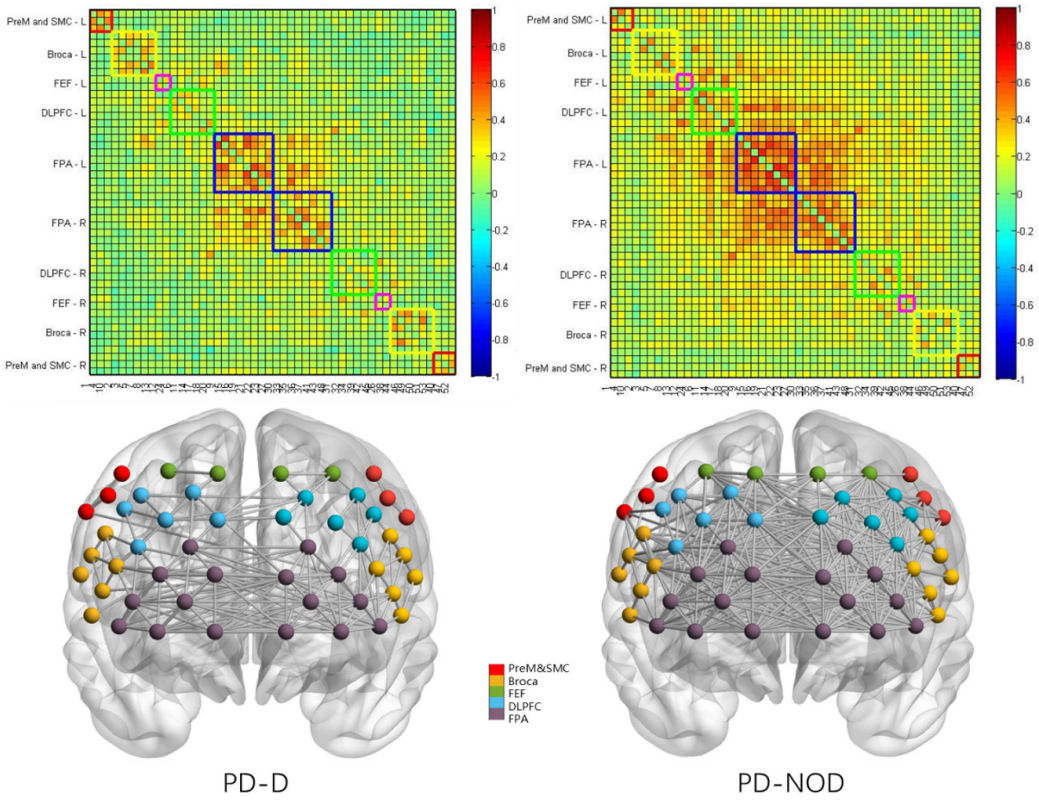

Figure 2. RSFC strength between regions of interest is lower in PD-D than in the PD-NOD group patients. PD-D, Parkinson's disease with depressive symptoms; PD-NOD, Parkinson's disease without depressive symptoms; RSFC, Resting-state functional connectivity; PreM and SMC-L, left Pre-Motor and Supplementary Motor Cortex; Broca-L, left Broca's area; FEF-L, left frontal eye fields; DLPFC-L, left dorsolateral prefrontal cortex; FPA-L, left frontal polar area; FPA-R, right frontal polar area; DLPFC-R, right dorsolateral prefrontal cortex; FEF-R, right frontal eye fields; Broca-R, right Broca's area; PreM and SMC-R, right Pre-Motor and Supplementary Motor Cortex; PreM & SMC, Pre-Motor and Supplementary Motor Cortex; Broca, Broca's area; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; FPA, frontopolar area.

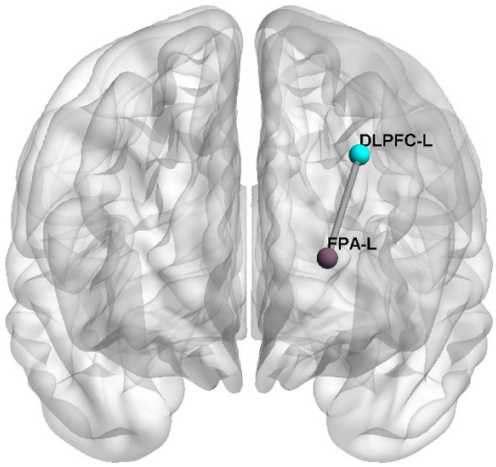

Figure 3. Low strength of FC between DLPFC-L and FPA-L in PD-D group patients compared to PD-NOD. PD-D, Parkinson's disease with depressive symptoms; PD-NOD, Parkinson's disease without depressive symptoms; FC, functional connectivity; DLPFC-L, left dorsolateral prefrontal cortex; FPA-L, left frontal polar area.

Brain network topology properties

The Sigma values of the PD-NOD and PD-D groups were > 1 at each absolute threshold, which suggests that the brain networks of the patients in both groups have small-world networks. Compared with the PD-NOD group, aSigma (0.56 ± 0.31 *vs*. 0.46 ± 0.26), aCp (0.12 ± 0.02 *vs*. 0.13 ± 0.04), aLp (1.36 ± 0.8 *vs*. 1.07 ± 0.86), and aEloc (0.14 ± 0.02 *vs*. 0.15 ± 0.04) were not statistically different in the PD-D group (all $p > 0.05$), whereas aEg (0.07 ± 0.02 *vs*. 0.09 ± 0.04, $p = 0.003$) in PD-D group was significantly lower; this suggests that the brain network of elderly PD patients with depressive symptoms is less efficient in information transmission.

Pearson correlation analysis showed that there was no correlation between aSigma, aCp, aLp, and aEloc and the HAMD scores (r = -0.037~0.101, all $p > 0.05$), whereas there was a significant negative correlation between aEg and the HAMD scores (r = -0.294, $p = 0.028$).

Compared to the PD-NOD group, aDc was significantly lower in the PD-D group in the DLPFC-L (1.61 ± 1.02 *vs*. 2.80 ± 1.86), FPA-L (1.98 ± 0.73 *vs*. 3.68 ± 2.19), and FPA-R (1.88 ± 0.97 *vs*. 3.0 ± 2.0); aBc was significantly lower in the FEF-L (2.73 ± 2.61 *vs*. 6.52 ± 5.14); aNe in the PreM and SMC-L (0.06 ± 0.03 *vs*. 0.08 ± 0.04), Broca-L (0.06 ± 0.03 *vs*. 0.08 ± 0.03), FEF-L (0.06 ± 0.03 *vs*. 0.09 ± 0.05), DLPFC-L (0.07 ± 0.03 *vs*. 0.10 ± 0.04), FPA-L (0.08 ± 0.02 *vs*. 0.12 ± 0.04), FPA-R (0.08 ± 0.02 *vs*. 0.11 ± 0.04), and DLPFC-R (0.07 ±

Table 2. Comparison of aDc of patients in the PD-D and PD-NOD groups

Region	PD-D (n = 30)	PD-NOD (n = 26)	t value	p value
DLPFC-L	1.61 ± 1.02	2.80 ± 1.86	-2.895	0.030
FPA-L	1.98 ± 0.73	3.68 ± 2.19	-3.778	0.010
FPA-R	1.88 ± 0.97	3.0 ± 2.0	-2.592	0.047

PD-D, Parkinson's disease with depressive symptoms; PD-NOD, Parkinson's disease without depressive symptoms; aDc, area under the curve of degree centrality; DLPFC-L, left dorsolateral prefrontal cortex; FPA-L, left frontal polar area; FPA-R, right frontal polar area.

Table 3. Comparison of aBc of patients in the PD-D and PD-NOD groups

Region	PD-D (n = 30)	PD-NOD (n = 26)	t value	p value
FEF-L	2.73 ± 2.61	6.52 ± 5.14	-3.391	0.020

PD-D, Parkinson's disease with depressive symptoms; PD-NOD, Parkinson's disease without depressive symptoms; aBc, area under the curve of betweenness centrality; FEF-L, left frontal eye fields.

Table 4. Comparison of aNe of patients in the PD-D and PD-NOD groups

Region	PD-D (n = 30)	PD-NOD (n = 26)	t value	p value
PreM and SMC - L	0.06 ± 0.03	0.08 ± 0.04	-2.323	0.040
Broca-L	0.06 ± 0.03	0.08 ± 0.03	-2.357	0.040
FEF-L	0.06 ± 0.03	0.09 ± 0.05	-2.266	0.040
DLPFC-L	0.07 ± 0.03	0.10 ± 0.04	-3.596	0.005
FPA-L	0.08 ± 0.02	0.12 ± 0.04	-4.213	< 0.001
FPA-R	0.08 ± 0.02	0.11 ± 0.04	-3.096	0.013
DLPFC-R	0.07 ± 0.03	0.09 ± 0.04	-2.450	0.040

PD-D, Parkinson's disease with depressive symptoms; PD-NOD, Parkinson's disease without depressive symptoms; aNe, area under the curve of node efficiency; PreM and SMC-L, left Pre-Motor and Supplementary Motor Cortex; Broca-L, left Broca's area; FEF-L, left frontal eye fields; DLPFC-L, left dorsolateral prefrontal cortex; FPA-L, left frontal polar area; FPA-R, right frontal polar area; DLPFC-R, right dorsolateral prefrontal cortex.

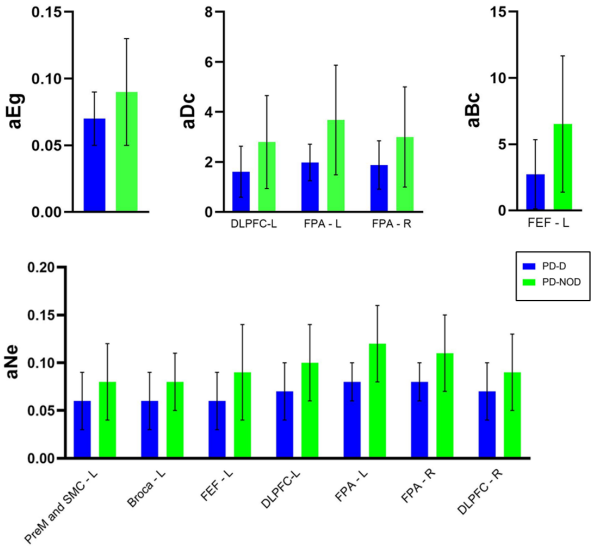

Figure 4. PD-D group patients' brain network properties are different from PD-NOD. PD-D, Parkinson's disease with depressive symptoms; PD-NOD, Parkinson's disease without depressive symptoms; aEg, area under the curve of global efficiency; aDc, area under the curve of degree centrality; aBc, area under the curve of betweenness centrality; aNe, area under the curve of node efficiency; PreM and SMC-L, left Pre-Motor and Supplementary Motor Cortex; Broca-L, left Broca's area; FEF-L, left frontal eye fields; DLPFC-L, left dorsolateral prefrontal cortex; FPA-L, left frontal polar area; FPA-R, right frontal polar area; DLPFC-R, right dorsolateral prefrontal cortex.

0.03 *vs.* 0.09 ± 0.04) were significantly reduced (FDR, all $p < 0.05$) (Tables 2–4, and Figure 4). aNLe and aNcp in 10 brain regions of the two groups had no statistical differences (all $p > 0.05$). A comparison of the local topological properties between the two groups illustrated that the elderly PD patients with depressive symptoms had abnormal topological parameters in several brain regions of the prefrontal lobe, and the brain network of PD-D patients were more sparse compared to the PD-NOD patients.

Pearson correlation analyses of the AUC of nodal metrics in each brain region and the HAMD scores showed significant negative correlations for aDc in FPA-L (r = -0.374, p = 0.004) and none of the other brain regions (p = 0.067~0.733); significant negative correlations for aBc in FEF-L (r = -0.330, p =0.013) and none of the other brain regions (p = 0.353 ~ 0.944); significant negative correlations for aNe in DLPFC-L (r = -0.311, p = 0.019) and FPA-L (r = -0.419, p = 0.001), and no correlation existed in any other brain regions (p = 0.064~0.400); significant negative correlations for aNLe in FPA-L (r = -0.267, p = 0.047); and aNcp did not correlate in any of the brain regions (p = 0.079~0.905). This suggests that the more severe the depressive symptoms in elderly PD patients, the more pronounced the local topological abnormalities in multiple brain regions.

Discussion

The relatively fixed anatomical structure of the brain serves as the physical basis for dynamic functional networks. The concept that a brain region may participate in multiple networks transcends structural constraints. The frontal lobe cortex, being the latest mature structure during brain development, is topologically central and plays a crucial role in emotion and cognition (*16*). The small-world network is an attractive model for complex brain networks, initially proposed by Watts and Strogatz in 1998 (*17*). Distinguished from regular networks (higher Cp and longer Lp) and random networks (lower Cp and shorter Lp), small-world networks exhibit higher Cp and shorter Lp, enabling the brain to achieve efficient local information segregation and global information integration with minimal wiring and energy consumption (*18*).

This study observed that the FC strength between

DLPFC-L and FPA-L was lower in the PD-D group compared to the PD-NOD group. Additionally, there was a significant negative correlation between the FC strength of DLPFC-L and FPA-L and the severity of depressive symptoms in the PD-D group. In the DLPFC-L (BA9, 46) and bilateral FPA (BA10, anterior portions of the superior and middle frontal gyrus), both aDc and aNe values in the PD-D group were lower than those in the PD-NOD group. Furthermore, the severity of depressive symptoms in patients was negatively correlated with the aNe value of DLPFC-L and the aDc, aNe, and aNLe values of FPA-L.

These findings are consistent with previous studies that identified four networks closely related to depression (*19-21*): the default mode network (DMN), which mainly includes the medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC), and which is negatively activated when there is an extraneous attention task, and positively activated when engaging in activities such as introspection, wandering, situational memory, and future envisioning; and the frontal-parietal network (FPN, also known as the executive control network, ECN), including the DLPFC, inferior parietal sulcus (IPS), and posterior parietal cortex (PPC), which is responsible for top-down regulation of attention and emotion; the salience network (SN), consisting mainly of the bilateral anterior insula (aINS) and dorsal anterior cingulate cortex (dACC), which is a bottom-up processor of salient experiences and can switch between the DMN and the FPN; the dorsal attentional network (DAN), associated with top-down control of attention activated by endogenous stimuli.

A Meta-analysis of RSFC in patients with MDD reported that hyper-connectivity within the DMN and hypo-connectivity within the FPN, increased connectivity between the FPN and DMN, and decreased connectivity between the FPN and the DAN may reflect patients' descent into ruminative thinking without attention to the external world (*19*). Sezer reviewed the mechanisms of mindfulness improving depression, in which the pathways of decreased connectivity between DMN and ACC, increased connectivity between PCC and DLPFC, increased connectivity between DMN and DAN, and increased connectivity between FPN and SN have been confirmed by several studies (*22*).

Although the location of lesions associated with depression is highly heterogeneous, these lesions map to connective brain circuits centered on the DLPFC-L (*23*). DLPFC is involved in cognitive or executive functioning and plays a role in the episode buffer of the depression schema feedback loop (*24*). Depressive PD patients were found the loss of grey matter in the prefrontal lobe, temporal lobe and some limbic regions and the reduction of white matter (*25*). Wei *et al.* (*26*) found that elevated FC in the left FPN and SN, and decreased FC in the DMN in depressed PD patients compared to non-depressed PD patients and that FC abnormalities in DMN, left FPN, and SN were correlated with depression severity in PD patients. Previous studies have also found abnormalities in the Dc of brain networks in depressed PD patients. Wang *et al.* (*27*) found that Dc in patients with depression (HAMD-17 scores ≥ 7) was abnormal in the right frontal middle gyrus (including BA9,10), bilateral anterior cingulate cortex, SMC, and cerebellar VI lobules, and the Dc of the right frontal middle gyrus was negatively correlated with the depression scores.

Currently, transcranial magnetic stimulation (TMS) is a well-established, non-invasive brain stimulation therapy for treating depressed patients with PD (*2*). A large number of studies have demonstrated that high-frequency stimulation on the left side of the DLPFC (≥ 5.0 Hz) or low-frequency stimulation on the right side of the DLPFC (≤ 1.0 Hz) can alleviate depressive symptoms (*28*). Notably, previous studies have varied but still demonstrated consistency. Our results reinforce the critical role of the DLPFC-L in depression and also suggest that depressive symptoms in elderly PD patients may share similar pathological changes with primary depression.

Our findings suggest that RSFC was sparser in the PD-D group, where the interhemispheric FC strength was significantly lower in the PD-D group than in the PD-NOD group; and the higher the depressive symptoms, the lower the interhemispheric FC strength. Interhemispheric coordination is the basis of coherent cognition, emotion regulation, and behavior, and the presence of imbalanced interhemispheric functional coordination in patients with MDD may be related to the impairment of the corpus callosum (the largest white matter connection between the hemispheres (*29*). Zhu *et al.* (*25*) found that middle-aged and elderly PD patients accompanied by depression had impaired interhemispheric synchrony.

Besides, Zheng *et al.* (*30*) found that impairment of interhemispheric FC in patients with recurrent MDD was associated with the severity of clinical depression in patients. All of the elderly PD patients in this study had economic small-world characteristics. The differences were not statistically significant compared with the PD-NOD group, although the PD-D group had higher aSigma, lower aCp and higher aLp. However, the brain network information transfer efficiency of the patients in the PD-D group was significantly lower than that of the PD-NOD group at the global level, and the more severe the depressive symptoms were, the lower the global transfer efficiency of the brain was. This suggests that elderly PD patients with depressive symptoms may have poorer network local interconnectivity and lower overall network routing efficiency. The global integration ability of elderly PD patients with depressive symptoms has been weakened, and the balance between local separation and global integration of brain networks has been impaired, and early intervention to avoid deterioration is necessary.

Chinese patients with MDD over 50 years of age

have been found to have significantly different overall brain network indices than normal controls, including decreased Eg, Eloc, Cp, and Sigma as well as increased Lp (*31*). Interestingly, a study that included resting-state fMRI scans of 30 first-episode, unmedicated MDD patients and 63 healthy control subjects found that MDD patients had shorter Lp, no change in Eloc, and higher Eg (*32*). These inconsistent and conflicting findings must be interpreted with caution because of the large differences between patients with first-episode unmedicated MDD and older PD patients with concomitant depressive symptoms.

In this study, patients in the PD-D group had lower aBc and aNe on the FEF-L (BA8, which belongs to the DAN) than those in the PD-NOD group, suggesting a decrease in both node influence and speed of information transfer. There was a significant negative correlation between the aBc value on the FEF-L and the severity of depressive symptoms. The pleasure deficit in depressed PD patients is related to the lack of attention to normal sensory perceptions, which in turn fails to activate reward loops (*25*). Froeliger *et al.* (*33*) compared the resting-state network of 7 experienced meditators and 7 beginners and found that the experienced meditators exhibited higher connectivity within the DAN (right anterior IPS and FEF-L, and right MT and FEF-L), between the DAN and DMN, and between the ECN and SN; this is related to the ability of experienced meditators to focus on sensory stimuli in the present moment.

Moreover, patients in the PD-D group in this study had significantly lower aNe values on PreM and SMC-L, Broca-L, and DLPFC-R than the PD-NOD group. These results are not surprising, as a large number of studies have demonstrated the presence of extensive brain function abnormalities in PD patients with depression. However, the variance in the results of different studies stems from different sample sizes, heterogeneity of PD patients (especially disease duration and medication status), dopaminergic treatment status, different brain imaging techniques and statistical methods. The homogeneity of the two groups in this study in terms of gender, age, cognitive function, duration of PD, H-Y stage, LEDD, and patients' motor function enhances the reliability of the findings.

This study has several limitations. Firstly, the fNIRS signals in this study were only collected from the prefrontal cortex, and regions such as the posterior cingulate gyrus, amygdala, and caudate nucleus, which are relevant to depression, were not investigated. Future studies of the whole brain will be useful in unveiling brain network characteristics and will contribute to a more in-depth understanding of the neural mechanisms of depressed PD. Secondly, considering the cultural sensitivity of the elderly population in China (such as being reluctant to express emotions and societal expectations), it is challenging to completely avoid false positives and false negatives in the assessment of depressive symptoms. Moreover, cultural values in East Asia foster an interdependent self-construal and shape the brain network, which may impose restrictions on the cross-cultural extrapolation of our conclusions. A more extensive testing approach could be beneficial in evaluating depression symptoms in PD patients. Finally, the relatively small sample size might impact the accuracy of the current analysis results, and further studies with larger samples are needed to validate our findings. Additionally, empirical studies targeting potential therapeutic targets would contribute to obtaining more reliable conclusions.

Conclusion

Overall, our data revealed that in elderly PD patients with depressive symptoms, the FC strength between the DLPFC-L and FPA-L was weakened, and the FC strength of DLPFC-L and FPA-L in elderly PD patients is negatively correlated with depressive symptoms. Additionally, abnormalities were observed in multiple nodal parameters of several brain regions, such as bilateral DLPFC and FPA. DLPFC-L and FPA-L are candidates for use as biological markers and preventive targets for the occurrence and development of depressive symptoms in elderly PD patients. Furthermore, elderly PD patients with depressive symptoms are less integrated and less efficient. Our findings provide new clues for exploring the pathogenesis of elderly PD patients with depressive symptoms and developing neural regulation methods.

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