

Functional Connectivity and Anxiety Improvement After Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease

Bowen Chang^{1,2,*}, Jiaming Mei^{1,2,*}, Chen Ni^{1,2}, Chaoshi Niu^{1,2}

¹Department of Neurosurgery, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, People's Republic of China; ²Anhui Province Key Laboratory of Brain Function and Brain Disease, Hefei, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chaoshi Niu, Email niuchaoshi@ustc.edu.cn

Background: Anxiety is one of the most common and disturbing non-motor symptoms of Parkinson's disease (PD). However, few studies have explored the relationship between functional connectivity (FC) and the rate of anxiety improvement after subthalamic nucleus deep brain stimulation (STN-DBS). Therefore, in this study, we aimed to explore the correlation between FC and the rate of anxiety improvement in patients with PD who underwent STN-DBS.

Methods: The resting-state functional magnetic resonance imaging (rs-fMRI) data of 62 patients with anxious PD (aPD), 68 patients with PD without anxiety (naPD), and 64 healthy controls (HCs) were analyzed according to FC. Intergroup comparison and correlation analyses of anxiety improvement rates were performed.

Results: The HC, aPD and naPD groups of zFCs were then used for the ANOVA test, and the results were FDR-corrected. There were 24 significant differences in FCs between the three groups. Post tests were conducted between groups found that 15 significantly different FCs were observed between the naPD and aPD groups. In addition, the two FCs in patients with aPD were significantly correlated with the rate of improvement in anxiety.

Conclusion: We found that the two FCs in patients with aPD (olfactory cortex and inferior frontal gyrus [IFG] pars orbitalis; inferior temporal gyrus and posterior orbital gyrus) were significantly correlated with the rate of improvement in anxiety. Our study may help us understand the underlying mechanisms by which STN-DBS improves anxiety in PD patients and identify more effective treatment strategies.

Keywords: Parkinson's disease, deep brain stimulation, anxiety, functional connectivity, fMRI

Introduction

Parkinson's disease (PD) is a progressive degenerative neurological disease that occurs in elderly individuals and has a higher incidence in men than in women. Resting tremor, bradykinesia, and rigidity are the common motor symptoms of patients with most PD.¹ In addition, a variety of non-motor symptoms (NMS), such as mood disorders, cognitive impairments, sleep disorders, and autonomic dysfunction, may be observed.^{2,3} Anxiety is one of the most common NMS of PD. Its prevalence among patients with PD is 31%, which is higher than that in patients with community or other diseases. It has shown to be a common worsening factor of the disease and is associated with a lower quality of life.⁴⁻⁶ With the recent development of neuromodulation therapy, deep brain stimulation (DBS) has become an effective treatment for advanced PD.^{7,8} It is widely suggested that DBS can significantly improve anxiety and depression in patients with PD, but the mechanism remains unclear.^{9,10}

Although functional magnetic resonance imaging (fMRI) has been developed in recent years, there is an increasing sophistication in the use of functional imaging to study the neural circuitry of brain diseases. However, the exact causal

brain network mechanisms by which DBS affects anxiety in PD patients are not known due to the safety and biosafety issues associated with high field strength MRI scanning of DBS equipment in the powered-on state.

Therefore, we used preoperative resting-state fMRI to explore the functional connectivity (FC) of patients with PD to provide some imaging evidence for revealing the mechanism of subthalamic nucleus DBS (STN-DBS) in improving motor symptoms in PD.^{11,12} Similarly, it is critical to study FC associated with anxiety improvement rates in post-DBS patients with PD. This will help us understand the underlying mechanism and identify more effective treatment strategies. Therefore, in this study, we aimed to explore the correlation between FC and the rate of anxiety improvement in patients with PD who underwent STN-DBS.

Materials and Methods

Patients

Medical records and questionnaire results were retrospectively collected from patients with PD who underwent STN-DBS at the First Hospital of the University of Science and Technology of China between September 2019 and April 2020. The study protocol was approved by the ethics committee of our hospital (2022-RE-154). The included patients had intermediate-to-advanced PD, and the exclusion criteria were moderate/severe cognitive impairment, persistent severe psychiatric disorders, severe atrophy or diffuse ischemic lesions on MRI, or systemic diseases that prevented surgery. None of the included subjects used any anxiolytic drugs. Moreover, the medical records of age- and sex-matched healthy participants who underwent annual physical checkups at the same hospital were collected as healthy controls (HCs).

Acquisition Clinical Assessment

Patients with anxiety-associated PD were diagnosed by an experienced psychiatrist according to the criteria of the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). Anxiety severity was measured using the 14 Hamilton Anxiety Assessment Scale (HAMA-14). An HAMA-14 score higher than 14 is necessary for a more accurate diagnosis of PD anxiety. PD patients were considered to have anxiety disorders when their HAMA-14 score was higher than 14. Exercise symptoms and disease severity were evaluated using the Movement Section of the Unified Parkinson's Disease Scale (UPDRS-III) and Hoehn and Yahr (H&Y) scale. All evaluations were performed before the MRI scan. Patients still use the HAMA-14 scale 2 years after surgery to evaluate anxiety and then calculate the rate of anxiety improvement (Improvement rate of HAMA-14 = (HAMA-14 Preop – HAMA-14 Postop)/HAMA-14 Preop). H&Y stage and HAMA-14 were measured in the medication state.

MRI Data and Preprocessing

For patients with PD and HCs, a 3T MRI scanner (Discovery MR750; General Electric Healthcare, Chicago, IL, USA) with an eight-channel phased-array head coil was used. Participants were instructed not to fall asleep during the entire scan. We further confirmed that the participants were awake throughout the scan. Functional and structural MRI data were acquired with a 3T GE (Achieva TX) MRI scanner in the OFF-medication state before DBS surgery, following an 8-h period of medication withdrawal. Structural images were acquired using a sagittal magnetization prepared rapid gradient echo three-dimensional T1-weighted sequence (repetition time [TR] = 8.5 ms, echo time [TE] = 3.2 ms, inversion time [TI] = 450 ms, flip angle [FA] = 12°). Functional MRI images were obtained using the following spin echo–echo planar imaging (SE-EPI) sequence: TR = 2000 ms, TR = 30 ms, slice thickness/gap = 3.6/0 mm, axial slices = 38 layers, FA = 90°, field of view (FOV) = 256 × 256 mm, matrix size = 64 × 64, and scanning time = 484 s.

Data preprocessing was conducted using a Resting-State fMRI Data Analysis Toolkit plus V1.25 (RESTplus V1.25, <http://restfmri.net/forum/index.php>), which is based on Statistical Parametric Mapping (SPM, <https://www.fil.ion.ucl.ac.uk/spm/>). Data from 242 volumes were acquired separately as functional scans of patients with PD and HCs. The first 10 volumes of each functional scan were excluded to correct for subject habituation to the scanning environment and magnetization stability. Slice-timing correction was performed to help compensate for differences in acquiring data across all slices with the FOV at any given time point; realignment for head-motion correction was also considered; data

from healthy control/PD subject whose head motion exceeded 3.0 mm or involved rotation exceeding 3.0° during the fMRI scanning was excluded. Individual 3D T1-weighted anatomical images were coregistered to functional images and spatially normalized to the Montreal Neurological Institute template. Each voxel was resampled to $3 \times 3 \times 3 \text{ mm}^3$. Subsequently, the resampled images were smoothed using a 6-mm full-width half-maximum (FWHM) isotropic Gaussian kernel, and a linear trend and bandpass filter (0.01 ~ 0.08 Hz) were used to remove the effect of high-frequency noise. Finally, cerebrospinal fluid signal, white matter, and the Friston-24 head motion parameter model were considered nuisance covariates and regressed from fMRI signals. The resulting data were further analyzed.

Functional Connectivity Analysis Based on Regions of Interest

In this study, each region of interest (ROI) in the AAL3-170 Atlas was extracted as a candidate feature. The AAL3-170 Atlas (www.oxcns.org/aal3.html, accessed June 4, 2022) is an improved version of the AAL2 Atlas that divides the entire brain into 166 ROIs. Two small areas of the AAL3 Atlas (Nos. 133–134) were not defined, as the size of the original $1 \times 1 \times 1 \text{ mm}^3$ was resampled to $3 \times 3 \times 3 \text{ mm}^3$; therefore, 164 areas remained in the AAL3-170 Atlas. Using these 164 ROIs, we calculated the ROI-wise FC with filtered data and obtained one FC graph each. The FC graph went through Fisher z transformation; we made the data fit normal analysis, obtained the zFC graph, and used the zFC graph for subsequent statistical analysis. The average resting state blood oxygenation level-dependent (BOLD) time series for each ROI was extracted. The BOLD time series for each ROI was then correlated with the BOLD time series of every other ROI (Pearson's correlation coefficient) for each participant. In calculating FC, we adjusted for sex, age, H-Y classification, and duration variables.

Statistical Analyses

According to the demographic data and the HAMA-14 scale, the participants were classified into three groups: HC, anxiety PD (aPD), and non-anxiety PD (naPD). The groups were tested using one-way analysis of variance (ANOVA) test was performed to compare the FC differences among the HC, aPD and naPD groups (a post hoc test with the post hoc two sample t -tests were used to compare FC between each pair of groups two comparisons was also performed on an ANOVA basis). The All intergroup multiple comparison correction comparisons of all intergroup were performed by using false discovery rate (FDR) correction ($q < 0.01$, $q = 0.01$). Pearson's correlation coefficient was used to analyze the correlation between FC and anxiety improvement rates with a significance level of $P < 0.05$. Multivariate regression was used to analyse the risk factors.

Results

Demographic and Clinical Characteristics

A total of 68 patients with naPD, 62 patients with aPD, and 64 HCs were included in our analysis. The differences in age, gender, and duration among the three groups were not statistically significant. Differences between the aPD and naPD groups were not statistically significant for UPDRS-III scores, H-Y grades, or levodopa equivalent dose (LED). In addition, the HAMA-14 scores were significantly higher in patients with aPD than in those with naPD or HCs. The improvement rate of anxiety in aPD group was significantly higher than that in naPD group (Table 1).

Functional Connectivity Analysis

The zFC matrix was calculated for each participant by determining the functional connectivity values of the ROIs. Three groups of zFCs were then used for the one-way ANOVA test, and the results were FDR-corrected. A matrix of FCs among the three groups was obtained. Twenty-four ROI-pair FCs (excluding redundant and diagonal elements) in the triangular portion of the matrix were preserved (Figure 1A and Table 2). Significant differences in FCs among the aPD, naPD, and HC groups are shown in Figure 1B. A post hoc test was conducted to compare groups, and we found 15 significantly different FCs between the naPD and aPD groups (Figure 2A and Table 3). Significantly different FCs between the HC and aPD groups are shown in Figure 2B.

Table I Demographic and Clinical Information of the Participants

	HC	naPD	aPD	P-value
No.	64	68	62	
Age	61.0 ± 6.6	58.7 ± 7.5	59.4 ± 8.4	0.199
Duration (years)	–	9.0 ± 3.6	8.3 ± 3.8	0.267
UPDRS-III drug off	–	53.5 ± 13.8	56.7 ± 12.6	0.175
UPDRS-III drug on	–	26.2 ± 11.0	28.9 ± 11.0	0.158
HAMA-14	4.0 ± 2.1	10.7 ± 2.4	2.25 ± 3.7	<0.001
LED	–	643.8 ± 437.2	669.4 ± 316.6	0.705
Drug improvement rate	–	0.5± 0.1	0.5 ± 0.1	0.200
Gender				0.644
Male	30 (46.9%)	36 (52.9%)	34 (54.8%)	
Female	34 (53.1%)	32 (47.1%)	28 (45.2%)	
H-Y				0.668
2.5	–	14 (22.6%)	11 (16.1%)	
3	–	29 (46.8%)	39 (57.4%)	
4	–	19 (30.6%)	18 (26.5%)	

Relationship Between Functional Connectivity and Anxiety Improvement Rate After STN-DBS

In FC with significant differences between naPD and aPD groups, we found that the correlation between the two FCs (Olfactory_L, Frontal_Inf_Orb_2_R; Temporal_Inf_L, OFCpost_L) in the aPD group and the HAMA score improvement rate was significant (Figure 3). We then used multivariate regression model to validate the effect of the two FCs mentioned above on the rate of improvement in HAMA scores. After adjusting for several variables, these two FCs still had a strong effect on the rate of improvement in anxiety in PD patients after STN-DBS (Table 4).

Discussion

Anxiety is a common NMS of PD that is associated with awakening, reduced visual processing, negative cognition, somatosensory symptoms, and autonomic manifestations.^{4,13,14} Despite some differences, these manifestations share common neurological abnormalities, mainly characterized by hyperactivation of the amygdala and brain islands and

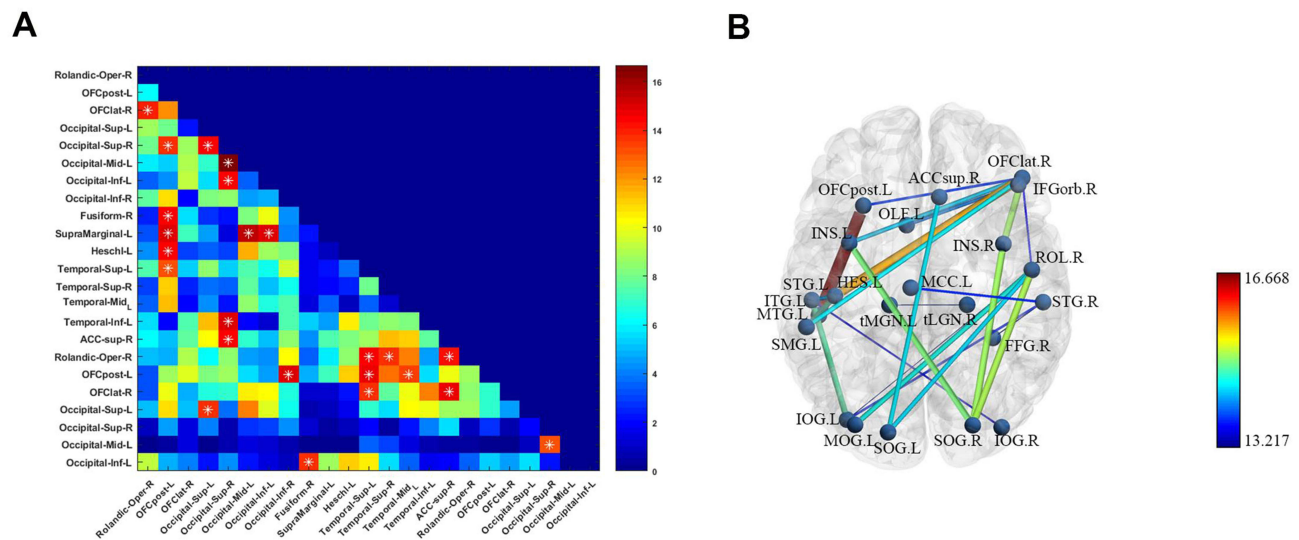


Figure 1 Significant differences in FCs among the aPD, naPD, and HC groups. (A) T-value matrix of functional connectivity between the three groups. (B) Visualization of differential functional connectivity.

Table 2 Significant Differences in FC Between HC, aPD, and naPD Groups

ROI1	ROI2	P-value	F
Olfactory_L	Frontal_Inf_Orb_2_R	9.804E-06	14.063
OFClat_R	Rolandic_Oper_R	1.350E-05	13.595
Occipital_Sup_L	Rolandic_Oper_R	7.982E-06	14.366
Occipital_Sup_R	Rolandic_Oper_R	4.908E-06	15.091
Occipital_Mid_L	Rolandic_Oper_R	7.066E-06	14.547
Occipital_Inf_L	Rolandic_Oper_R	1.732E-05	13.235
OFClat_R	OFCpost_L	6.956E-06	14.570
Temporal_Inf_L	OFCpost_L	1.193E-05	13.776
Insula_L	OFClat_R	1.750E-06	16.668
Insula_R	OFClat_R	8.208E-06	14.325
SupraMarginal_L	OFClat_R	5.182E-06	15.010
Heschl_L	OFClat_R	7.586E-06	14.441
Occipital_Sup_R	Insula_L	3.448E-06	15.625
Occipital_Sup_R	Insula_R	5.470E-06	14.928
Temporal_Sup_R	Cingulate_Mid_L	5.097E-06	15.034
ACC_sup_R	Occipital_Sup_L	1.254E-05	13.703
Temporal_Sup_L	Occipital_Inf_L	7.803E-06	14.400
Temporal_Sup_R	Occipital_Inf_L	6.059E-06	14.775
Temporal_Mid_L	Occipital_Inf_L	1.233E-05	13.727
Temporal_Sup_L	Occipital_Inf_R	1.370E-05	13.574
Temporal_Sup_R	Fusiform_R	1.660E-05	13.297
Temporal_Sup_L	Heschl_L	8.936E-06	14.199
Temporal_Mid_L	Heschl_L	6.327E-06	14.711
Thal_MGN_L	Thal_LGN_R	1.754E-05	13.217

pathological changes in FC.¹⁵ In the general population, the current hypothesis is that anxiety results from top-down control impairment of the medial prefrontal cortex (mPFC) in the amygdala, resulting in increased activity and affecting the downstream cortical/subcortical region.^{16,17}

Thus far, it is unclear whether anxiety in people with PD has the same underlying mechanism as that described in the general population.¹⁸ Clinically, anxiety may occur at any stage of the disease, even before motor symptoms. Anxiety in

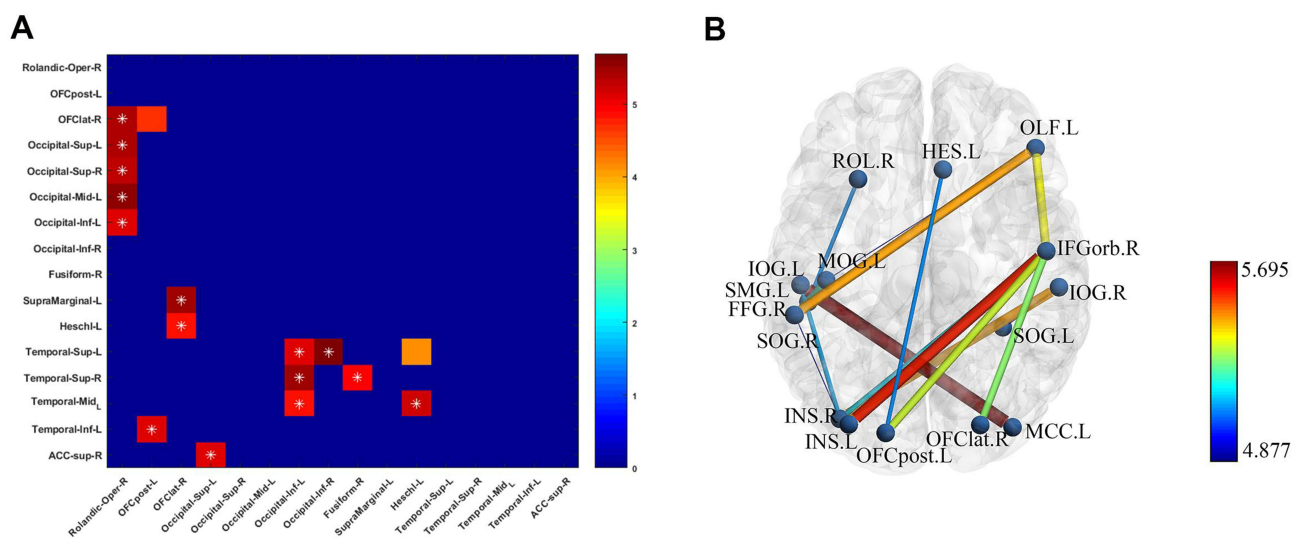


Figure 2 Significantly different FCs between the naPD and aPD groups. **(A)** T-value matrix of functional connectivity between the two groups. **(B)** Visualization of differential functional connectivity.

Table 3 Significant Differences in FC Between aPD, and naPD Groups

ROI1	ROI2	P	T
OFClat_R	Rolandic_Oper_R	1.871E-06	5.382
Occipital_Sup_L	Rolandic_Oper_R	2.148E-06	5.343
Occipital_Sup_R	Rolandic_Oper_R	2.528E-06	5.297
Occipital_Mid_L	Rolandic_Oper_R	9.714E-07	5.567
Occipital_Inf_L	Rolandic_Oper_R	4.172E-06	5.154
Temporal_Inf_L	OFCpost_L	5.360E-06	5.083
SupraMarginal_L	OFClat_R	1.387E-06	5.466
Heschl_L	OFClat_R	1.096E-05	4.877
ACC_sup_R	Occipital_Sup_L	5.344E-06	5.084
Temporal_Sup_L	Occipital_Inf_L	4.784E-06	5.115
Temporal_Sup_R	Occipital_Inf_L	1.436E-06	5.457
Temporal_Mid_L	Occipital_Inf_L	1.051E-05	4.889
Temporal_Sup_L	Occipital_Inf_R	6.136E-07	5.695
Temporal_Sup_R	Fusiform_R	7.676E-06	4.980
Temporal_Mid_L	Heschl_L	3.208E-06	5.229

patients with PD is often associated with gait disorders, unstable posture, and freezing gait.^{19,20} Preliminary studies have revealed impaired connectivity of the amygdala with the basal ganglia, supplementary motor regions (SMA), and other frontal regions in patients with PD.^{21,22} In our study, between the aPD and naPD groups, we found 15 distinct FCs among the occipital cortex and the rolandic operculum, olfactory and frontal cortex, temporal lobe and occipital cortex, orbital gyrus and superior marginal gyrus, and orbital gyrus and temporal cortex. This is similar to previous findings indicating anxiety in patients with aPD is mainly due to abnormal FC between the limbic system and other brain regions.

This study not only investigated FC differences in HC, naPD, and aPD groups but also explored the correlation of these FCs with the improvement rate of anxiety after STN-DBS. We observed no FCs in the naPD group that were significantly associated with anxiety improvement rates, whereas the two FCs in the aPD group were closely associated with anxiety improvement rates.

Numerous studies have shown that STN-DBS improves anxiety in patients with PD. In a 15-month follow-up study that included 33 patients, anxiety symptoms significantly improved after DBS.²³ Similarly, a definitive study published in 2008 included 156 patients with DBS and PD; 123 patients completed multiple NMS scores, showing anxiety symptoms improved after DBS.²⁴ The present study shows several possible reasons for improvement in the mechanism of anxiety. The first is intervention in STN-mediated fear processing, the second is intervention in marginal system loops near the STN, and the third is indirect regulation of the dopamine metabolism.²⁵ In this study, we found significant negative

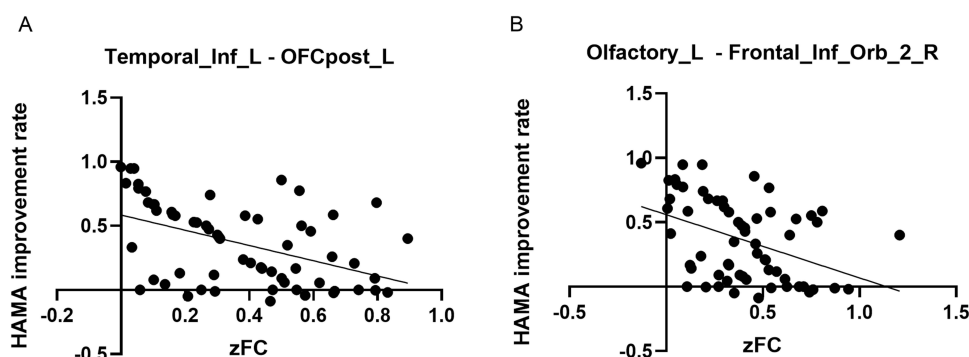


Figure 3 Correlation between FC and anxiety improvement rate after STN-DBS. (A) inferior temporal gyrus and posterior orbital gyrus. (B) Olfactory cortex and inferior frontal gyrus [IFG] pars orbitalis close.

Table 4 Multivariate Regression for Effect of FC on the HAMA Improvement Rate After STN-DBS

Variable	Model I		Model II	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Temporal_Inf_L -OFCpost_L (zFC)	-0.59 (-0.87, -0.30)	<0.001	-0.60 (-0.89, -0.31)	<0.001
Olfactory_L -Frontal_Inf_Orb_2_R (zFC)	-0.49 (-0.76, -0.22)	<0.001	-0.49 (-0.76, -0.22)	<0.001

Notes: Model I adjusted for age and gender. Model II adjusted for age, gender, LED, H-Y and duration.

Abbreviations: CI, confidence interval; OR, odds ratio.

correlations between the anxiety improvement rate and FCs of the olfactory cortex and inferior frontal gyrus (IFG) pars orbitalis and the inferior temporal gyrus and posterior orbital gyrus in the aPD group. These results indicate that these two FCs may affect the anxiety improvement rate of patients with aPD after STN-DBS.

In recent years, it has been found that the abnormal structure and function of prefrontal cortex (PFC), amygdala hippocampal loop play an important role in excessive anxiety, each structure plays a unique role in different emotional components, and PFC and hippocampus are key parts regulating positive and negative emotions.²⁶ The PFC is an important part of the emotional central pathway, its function consists of different components, such as the dorsolateral prefrontal cortex (DLPFC), the medial prefrontal lobe (MPFC) and orbitofrontal cortex (OFC), each of which plays different roles in emotional processing. An fMRI-based study showed that social anxiety was positively correlated with cortical gray matter volume of OFC and functional connectivity of OFC-amygdala, indicating that the abnormal structure of OFC and its abnormal connection with amygdala were the neural basis of social anxiety.²⁷ Similarly, a study on cortical morphology in patients with generalized anxiety disorder (GAD) found that bilateral OFC cortical thickness was significantly reduced in GAD patients compared with healthy controls.²⁸ In conclusion, the abnormal structure and function of OFC are the important neural basis of anxiety. In PD patients, previous studies have found that anxiety is associated with changes in the fear loop. In the fear loop of aPD patients, functional connections between amygdala, OFC and hippocampus are increased, while functional connections between MPFC and OFC are decreased.²⁹

Studies have shown that there is a close relationship between the stimulation contact and the location of STN subregion and the stimulation effect after electrode implantation in nuclear mass, that is, different subregions of STN correspond to different stimulation effects.³⁰ STN can be divided into three functional territory: dorsolateral sensorimotor territory, intermediate associative territory and ventromedial limbic territory. Studies have shown that STN, as one of the components of the basal ganglia, plays an important role in the mediation of motor, cognitive and emotional behaviors, and is the link that integrates motor, cognitive and emotional behaviors. Information from the anterior cingulate cortex (ACC), OFC, and hippocampus is transmitted to the STN limbic territory.³¹

It has been confirmed that patients can obtain the best relief of motor symptoms when stimulating the dorsolateral sensorimotor territory of STN. In terms of emotion, studies based on the neuroanatomy of STN show that the ventral or ventral STN is closely related to afferent and efferent fibers in the limbic territory. Therefore, studies have shown that stimulation of more ventral STN may cause transient manic symptoms, but in the long term, anxiety and depression can be improved better than that of dorsal and intermediate territory.^{32,33} It can be seen that DBS stimulation of different subregions of STN has different effects on anxiety in PD patients. At the neuroanatomical level, the OFC projects to the middle part of the STN and extends to the lateral hypothalamus. Because of this anatomical connection, STN is also one of the commonly used stimulus targets in the treatment of DBS for obsessive-compulsive disorder. The cortex-thalamic-basal ganglia network consists of a complex set of periodic excitatory and inhibitory loop systems. As a regulatory target of obsessive-compulsive disorder, STN mainly affects circuits related to reward, avoidance and cognitive control in this network, mainly FC of OFC.³⁴ This suggests that regulation of OFC-related brain networks can affect the emotional activity of patients. In conclusion, STN-DBS may regulate anxiety in aPD patients through OFC-related FCs.

There are several new aspects of our research. First, this study is one of few to explore the FC associated with the improvement rate of anxiety after STN-DBS. In addition, we explored the relationship between FC and anxiety improvement rates in patients with PD with different states of anxiety. Our results provide evidence for the mechanisms

by which STN-DBS improves anxiety in patients with PD. With the development of DBS devices, we can obtain 3T rs-fMRI images in the DBS power-on state, which will help to further explain the mechanism of anxiety improvement.

The present study had several limitations. First, it was retrospective and lacked reproducibility analysis (testing the same individual under the same conditions at two different time points). This may be a potential confounder of unknown significance. Moreover, the required sample size and statistical efficacy were not estimated at this time due to the study's retrospective nature, and predictive analyses were performed after the collection of follow-up information. We did not collect postoperative fMRI data because of possible artifacts and MRI heating of the implant. Therefore, for safety reasons, we recommend performing long-term follow-up prior to postoperative data collection.

Conclusion

In this study, we explored the correlation between FC and the rate of anxiety improvement after STN-DBS in patients with PD. We found that the two FCs in patients with aPD (olfactory cortex and IFG pars orbitalis; inferior temporal gyrus and posterior orbital gyrus) were significantly correlated with the rate of improvement in anxiety. Our study may help us understand the underlying mechanisms by which STN-DBS improves anxiety in PD patients and identify more effective treatment strategies.

Ethics Statement

The studies involving human participants were reviewed and approved by Ethics Committee of the First Affiliated Hospital of USTC. Confidentiality of patient data and adherence to the Declaration of Helsinki were maintained. The patients/participants provided their written informed consent to participate in this study.

Disclosure

Bowen Chang and Jiaming Mei are co-first authors for this study. The authors report no conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

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