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Research article

Altered functional connectivity within the brain fear circuit in Parkinson's disease with anxiety: A seed-based functional connectivity study

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ABSTRACT

Objectives: Aimed to investigate whether there are abnormal changes in the functional connectivity (FC) between the amygdala with other brain areas, in Parkinson's disease (PD) patients with anxiety.

Methods: Participants were enrolled prospectively, and the Hamilton Anxiety Rating (HAMA) Scale was used to quantify anxiety disorder. Rest-state functional MRI (rs-fMRI) was applied to analyze the amygdala FC patterns among anxious PD patients, non-anxious PD patients, and healthy controls.

Results: Thirty-three PD patients were recruited, 13 with anxiety, 20 without anxiety, and 19 non-anxious healthy controls. In anxious PD patients, FC between the amygdala with the hippocampus, putamen, intraparietal sulcus, and precuneus showed abnormal alterations compared with non-anxious PD patients and healthy controls. In particular, FC between the amygdala and hippocampus negatively correlated with the HAMA score ($r = -0.459$, $p = 0.007$).

Conclusion: Our results support the role of the fear circuit in emotional regulation in PD with anxiety. Also, the abnormal FC patterns of the amygdala could preliminarily explain the neural mechanisms of anxiety in PD.

1. Introduction

Approximately 30–49% of PD patients suffer from anxiety [1], much higher than in other chronic neurodegenerative diseases or healthy elderly [2]. Furthermore, anxiety disorders are related to poor quality of life and a heavy mental burden in PD patients [3,4]. However, the potential mechanisms of anxiety in PD remain unclear.

Previous studies have reported that anxiety may have a similar neural mechanism to fear. Fear is often considered an unusual emotion that triggers alertness in the face of threats that causes an abnormal psychological state of anxiety [5]. More precisely, fear as a sense is felt in dealing with existing threats, while anxiety is an emotional reaction in the face of anticipated or imagined future threats

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[6]. In many anxiety animal models, negative behaviors such as fear, escape, or avoidance are commonly observed [7,8]. Based on animal studies, a neuroanatomical hypothesis was proposed, arguing that a hypothetical network called the 'fear circuit,' including the amygdala [9], striatum, anterior cingulate (ACC), medial prefrontal cortex (mPFC), hippocampus, and insular [10,11], is one of the essential neural mechanisms for mediating fear- and anxiety-related emotions [8,12,13]. The amygdala, as the core of the fear circuit, receives neural inputs from the mPFC, ACC, hippocampus, and thalamus and outputs to the striatum and hypothalamus [5], which has a vital role in connecting exoteric stimuli with responses to anxiety in humans [9,10,14]. Many studies have reported that the pathogenesis of anxiety in PD may also be linked to the 'fear circuit' [5,15]. However, it remains unclear which node of the 'fear circuit' shows abnormal changes because of pathological changes in PD.

According to an autopsy study, the amygdala of PD patients underwent severe pathological changes, where Lewy bodies and Lewy neurites increasingly occupied the nuclear complex in a specific way as PD aggravated. However, few detectable atrophies of the amygdala could be observed [16]. Hence, we considered that the anxiety symptoms in PD were likely to be closely associated with the progressive pathological changes of the amygdala in PD. Previous studies reported aberrant amygdala alterations in anxious PD patients, such as a reduced amygdala volume and the dysfunctional innervation of dopamine and noradrenaline in the amygdala. These aberrant alterations correlated with the degree of anxiety symptoms [17,18]. However, these studies only illustrated abnormal changes in the PD patients' amygdala with anxiety, ignoring changes in the inter-relation of the amygdala with other brain regions. As an integral brain network, the abnormal changes of the core hub in the 'fear circuit' cannot be regarded independent. Further studies are needed to establish which brain regions show abnormal connectivity with the amygdala and how the abnormal functional connectivity affects the 'fear circuit' function in regulating anxiety.

In earlier functional MRI (fMRI) studies of anxious PD patients, only a few applied the functional connectivity (FC) analysis based on the amygdala to investigate the functional alterations within the fear circuit. However, according to the study of PD patients with mild anxiety with FC analysis based on the amygdala, no significantly abnormal amygdala FC was observed with other brain areas [14]. This result was inconsistent with the fact that PD patients' amygdala had severe pathological changes and the results of existing research are that the amygdala of PD patients with anxiety had abnormal structure [17] or metabolism [18], which might be because of the relatively slow pathological changes of the amygdala in the progression of PD [16]. Therefore, we speculated that the mild pathological involvement of the amygdala leads to slight functional changes in the amygdala at the early PD time, which are difficult to be reflected by conventional fMRI BOLD signals. Hence, a more sensitive and stable fMRI scanning technology is needed to observe the amygdala's functional changes in early PD patients with anxiety.

Simultaneous multislice (SMS) technology is an advanced MRI technique that improves spatial and temporal resolution of images, acquires BOLD signals more sensitively, and has more time points in a shorter time than conventional fMRI scanning technology used in past fMRI studies for PD with anxiety [19]. In this study, we used SMS to deeply and more sensitively explore the differences in the BOLD signals more deeply and sensitively in PD with anxiety. Moreover, no healthy elderly control groups were set up in the past studies of FC of the amygdala in anxious PD. Therefore, it was hard to distinguish whether the abnormal amygdala FC with other brain regions is caused by PD or its accompanying anxiety symptoms, an issue we tried to address in this study.

We assumed that abnormal functional alteration of the amygdala might exist in anxious PD patients based on pathological changes in the amygdala, considering the above-reported studies. Therefore, we aimed to apply the rest-state fMRI (rs-fMRI) with SMS technology to investigate further whether there is abnormal FC between the amygdala with other brain areas, especially with the internal nodes of the fear circuit, among three groups of participants, namely, the anxious PD group (PD-A), the non-anxious PD group (PD-NA), and the healthy control group (HC). In addition, Voxel-Based Morphometry Analysis (VBM) was run to explore whether functional alterations are attributable to underlying structural differences among the three groups.

2. Materials and methods

2.1. Participants

Thirty-nine PD patients attending the PD Clinic at the Affiliated Wuxi People's Hospital of Nanjing Medical University were prospectively and consecutively recruited into this study between August 2021 and February 2022, as they were diagnosed with idiopathic PD according to the UK Parkinson's Disease Brain Bank criteria [20]. Nineteen non-anxious healthy people matched for age- and sex was also enrolled as controls. The ethics committee's approval of the Affiliated Wuxi People's Hospital of Nanjing Medical University was acquired, and written informed consent was obtained from all participants according to the Declaration of Helsinki. All dopaminergic therapy was withheld for at least 12 h before the MRI scanning to alleviate the impact of drugs.

2.2. Inclusion criteria

PD patients were included if they (1) were coincident with the PD diagnosis standard according to the UK Parkinson's Disease Brain Bank criteria [20]; (2) were aged 40–80 years old; (3) were right-handers; (4) were able to perform MRI scans and finish the neurological and psychological assessment; (5) had no cognitive impairment; and (6) were willing to take part in this research.

2.3. Exclusion criteria

PD patients were excluded if: (1) inability to cooperate with clinical assessment or MRI examination; (2) max head motion $\geq$ 2.5 mm or 2.5°; (3) Mini-Mental State Examination (MMSE) score $<$24; and (4) history of severe neurological or cerebrovascular diseases

besides PD.

2.4. Clinical assessment of participants

All the participants' age, gender, education, disease duration, levodopa equivalent daily dose (LEDD), and other demographic characteristics were collected on the same day of the MRI scan. A detailed neurological and psychological assessment was performed for all participants by neurologists with years of clinical experience, including (1) Unified Parkinson's Disease Rating Scale (UPDRS-III); (2) Hoehn & Yahr scales (H&Y); (3) Hamilton Anxiety Rating Scale (HAMA); (4) 17-item Hamilton Depression Rating Scale (HAMD); (5) MMSE; (6) Frontal Assessment Battery (FAB), and (7) Freezing of Gait Questionnaire (FOGQ). First, we applied the UPDRS-III scale and H&Y staging to evaluate PD motor severity and disease stage. After which, the HAMA scale and HAMD scale reflected the mental state of the PD patients (according to HAMA scores $\geq$12 and $<$12 [21,22], PD patients were respectively divided into PD-A group and PD-NA group). Then, we assessed the PD patients' cognitive function using the MMSE scale. Next, FOGQ was used to assess freezing of gait (FOG) symptoms. Finally, the frontal executive function was measured through the FAB scale. For HCs, similar demographic and clinical data were gathered.

2.5. Imaging parameters

Magnetic resonance images were obtained on a 3.0T MRI equipment (Magnetom 3T Siemens, Prisma, Germany) with the 20-channel head coil in the morning. When shifting lying positions, we used a foam pad to minimize head motion and earplugs to reduce scanner noise. In addition, all the participants were instructed to stay awake, close their eyes, and try not to think about anything during the examination [23,24].

We obtained T1-weighted anatomical data using a volumetric 3D-magnetization prepared rapid acquisition gradient echo (3D-T1WI MP-RAGE) sequence with the following parameters: repetition time (TR) = 2300 ms, echo time (TE) = 2.98 ms, inversion time (TI) = 900 ms, flip angle (FA) = 9°, slice thickness = 1 mm, slices per slab = 192, the field of view (FOV) = 256 × 256 mm^2, matrix size = 256 × 256, and voxel size = 1 × 1 × 1 mm^3. The 3D-T1WI MP-RAGE scanning duration was 5 min and 30 s.

SMS technology was applied for the rs-fMRI imaging data collection with gradient recalled echo echo-planar imaging (GRE-EPI) sequence to effectively achieve faster scanning and obtain more time points, which improved spatial and temporal resolution of images and more sensitively acquired BOLD signals at the same time [18]. The parameters for rs-fMRI were: TR = 1500 ms, TE = 31 ms, FA = 70°, FOV = 211 × 211 mm^2, in-plane matrix = 64 × 64, slices = 60, slice thickness = 2.4 mm, no slice gap, voxel size = 2.4 × 2.4 × 2.4 mm^3, time points = 300. The rs-fMRI scanning duration was 7 min and 40 s.

2.6. Rs-fMRI data preprocessing

DPARSFA [25] (a data processing assistant for rs-fMRI, http://www.restfmri.net/forum/dparsf), which is based on Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm) and the toolbox for Data Processing & Analysis of Brain Imaging (DPABI [26], Yan et al. (2016), http://rfmri.org/DPABI), was applied to conduct rs-fMRI data preprocessing on the MATLAB R2016b platform. The following eight steps were involved in preprocessing: (1) removing the initial 15 time points; (2) slice timing for the fMRI data obtained from the SMS technique was automatically handled by DPARSFA (enter 0 in the slice number and reference slice options); (3) realignment and the calculation of realign parameters; (4) spatial normalization: three steps were taken to conduct this, i.e., anterior commissure was set as the origin for each participant's 3D-T1WI data, registrating 3D-T1WI data to rs-fMRI, dividing the 3D-T1WI MP-RAGE with DARTEL (Ashburner, 2007) toolkit and generating a group template; transforming and normalizing the obtained alignment data to the Montreal Neurological Institute (MNI) space; (5) resampling images with spatial resolution of 3 × 3 × 3 mm^3; (6) spatial smoothing at 8 × 8 × 8 mm^3 full-width-at-half-maximum (FWHM) Gaussian kernel; (7) nuisance covariates regression (cerebrospinal fluid and white matter signal; parameters of Friston-24 head [27]; linear detrended removal was included in this step); and (8) filtering (0.01–0.1 Hz).

2.7. FC analysis

Seed-based voxel-wise FC analyses were used to evaluate the temporal correlations between each ROI's resting-state time courses and each voxel of the whole brain. Based on the Anatomical Automatic Labeling (AAL) template, the bilateral amygdala were defined separately as two seeds to study the connectivity of the central hub of the fear circuit and other regions in the brain. Pearson's correlation coefficient maps were generated for each participant and were converted to a z-value by Fisher's z-transformation for subsequent statistical analysis.

2.8. VBM analysis

We applied Computational Anatomy Toolbox (CAT) 12 software [28] to run the VBM analysis on the MATLAB R2016b platform to explore structural differences among the three groups. The VBM analysis consists of the following three steps: (1) segmenting the 3D-T1WI MP-RAGE data of each participant into the cerebrospinal fluid, white matter, and gray matter; (2) spatially normalizing and transforming the gray matter images into MNI space; (3) spatial smoothing at 8 × 8 × 8 mm^3 FWHM Gaussian kernel.

2.9. Statistical analysis

SPSS 26.0 software was used to run the statistical analysis of the clinical and demographic information among three groups based on age, gender, disease duration, years of education, H&Y scale, UPDRS-III score, HAMA score, HAMD score, MMSE score, and FAB score. Continuous data were shown as the mean values ± standard deviation. Discontinuous data were shown as proportions. After assessing normality and homoscedasticity, two-sample *t*-test, one-way analysis of variance (ANOVA), Kruskal-Wallis test, and chi-square test were performed, and a P-value < 0.05 (corrected by Bonferroni) was considered statistically significant.

An analysis of covariance (ANCOVA) was used for each amygdala FC analysis to distinguish the significant differences in functional connections among three groups with age, gender, years of education, and HAMD scores as covariates, and the brain areas with differences were extracted as a mask. Then, with the same covariates listed above, a two-sample post hoc *t*-test was performed within the mask obtained from ANCOVA between every two groups (PD disease duration was included as an additional covariate in comparison between the PD subgroups). The significance was set at a level of voxel-wise $P < 0.001$ and cluster-wise FWE (family-wise error)-corrected $P < 0.05$. The marked results were shown by XjView software following MNI coordinates. Finally, a similar statistical analysis was applied to the VBM analysis (the total intracranial volume calculated from VBM analysis was added as a covariate).

Finally, the clusters with significant FC differences between the PD-A and PD-NA groups were defined as ROIs, and the mean FC values of the ROIs were extracted. Then, using SPSS 26.0, we applied a Spearman analysis to investigate the correlation between the HAMA scores with the FC values of each ROI in total PD patients. As to account for spurious correlations [29], next the mean FC values of the amygdala with the entire brain region containing the ROI that showed altered functional connectivity, but not just the significant cluster within the ROI, were extracted and Spearman correlated to the HAMA scores in the total PD group, as well as, each subgroup separately. As the entire brain region still contains clusters that were shown to have significantly different FC between the subgroups, a spearman permutation test was performed to ensure the robustness of this correlation using an R package coin (iteration = 1000) [30], the R package coin could be obtained in Supplementary Material.

3. Results

3.1. Population

Six PD patients were excluded for severe neurological or cerebrovascular diseases besides PD (n = 4), head motion (n = 1), and low MMSE score (n = 1). Finally, 33 PD patients and 19 HCs were enrolled in the analyses and were grouped as PD-A (n = 13, HAMA score $\geq$12), PD-NA (n = 20, HAMA score <12), and HC (n = 19).

3.2. Demographic and clinical data

No significant differences were found among the three groups in age, gender, years of education, H&Y staging, UPDRS-III, LEDD, MMSE, FAB, and FOGQ (all $P > 0.05$, corrected by Bonferroni). As expected, the PD-A participants' HAMA and HAMD scores were superior to PD-NA and HC participants (all $P < 0.05$), but those of PD-NA participants were similar in comparison to HC participants (all $P > 0.05$). Meanwhile, PD-A participants suffered from PD longer than PD-NA participants ($P < 0.05$). See Table 1 for details.

Table 1
Comparison of demographic and clinical data among study subgroups.

	PD-A (n = 13)	PD-NA (n = 20)	HC(n = 19)	P-value
Gender (M/F)	6/7	13/7	10/9	0.534[a]
Age (years)	68.92 ± 6.02	62.1 ± 8.54	63.95 ± 8.95	0.069[b]
Years of education (years)	10.27 ± 2.22	10.13 ± 3.55	10.42 ± 3.64	0.768[c]
LEDD (mg)	457.69 ± 202.24	331.25 ± 138.87	NA	0.063[d]
Disease duration (years)	6.23 ± 3.68	3.08 ± 2.15	NA	0.012[d,*]
H&Y	2.35 ± 0.83	1.83 ± 0.69	NA	0.059[d]
UPDRS-III	25.85 ± 13.4	19.80 ± 8.92	NA	0.129[d]
FOGQ	6.54 ± 8.33	2.35 ± 4.63	NA	0.117[d]
HAMA	18.92 ± 5.22	6.1 ± 2.65	3.53 ± 1.9	0.000[b,*]
HAMD	12.85 ± 5.34	4.35 ± 2.21	4.26 ± 1.76	0.000[b,*]
MMSE	28.69 ± 1.38	28.95 ± 0.95	29.16 ± 0.9	0.672[c]
FAB	17.23 ± 1.36	17.3 ± 0.66	17.63 ± 0.6	0.246[c]

Abbreviations: PD-A, Parkinson's disease patients with anxiety; PD-NA, Parkinson's disease patients without anxiety; HC, healthy controls; LEDD, levodopa equivalent daily dose; H&Y, Hoehn & Yahr scales; UPDRS-III, Unified Parkinson's Disease Rating Scale; FOGQ, Freezing of Gait Questionnaire; HAMA, Hamilton Anxiety Rating Scale; HAMD, 17-item Hamilton Depression Rating Scale; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; NA, not applicable.
[a]: chi-square test; [b]: one-way analysis of variance (ANOVA); [c]: Kruskal-Wallis test; [d]: two-sample *t*-test.
*Signifies a significant difference between PD-A and both PD-NA and HC groups ($p < 0.05$) but not between PD-NA and HC groups.

3.3. Voxel-based morphometry results

According to the VBM analysis, no significant structural difference was found among the three groups.

3.4. Functional connectivity results

Regarding FC analysis based on the left amygdala, significant FC alterations were observed in the left intraparietal sulcus and precuneus. Similarly, FC analysis based on the right amygdala revealed significant FC alterations in the left hippocampus and putamen.

Then, we conducted the two-sample post hoc t-tests to investigate pair-wise differences in FC of each amygdala among three study groups. The brain areas with significant differences were reported in Table 2. In detail, compared with the PD-NA group, the PD-A participants' FC increased between the left amygdala and the left intraparietal sulcus extending to the precuneus. However, in the FC based on the right amygdala, the PD-A participants' FC values of the left hippocampus were decreased compared to the PD-NA group. The detailed results are displayed in Fig. 1.

No significant FC difference was found between PD-A and HC groups based on the left amygdala. However, the lower FC between the left putamen and right amygdala was observed in the PD-A group than in the HC group. The detailed results are shown in Fig. 2.

Compared to HC participants, no amygdala FC alteration was found in the PD-NA groups in this study.

3.5. Correlation between FC alterations and HAMA score

The relevance of the HAMA score with mean FC values of the two clusters with significant FC alterations between PD-A and PD-NA groups was explored using the Spearman correlation analysis. According to our results, a significantly negative correlation was observed between the HAMA score with the FC values of the cluster mainly located in the left hippocampus in the FC analysis based on the right amygdala in the total PD patients, which may be spurious [29]. As to account for the spurious correlation, next the mean FC values of the total left hippocampus based on the right amygdala were extracted for the Spearman correlation analysis with the HAMA scores. The results show that this correlation still exists in the total PD patients ($r = -0.459$, $p = 0.007$), as shown in Fig. 3. Then, the results of the permutation test also support the correlation between the mean FC values of the total left hippocampus based on the right amygdala and the HAMA scores in the total PD patients ($Z = -2.681$, $p = 0.01$). However, no correlation was observed between the FC values of the total left hippocampus with the HAMA scores within each PD subgroup. Additionally, there were no significant correlations between the HAMA score and mean FC values of the cluster in the FC analysis based on the left amygdala in the total PD patients.

4. Discussion

This study aimed to identify significant FC alterations between the bilateral amygdala and other brain areas in anxious PD compared to non-anxious PD patients and healthy participants. FC analysis revealed increased FC between the left amygdala with the left intraparietal sulcus and precuneus and decreased FC between the right amygdala with the left putamen and hippocampus in anxious PD patients. Besides, a negative correlation was found between the HAMA score and right amygdala FC with the left hippocampus. As mentioned above, this study shows unusual FC within the fear circuit in PD-A participants.

In this study, we found that PD-A subjects suffered from PD longer than PD-NA subjects, which might be related to gradual pathological changes in the amygdala in PD patients [16]. An unbalance in the fear circuit may cause PD anxiety because of the amygdala's hyperactivity [31]. Responsible for the export and import functions of the fear circuit, the amygdala takes part in discovering fear threats, transferring messages to other areas of the fear circuit, then finally generating anxiety emotions [14,32]. Numerous previous studies have reported that abnormal alterations in the amygdala closely correlate with anxiety in or not in PD. The amygdala shows special hyperactivity in the face of fearful visual inputs in PD patients, which may indicate that the amygdala has an essential role in the adverse adaptive response to threatening visual stimuli [33]. According to a morphological study, the VBM study reported the reduced volume of the left amygdala in anxious PD patients, supporting the biological underpinnings of the amygdala in anxiety [17]. An animal study revealed that somatostatin interneurons in the amygdala participate in fear discrimination retrieval

Table 2
Regions with FC differences based on amygdala between every two groups.

				Peak-point MNI coordinate			
Regions (AAL)	Side of amygdala based	Side	Cluster size	X	Y	Z	Z value
PD-A increased vs. PD-NA							
Intraparietal sulcus/Precuneus	L	L	90	−30	−60	63	5.429
PD-A decreased vs. PD-NA							
Hippocampus	R	L	89	−30	−15	−15	−7.540
PD-A decreased vs. HC							
Putamen	R	L	79	−27	−18	9	−6.474

Abbreviations: FC, functional connectivity; AAL, Anatomical Automatic Labeling; MNI, Montreal Neurological Institute; PD-A, Parkinson's disease patients with anxiety; PD-NA, Parkinson's disease patients without anxiety; HC, healthy controls; L, left hemisphere; R, right hemisphere.

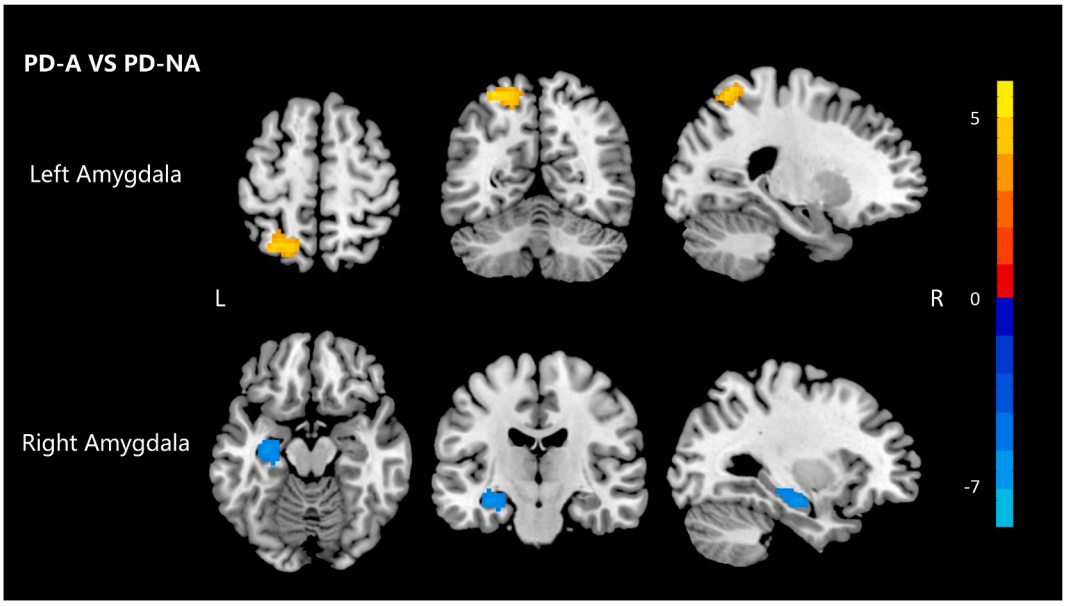

Fig. 1. PD-A VS PD-NA: Brain regions with significant FC differences between PD-A and PD-NA groups. PD-A: Parkinson's disease patients with anxiety; PD-NA: Parkinson's disease patients without anxiety; Left Amygdala: results of FC analysis based on the left amygdala; Right Amygdala: results of FC analysis based on the right amygdala; L: left; R: right (Hot/cold colors demonstrate higher/lower FC values in the PD-A group than the PD-NA group). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

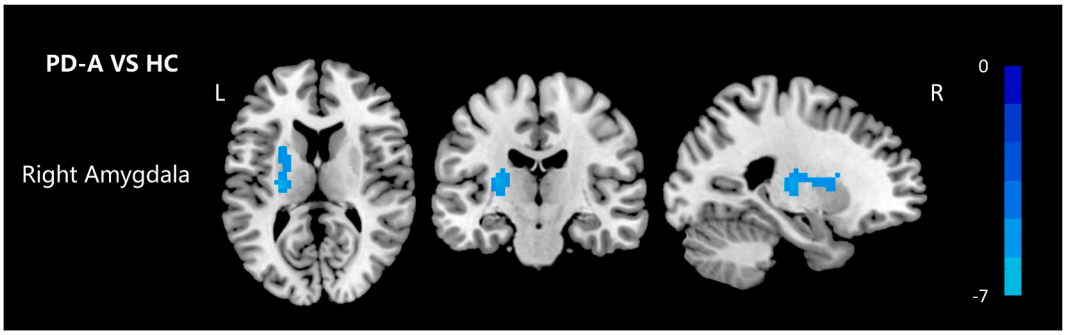

Fig. 2. PD-A VS HC: Brain regions with significant FC differences between PD-A and HC groups. PD-A: Parkinson's disease patients with anxiety; HC: healthy controls; Right Amygdala: results of FC analysis based on the right amygdala; L: left; R: right (Cold colors demonstrate lower FC values in the PD-A group than HC group). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

[34].

Moreover, explicit threat memory and threat assessment conditions also cause changes in the amygdala-frontal circuit [35]. Besides, changes in some neurotransmitter receptors in the amygdala, such as metabotropic glutamate receptor 5 and CB1 receptor, are also related to anxiety severity [36,37]. Therefore, we considered that longer PD duration in PD-A participants than in PD-NA participants could be used to explain possible persistent pathological changes in the amygdala in PD with anxiety and its influence on emotional disorders. However, this is also why we mainly focused on exploring the relationship between patterns of amygdala FC with anxiety disturbances.

Reduced FC of the right amygdala was found with another important node in the fear circuit, i.e., the hippocampus in PD-A participants relative to PD-NA participants, which negatively correlated with the severity of anxiety. The hippocampus has an important effect on emotional regulation by encoding and retrieving contextual representations [11,38]. Therefore, decreased ability of the hippocampus to control contextual retrieval, which leads to recovering cleared fear conditioning, is considered one of the possible mechanisms in the development of anxiety [39]. Additionally, the hippocampus inhibits fear conditioning by extinction to downregulate amygdala activity [31]. These studies show that the interaction between the amygdala with hippocampus affects human anxiety emotional regulation. Besides, the hippocampus also assesses the threat level [31]. For example, a rat study reported that the mouse's hippocampus participates in the reaction to acute stress [40], showing that alterations of the hippocampus may induce an

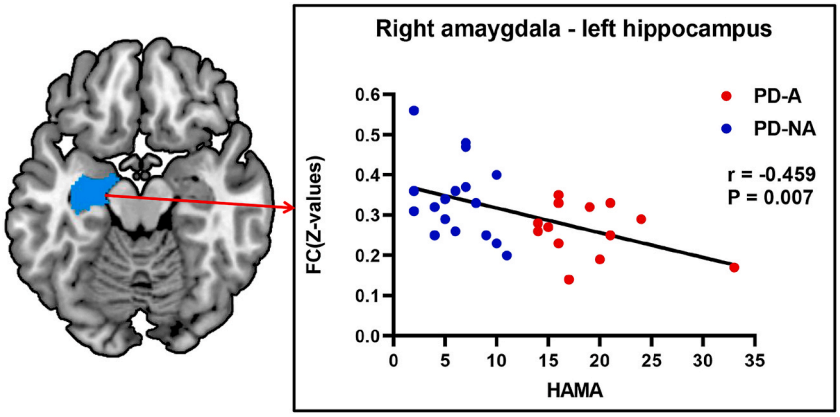

Fig. 3. Correlation analysis between the HAMA score and mean FC values of the left hippocampus with significant differences in the FC analysis based on the right amygdala in total PD patients. PD-A: Parkinson's disease patients with anxiety; PD-NA: Parkinson's disease patients without anxiety; FC, functional connectivity; HAMA, Hamilton Anxiety Rating Scale.

aberrant acute stress response, which in turn may cause anxiety disorder. Consequently, we assumed that the decreased FC between the amygdala and hippocampus presumably reflected the weakened down-regulation of the hippocampus on the amygdala, leading to amygdala hyperactivation, generating anxiety emotions.

The putamen is also a vital node of the fear circuit, which is in charge of emotional and motor regulation, that was observed to have decreased FC with the right amygdala in PD-A participants compared with HC participants. In a previous study using FC analysis based on the putamen, the decreased putamen FC with the other brain areas of the fear circuit, such as ACC and insular, was detected in anxious PD patients [22]. Our results further support decreased FC within the fear circuit in anxious PD patients. In addition, it has been reported that anxiety may be closely related to FOG in PD [41], but no statistical difference in FOGQ scores was found between PD subgroups in this study. Contrary to our results, increased putamen FC with the amygdala was detected in PD patients with FOG [42]. This may be related to the overactivation of the amygdala at the resting state in which case the conditions required to trigger the threshold of fear are reduced, making it more prone to generate fear emotion in the face of the potential risk of falling [43], and the synchronous activity of putamen ready for the promotion of motor regulation when necessary [44] in PD patients suffering from FOG. Relatively, the reduced amygdala FC with the putamen in our study may be attributed to the dopamine deficiency in the putamen in PD patients with anxiety, leading to difficulty transferring attention away from the external fear stimuli [45] because of the putamen hypoactivation. Some PET or SPECT studies showed that lower dopamine transporter density in the putamen predicts more severe anxiety disorder in PD [46,47]. Additionally, the animal model with PD showed a strong relationship between dopamine deficiency in the putamen and anxiety severity [48,49].

The intraparietal sulcus and precuneus showed increased FC, with the left amygdala separately as the key part of the dorsal attention network (DAN) and default mode network (DMN). The intraparietal sulcus in the human brain, like the monkey brain, participates in monitoring and responding to threatening stimuli evoking fear together with the amygdala [50]. Hence, high connectivity between the intraparietal sulcus and amygdala serves a purpose in anxiety observed in PD. In addition, precuneus activation is involved in self-relevant emotional processing [51] and self-focused sustained attention [52], which may cause anxiety. It has also been shown that increased FC density in the precuneus of PD patients compensates for abnormal brain function [53]. Therefore, the increased amygdala FC with the precuneus may reflect a high degree of synchronization between self-attention concentration and anxiety output. Furthermore, the low putamen FC with the precuneus was detected in PD patients with anxiety [40], which was indirectly consistent with our results. Besides, the volume of precuneus is negatively associated with anxiety severity in both anxious patients with or without PD [54,55], supporting the pathological basis of the precuneus in anxiety.

Overall, the clusters with significant amygdala FC differences are all located in the left hemisphere in this study, which is consistent with previous studies that anxiety in PD is closely related to left hemisphere involvement [56]. For instance, stroke patients in the left hemisphere tend to be more prone to anxiety [57]. In addition, the right amygdala may respond to existing danger or threat [58], which may correspond to reduced hippocampus control over contextual retrieval and the concentration of attention on external stimuli mediated by the putamen. Additionally, the left amygdala may respond to probable or imagined threats in future [58], which may be related to sustained attention on the internal self mediated by the precuneus.

Furthermore, although previous studies have proposed to observe a reduction in the amygdala, hippocampus, and precuneus volume in anxious patients with or without PD [17,54,55,59], no similar structural changes were found in this study. Therefore, we thought this might show that atrophic structural changes result from long-term functional changes in PD with anxiety and that fMRI using the SMS technique may be a more sensitive neuroimaging marker for anxiety in PD.

Several limitations should be pointed out in the research: (1) firstly, the sample number of this research was too small. It was difficult to run a comparison between subgroups of anxiety in PD. Besides, the deficiency of correlation between the HAMA scores with the left hippocampus FC values in each PD subgroup may be on account of the small sample size of each subgroup. (2) Although we had conducted screening and excluded the PD patients with obvious clinical depression at the PD clinic, the PD-A participants' HAMD score

was greater than that of miscellaneous participants, which was in line with that anxious PD patients are more possible to suffer from depression [3]. In addition, this may also be because of partial overlap of rating rubrics of the HAMA and HAMD scales. Although the HAMD score was chosen as one of the covariates, its impact on the outcomes could not be eliminated. (3) While the complete amygdala was chosen for FC seed selection in this study, there are more detailed subdivisions in the amygdala structure [9,60]. Subsequent studies should focus on the role of subtle amygdala subunits to further investigate the mechanism of anxiety in PD. (4) Lastly, we had not finished the follow-up work. This was a cross-sectional survey at present. The longitudinal changes in anxiety severity in PD cannot be studied at present. After finishing the follow-up work, we would try our best to further investigate the potential neuromechanisms in the anxiety of PD.

5. Conclusion

Our results showed that PD-A subjects had abnormal FC alterations between the amygdala with the left hippocampus, putamen, intraparietal sulcus, and precuneus relative to PD-NA and HC participants. Furthermore, the amygdala FC with the hippocampus negatively correlated with the severity of anxiety of PD. These abnormal brain areas may serve as new neural targets for treating anxiety in PD. Our findings more concretely revealed the FC pattern within the fear circuit in anxious PD patients, which may help further to elucidate the neuromechanism in the anxiety of PD. However, aberrant functional changes of 'the fear circuit' are not the only mechanism. Anxiety disorder in PD is the result of the interaction of multiple complex circuits in the brain, and further studies are required to explain how these circuits work together to cause or aggravate anxiety symptoms in PD.

Ethics statement

The ethics committee's approval of the Affiliated Wuxi People's Hospital of Nanjing Medical University was obtained. All the subjects signed written informed consent.

Author contribution statement

Kaidong Chen: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Li Zhang: Conceived and designed the experiments; Performed the experiments.

Feng Wang: Conceived and designed the experiments.

Haixia Mao, Qunfeng Tang, Guofeng Shi, Yiping You, Qingfang Yuan, Bixue Chen: Contributed reagents, materials, analysis tools or data.

Xiangming Fang: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e15871.

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