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Disrupted emotion regulation and spontaneous neural activity in panic disorder: a resting-state fMRI study

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Abstract

Background: Emotional dysregulation, particularly unconscious catastrophic cognitions, plays a pivotal role in the genesis of panic disorder (PD). However, no studies have yet applied the percentage of amplitude fluctuation (PerAF) metric in resting-state functional magnetic resonance imaging to examine spontaneous neural functioning and its relation to catastrophic cognitions in PD.

Objectives: To explore the interplay between resting-state neural activity, functional connectivity (FC), and unconscious emotion regulation in individuals with PD.

Design: Cross-sectional study.

Methods: The study encompassed 51 participants, including 26 PD patients and 25 healthy individuals. The PerAF algorithm was employed to explore the local spontaneous neural activity in PD. Regions exhibiting aberrant spontaneous neural activity were used as seed points for whole-brain FC analysis. Correlations were utilized to examine associations between local neural activity patterns and neurocognitive assessments in PD.

Results: The study revealed that compared to healthy individuals, PD patients exhibited elevated PerAF values in key emotion-regulation-related brain regions, including the ventromedial prefrontal cortex (vmPFC), striatum, amygdala, dorsomedial prefrontal cortex (dmPFC), and cerebellum. In addition, the resting-state FC between vmPFC and precuneus, as well as between the cerebellum and precuneus, was weakened in PD patients. Furthermore, positive associations were noted between PerAF measurements of vmPFC and amygdala and catastrophizing scores.

Conclusion: PD involves regional and network-level alterations in resting-state brain activity. The fronto-striatal-limbic circuits play a critical role in catastrophic-style emotion regulation in PD patients. Reduced FC within the default mode network and cerebellum-default mode network may signify a coordination anomaly in introspection and cognitive activities in PD. These findings complement the model of implicit emotion regulation in PD and suggest potential intervention targets.

Plain language summary

Understanding emotion control and brain activity in panic disorder using brain scans

Panic disorder is a condition where people experience sudden and intense episodes of fear and anxiety. This study investigates how the brains of people with panic disorder function when they are at rest and how they manage their emotions. We used a special brain scan called resting-state fMRI to measure spontaneous brain activity. We studied 51 people, including 26 with panic disorder and 25 healthy individuals. Our results

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showed that people with panic disorder have higher levels of brain activity in areas related to emotion control, such as the ventromedial prefrontal cortex (vmPFC), striatum, amygdala, dorsomedial prefrontal cortex (dmPFC), and cerebellum. Additionally, connections between certain brain areas, such as the vmPFC and precuneus, and the cerebellum and precuneus, were weaker in those with panic disorder. We also found that higher activity in the vmPFC and amygdala was linked to stronger feelings of catastrophic thinking, where minor issues are perceived as major problems. These findings suggest that panic disorder is associated with changes in brain activity and connectivity, particularly in regions involved in emotion regulation. Understanding these changes can help us develop better treatments for panic disorder by targeting specific brain areas and networks involved in managing emotions.

Keywords: catastrophic cognition, emotion regulation, functional connectivity, panic disorder, prefrontal cortex

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Introduction

Panic disorder (PD) is a severe anxiety disorder that significantly affects both mental and physical well-being, with a lifetime prevalence of 2%–5%.[1] It is characterized by recurrent, unpredictable, and intense panic episodes, often accompanied by a sense of impending doom or loss of control. Following such episodes, patients commonly experience anticipatory anxiety due to the fear of a recurrence.[2] The emotion regulation theory asserts that a disparity in strategies for regulating emotions is a crucial element in the development of PD,[3,4] where the catastrophic cognition approach plays a pivotal role in its onset.[5] According to the catastrophic cognition model, panic attacks stem from a catastrophic misinterpretation of physical sensations, which may become conditioned triggers, initiating and perpetuating episodes of PD.[5,6]

Emotion regulation can be categorized into explicit (conscious) and implicit (automatic) forms based on conscious involvement.[7] However, applying brain stimulation treatments targeting regions associated with explicit emotion regulation in PD did not result in significant symptom relief for patients.[8] Despite efforts, recent meta-analyses focusing on the application of repetitive transcranial magnetic stimulation (rTMS) in treating PD have not produced conclusive evidence of efficacy.[9,10] Additional research is warranted to identify more promising therapeutic targets.

Research in psychopathology has indicated that difficulties in emotion regulation within the domain of anxiety are fundamentally associated with the failure of implicit emotion regulation strategies within individuals.[11] When individuals with PD experience negative emotions, they tend to employ maladaptive strategies like catastrophic thinking, resulting in uncontrollable and repetitive contemplation, and exaggeration of the impact of negative events.[12] They automatically interpret otherwise non-threatening interoceptive and exteroceptive stimuli as threats, ultimately culminating in panic attacks and anticipatory anxiety.[5] The above theories and clinical practices highlight the pivotal role of implicit emotion regulation in PD onset.

ERP (event-related potentials) study has identified automatic processing abnormalities in individuals with PD, spanning responses to both emotional and non-emotional visual and auditory stimuli.[13] These anomalies are characterized by altered negative wave amplitudes, indicating disrupted automatic information processing. Zhang et al., employing implicit emotion regulation tasks, coupled with ERP and functional magnetic resonance imaging (fMRI), pinpointed emotional automatic regulation deficits in PD. These were marked by a diminished late positive potential amplitude effect,[14,15] along with reduced activity in the dorsolateral prefrontal cortex (dlPFC) and dorsomedial prefrontal cortex (dmPFC).[16]

Therefore, we infer that the core mechanism underlying emotion regulation disturbances in PD is more likely to originate from implicit and automatic aberrations in emotion regulation.

Resting-state MRI provides a valuable approach for exploring the implicit emotion regulation features in psychiatric disorders.[17] It allows the capture of spontaneous brain activity,[18] crucial for understanding how individuals, especially those with PD, navigate their emotions during non-task-oriented moments. Previous studies on anxiety disorders using resting-state fMRI revealed a notable increase in the amplitude of low-frequency fluctuation (ALFF) values within the medial prefrontal cortex (PFC) linked to emotion regulation, encompassing the ventromedial prefrontal cortex (vmPFC) and the dmPFC,[19] along with regions within the limbic system associated with fear processing.[20] In addition, weakened functional connectivity (FC) between the medial PFC and the precuneus was observed, closely tied to pathological fear and avoidance.[21] PD patients also exhibited increased ALFF values in the striatum related to emotional assessment and integration.[22] These findings suggest that PD may involve aberrant spontaneous neural activity across multiple brain regions, manifesting in both regional and network domains.

The percent amplitude of fluctuation (PerAF) presents an innovative approach to resting-state fMRI analysis.[23] Unlike traditional voxel-level assessment of blood oxygenation level-dependent (BOLD) signals, PerAF measures the percentage of BOLD fluctuations relative to the mean BOLD signal intensity at each time point, offering a direct gauge of the variability in BOLD signals during resting-state conditions.[24] PerAF metrics exhibit reduced vulnerability to errors in signal strength, as they do not rely on arbitrary units and remain unaltered by the original signal. In comparison to standard metrics like ALFF, PerAF allows for direct analysis of data at the group level.[24] Moreover, when using fractional ALFF, PerAF effectively eliminates potential confounds related to voxel-specific fluctuation amplitudes.[24] Research has shown that PerAF demonstrates superior accuracy compared to other fMRI analysis techniques such as ALFF, regional homogeneity, and degree centrality.[23,25] Consequently, PerAF emerges as a reliable, efficient, and direct voxel-level index for investigating resting-state fMRI, offering insights into spontaneous neural activity changes. Despite its extensive application in psychiatric and neurological disorders,[26–28] there remains a scarcity of research utilizing PerAF to explore spontaneous neural activity alterations in individuals with PD.

This study aims to explore emotional regulation and spontaneous neural activity in PD using neuropsychological assessments and resting-state fMRI. Fronto-striatal-limbic circuits, closely tied to catastrophic cognitions,[29,30] play a pivotal role in emotional regulation.[31] Specifically, overactivation of the vmPFC is associated with excessive introspection and attention to internal emotions and bodily sensations,[32] while hyperactivity in the amygdala (a component of the limbic system) is associated with heightened worry and fear, resulting in catastrophic thinking in PD.[29] In addition, the striatum serves as a crucial mediator, integrating emotional information from the prefrontal and limbic systems.[33] Interaction between catastrophic thinking and brain networks has been observed.[34] Based on these findings and previous research, we hypothesize that PD patients exhibit abnormal spontaneous neural activity in the fronto-striatal-limbic circuits, influencing their catastrophic-style emotional regulation. Furthermore, this aberrant spontaneous neural activity in PD may manifest at both regional and network levels.

Materials and methods

Participants

The study, conducted as a case–control study, involved 26 individuals diagnosed with PD, alongside 25 healthy controls (HC), with matching criteria including age, sex, and educational background. The sample size for this study was determined based on previous imaging studies of PD.[13,14] They were sourced from the First Affiliated Hospital of Dalian Medical University, including its emergency and inpatient departments, as well as from the surrounding communities. Demographic and clinical data are consistent with our previous report.[16] PD patients met the diagnostic criteria for PD as specified in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).[35] HC underwent screening for DSM-5 Axis-I history to verify the non-existence of mental disorders. The eligibility prerequisites for participants were as delineated below: (1) a minimum of 2 weeks without antipsychotic drugs (with a 48-h medication-free period for benzodiazepine intake) prior to the

scan; (2) an age range of 18–65 years, regardless of gender; (3) right-handedness; (4) no contraindications for fMRI examination; (5) the Mini-Mental State Examination (MMSE) score of 24 or higher; (6) absence of a past record of substance dependence or serious brain or other physical illnesses; and (7) voluntary participation with the signing of informed consent. The reporting of this study conforms to the STROBE statement (Supplemental Material).[36] This study strictly adhered to the principles outlined in the Helsinki Declaration and received approval from the Ethics Committee of Dalian Medical University.

Neuropsychological assessments

Every participant underwent the Hamilton Anxiety Rating Scale (HAMA) for the evaluation of anxiety indicators, and the Hamilton Depression Rating Scale (HAMD) to appraise depressive signs. We also employed the MMSE to assess cognitive status, and the Cognitive Emotion Regulation Questionnaire (CERQ) to understand individual cognitive emotion regulation strategies.[37] For PD patients, we used the Panic Disorder Severity Scale (PDSS) to assess the severity of their condition.[38]

MRI data acquisition

Every participant underwent scanning with a 3.0T magnetic resonance imaging machine from GE Healthcare in Chicago, IL, USA. Throughout the scans, participants were in a supine position, employing earplugs to mitigate noise, and a foam pad to minimize head motion. They were directed to stay awake with closed eyes, refrain from active contemplation, and maintain a steady head posture. Prior to data collection, each participant underwent T2-Weighted Imaging (T2WI) and Fluid-Attenuated Inversion Recovery (FLAIR) scans to exclude subjects with structural brain abnormalities or evident brain disorders. Resting-state functional images were collected employing echo planar imaging and the subsequent parameters were utilized: Repetition Time (TR) = 2000 ms, Echo Time (TE) = 30 ms, flip angle = 90°, 36 slices, slice thickness = 2.6 mm, gap = 1.4 mm, Field of View (FOV) = 64 mm × 64 mm, voxel size = 3 mm × 3 mm × 3 mm, and 180 time intervals were recorded in the transverse plane. High-resolution T1-weighted anatomical scans were acquired via the BRAVO sequence, featuring the subsequent settings: TR = 8.8 ms, TE = 1 ms, flip angle = 12°, slice thickness = 1 mm, FOV = 256 mm × 256 mm, voxel size = 1 mm × 1 mm × 1 mm, and acquired in the sagittal plane.

fMRI at preprocessing

The processing of resting-state fMRI data was carried out utilizing RESTplus V1.24 software[24] in MATLAB 2014a (MathWorks, Natick, MA, USA). The first 10 time points were excluded to accommodate for potential scanner instability while participants acclimated to the scanning noise. This was followed by slice timing correction and motion realignment. The individual anatomical images were aligned with the average functional image and subsequently partitioned into distinct tissue categories. Following this, the realigned images underwent normalization to the standard Montreal Neurological Institute template with a voxel size of 3 mm × 3 mm × 3 mm, followed by a smoothing process using a 6 mm full-width at half maximum (FWHM) Gaussian kernel. Linear detrending was subsequently employed on the smoothed images, and nuisance signals (comprising Friston-24 model head motion parameters, white matter, and cerebrospinal fluid) were regressed out to mitigate physiological artifacts. Finally, a band-pass filter ranging between 0.01 and 0.08 Hz was applied to attenuate low-frequency fluctuations. Following data preprocessing, PerAF values, serving as indicators reflecting the strength of neuronal activity with high sensitivity and specificity,[24] were computed, resulting in the generation of PerAF, mPerAF, and zPerAF maps. mPerAF represents the mean percentage amplitude fluctuation, while zPerAF represents the standardized percentage amplitude fluctuation. PerAF computation is performed for each voxel, resulting in each voxel receiving a corresponding PerAF value. During correlation analysis, the average value of each region was utilized.

Functional connectivity

This study employed a seed-based approach using brain regions that showed significant differences in PerAF values between the PD group and the HC group for whole-brain FC analysis. To generate FC maps, the average time series of voxels within each participant's seed regions was extracted. Pearson's correlation values were computed between the average temporal patterns of the seed regions and the temporal profiles of voxels across

Table 1. Demographics and neuropsychological data of PD and HC groups.

Variable	PD group	HC group	*p* Value
Gender distribution	M:F (13:13)	M:F (12:13)	0.89[a]
Age (years)	35.6 ± 8.0	35.2 ± 6.7	0.86
Education level (years)	13.0 ± 3.1	14.4 ± 2.0	0.07
PDSS score	10.3 ± 5.0	N/A	N/A
HAMA (anxiety)	15.3 ± 6.3	2.3 ± 2.1	<0.001
HAMD (depression)	10.8 ± 5.2	3.5 ± 1.8	<0.001
CERQ (catastrophizing)	5.7 ± 2.0	3.4 ± 1.3	<0.001

[a]*p* Value for chi-square test, $\chi^2 = 0.20$.
CERQ, Cognitive Emotion Regulation Questionnaire; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; HC, healthy controls; PD, panic disorder; PDSS, Panic Disorder Severity Scale.

the entire brain. To enhance normality, the correlation coefficients were subjected to Fisher's *r*-to-*z* transformation for conversion into *z*-values. These resulting *z*-score maps were subsequently utilized for second-level analysis.

Statistical analyses

Demographic data were analyzed using SPSS 26.0 (IBM Corporation, Armonk, NY, USA). Continuous variables underwent independent samples *t*-tests if they followed a normal distribution; otherwise, non-parametric tests were employed. Categorical variables underwent assessment via chi-square tests. A significance level of $p < 0.05$ was established for all analyses. Image data were statistically analyzed using DPABI V4.0 software (Institute of Psychology, Chinese Academy of Sciences, Beijing, China).[39] Two-sample *t*-tests were employed to compare PerAF values between the two groups, with statistical significance defined at $p < 0.05$. We applied Gaussian Random Field (GRF) theory to correct for multiple comparisons, with a significance threshold set at $p < 0.01$ at the voxel level and $p < 0.05$ at the cluster level, using a two-tailed approach. Two-sample *t*-tests were also used to compare FC values between the two groups, with a significance level of $p < 0.05$ (GRF corrected). Pearson correlation analyses were performed to assess the associations between abnormal PerAF values in the PD group, FC brain regions' *z*-scores, and patients' scores on HAMA, HAMD, the catastrophizing dimension in CERQ, and PDSS. The statistical significance level was set at $p < 0.05$.

Results

Demographics and clinical characteristics

Table 1 summarizes the demographics and neuropsychological data. Gender distribution did not significantly differ between groups ($\chi^2 = 0.20$, $p > 0.05$), and there were no significant age disparities (PD: 35.6 ± 8.0 years, HC: 35.2 ± 6.7 years, $p > 0.05$). Although the variance in education level was marginally significant (PD: 13.0 ± 3.1 years, HC: 14.4 ± 2.0 years, $p > 0.05$), it was not considered a substantial difference. In the PD group, the PDSS score averaged 10.3 ± 5.0. Notably, significant disparities were evident in anxiety (HAMA—PD: 15.3 ± 6.3, HC: 2.3 ± 2.1, $p < 0.05$) and depression levels (HAMD—PD: 10.8 ± 5.2, HC: 3.5 ± 1.8, $p < 0.05$) between PD and HC participants. Regarding CERQ results, the PD group demonstrated notably lower catastrophizing scores (PD: 5.7 ± 2.0, HC: 3.4 ± 1.3, $p < 0.05$).

Group differences in PerAF

Significant differences in spontaneous neural activity patterns were observed when comparing the PD group to the HC cohort. In contrast to the HC group, PD patients exhibited increased PerAF values ($p < 0.05$, GRF-corrected) in the vmPFC, striatum (including pallidum, putamen, and caudate), the limbic system (including amygdala and hippocampus), dmPFC, and cerebellum (see Figure 1 and Table 2). In addition, even with a more stringent GRF correction threshold ($p < 0.001$ at the voxel level and $p < 0.05$ at the

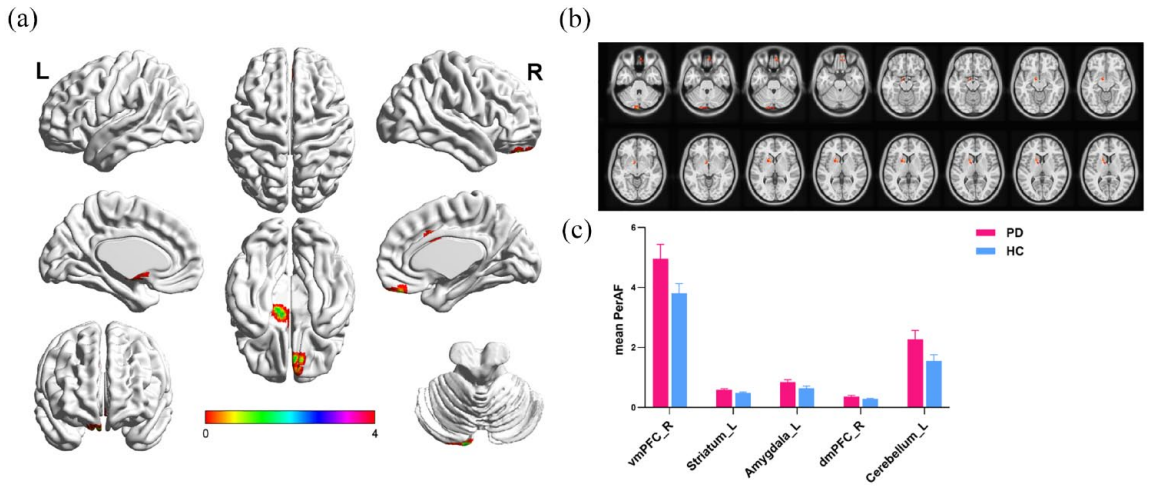

Figure 1. PerAF signal comparison: PD versus HC. Panels (a) and (b) highlight regions with elevated PerAF values in the PD group, encompassing the vmPFC, striatum, amygdala, dmPFC, and cerebellum. The color bar indicates regions with heightened PerAF values. Panel (c) illustrates the mean PerAF values for both groups, with significant differences observed in each brain region (all $p < 0.05$, GRF-corrected).
dmPFC, dorsomedial prefrontal cortex; HC, healthy controls; L, left; PerAF, percentage of amplitude fluctuation; PD, panic disorder; R, right; vmPFC, ventromedial prefrontal cortex.

cluster level), the striatum (including the pallidum and putamen) still showed significant activation ($p < 0.05$, GRF-corrected).

Differences in resting-state FC between groups

In contrast to the HC group, PD patients exhibited reduced FC between the right vmPFC and the medial PFC (extending into the dmPFC), as well as diminished FC between the vmPFC and the precuneus (extending into the posterior cingulate cortex and inferior parietal lobule; Figure 2(a)–(c), Table 3), indicating decreased FC within the default mode network (DMN). In addition, PD patients exhibited reduced FC between the left cerebellum and the precuneus (Figure 2(d)and (f), Table 3), suggesting reduced FC between the DMN and cerebellar networks, all with $p < 0.05$ (GRF-corrected).

Table 2. Brain regions with aberrant PerAF values in the PD group compared to the HC group.

Brain regions	Hemisphere	Brodmann area	Cluster (mm^3)	Peak *t* values	MNI coordinates		
					x	*y*	*z*
Ventromedial prefrontal cortex	Right	11	675	3.6819	6	57	−27
Striatum (pallidum, putamen, and caudate)	Left	/	918	4.0615	−9	6	−3
Amygdala ext. hippocampus	Left	35	324	3.4191	−15	− 7	−18
Dorsomedial prefrontal cortex	Right	32	324	3.1203	13	13	35
Cerebellum	Left	/	675	3.7530	−6	−93	−33

Statistical threshold of Gaussian random field theory $P_{GRF} < 0.05$ was utilized for cluster correction.
ext., extending into; HC, healthy controls; MNI, the Montreal Neurological Institute coordinates; PerAF, percentage of amplitude fluctuation; PD, panic disorder.

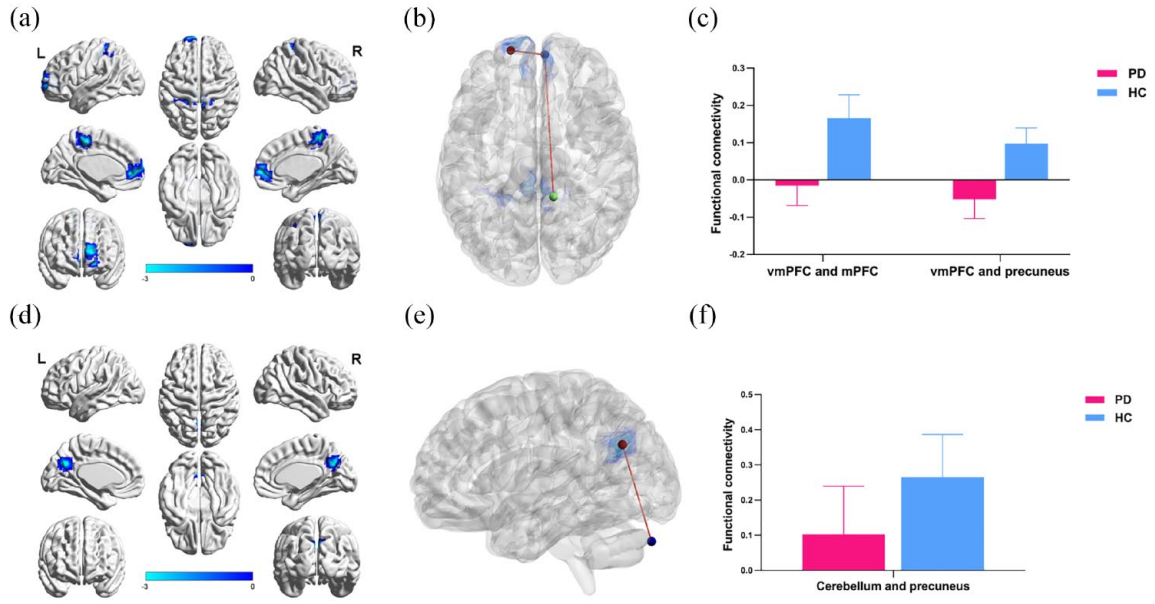

Figure 2. Brain functional connectivity: PD versus HC. Panels (a, b) show reduced connectivity in PD between vmPFC and mPFC as well as precuneus. Panel (c) displays average connectivity values for vmPFC-medial PFC and vmPFC-precuneus. Panels (d, e) indicate decreased connectivity in PD between the cerebellum and precuneus. Panel (f) presents average connectivity values for cerebellum-precuneus. Blue in the color bar signifies decreased connectivity.
HC, healthy controls; L, left; mPFC, medial prefrontal cortex; PD, panic disorder; R, right; vmPFC, ventromedial prefrontal cortex.

Correlation analysis

In the PD patient group, the PerAF value of the right vmPFC showed a positive correlation with the catastrophizing score (R-squared = 0.151, $p = 0.050$; Figure 3(a)). Similarly, the PerAF metric of the left amygdala demonstrated a positive association with the catastrophizing score in this group (R-squared = 0.178, $p = 0.032$; Figure 3(b)). No substantial correlations were observed between the PerAF value of the left putamen, as well as the FC values of right vmPFC-medial PFC, right vmPFC-precuneus, and left

Table 3. Whole-brain functional connectivity with vmPFC/Cerebellum as seed regions in the PD group compared to the HC group.

Brain regions	Hemisphere	Brodmann area	Cluster (mm^3)	Peak *t* values	MNI coordinates		
					x	*y*	*z*
Left ventromedial prefrontal cortex as a seed							
Medial prefrontal cortex ext. dorsomedial prefrontal cortex	Bilateral	10/32	9153	−4.038	−18	60	−6
Precuneus ext. posterior cingulate cortex inferior parietal lobule	Bilateral	2/5/40	7992	−5.067	12	−42	63
Left cerebellum as a seed							
Precuneus	Bilateral	7/19/23	7587	−5.092	−9	−66	30

Statistical threshold of Gaussian random field theory $P_{GRF} < 0.05$ was utilized for cluster correction.
ext., extending into; HC, healthy controls; MNI, the Montreal Neurological Institute coordinates; PD, panic disorder; vmPFC, ventromedial prefrontal cortex.

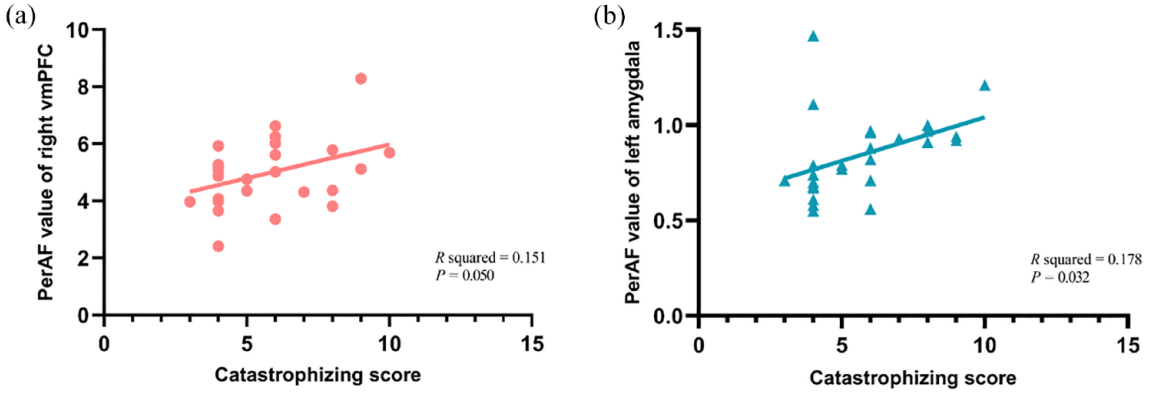

Figure 3. PerAF values and emotion regulation strategies in PD patients. (a) Right vmPFC PerAF positively correlates with catastrophizing score. (b) Left amygdala PerAF positively correlates with a catastrophizing score.
PerAF, percent amplitude of fluctuation.; PD, panic disorder; vmPFC, ventromedial prefrontal cortex.

cerebellum-precuneus, with clinical symptoms (HAMA total score, HAMD total score, and PDSS total score) in the patient group ($p > 0.05$).

Discussion

Currently, research on the neural underpinnings of emotion regulation in PD patients has primarily focused on task-related brain functional circuits. This study, based on the theory of catastrophizing emotion regulation, is the first to utilize the PerAF metric from resting-state fMRI to explore the connection between spontaneous neural activity and automatic emotion regulation in PD patients. Our results revealed that, compared to HC, PD patients exhibited a significant increase in catastrophizing scores and elevated PerAF values in the vmPFC, striatum, amygdala, and cerebellum. Furthermore, we observed decreased FC between the vmPFC and the precuneus, as well as reduced FC between the cerebellum and the precuneus in PD patients compared to HC. In addition, we found positive correlations between the PerAF values of the vmPFC and amygdala and catastrophizing scores. These findings highlight the pivotal role of the vmPFC-striatum-amygdala circuit in PD's catastrophizing emotion regulation, manifesting not only at the regional but also at the network level.

In line with our previous research,[12] PD patients demonstrated significantly higher catastrophizing scores compared to healthy individuals using the CERQ. This suggests a tendency in PD individuals to engage in a cognitive pattern characterized by catastrophizing involving an exaggeration of both internal and external stimuli threats, a heightened emphasis on negative event aspects, and increased self-reflection.[12] Consequently, this catastrophizing emotion regulation pattern leads to reduced emotional regulation abilities, resulting in heightened negative emotions, diminished positive emotions, and ultimately, increased severity and frequency of panic attacks.[40]

Enhanced spontaneous neural activity was observed in key regions closely associated with emotion regulation, including the vmPFC, striatum, amygdala, dmPFC, and cerebellum. The vmPFC plays a pivotal role in cognitive functions such as emotional regulation, self-awareness, and introspection,[32] and is involved in processing self-relevant emotional information.[41] Studies indicate that increased spontaneous activity in the vmPFC is a prominent feature of affective disorders.[42] The heightened PerAF in the vmPFC may indicate increased resting-state activity in PD patients. This could lead to a tendency toward internal thoughts and self-focus, resulting in excessive attention to internal emotions and bodily sensations—characteristic of catastrophizing cognition. Ultimately, this may contribute to the onset of panic attacks.

The amygdala, as a component of the limbic system, is closely connected to the vmPFC and plays a crucial role in emotion regulation, particularly in relation to threat perception and fear.[43] Elevated PerAF values may indicate that the amygdala is hyperactive in PD patients during resting state, leading to an exaggerated sensitivity to potential threats and resulting in heightened

levels of anxiety and fear.[20,44] In addition, the striatum serves as a crucial mediator, integrating emotional information from the prefrontal and limbic systems.[33] Studies indicate that striatal activation plays a significant role in anticipatory anxiety in PD patients.[44] The dmPFC is linked to elucidating the emotional significance of stimuli and overseeing emotional experiences[45] and it also pertains to implicit emotion regulation in PD.[16,46] Our findings suggest that in spontaneous situations, PD patients exhibit enhanced activity in monitoring and reflecting upon emotional stimuli.[16]

In our study, the vmPFC, dmPFC, striatum, and amygdala collectively constitute the fronto-striatal-limbic circuits. Neurocircuits of fear and anxiety propose that coordinated activity between the medial PFC, striatum, and amygdala assesses the presence of threats.[31] These brain regions are closely interconnected, and emotions of fear and anxiety involve multiple pathways, including those from the amygdala to the striatum and mPFC, and from the mPFC to the striatum and amygdala.[47,48] In this study, PD patients exhibit heightened spontaneous neural activity in the fronto-striatal-limbic circuits, indicating disrupted neurocircuitry function, leading to excessive rumination and attention to threat information, ultimately triggering panic attacks and anticipatory anxiety. The observed positive correlations between PerAF values in the vmPFC and amygdala and catastrophizing scores suggest that as catastrophizing emotion regulation becomes more pronounced in PD patients, there is a corresponding increase in the abnormal spontaneous neural activity within the fronto-striatal-limbic circuits. This further underscores the pivotal role of this circuitry in implicit emotion regulation in PD.

Interestingly, we noted a diminished resting-state FC between the vmPFC and the medial PFC as well as the precuneus. The vmPFC, medial PFC, and precuneus are integral components of the DMN.[46] The DMN is a network of brain areas associated with introspection, self-assessment, memory, and future planning, among other inward-focused cognitive activities,[46] and its dysregulation has been closely linked to the occurrence of anxiety disorders.[49] This reduction may indicate potential difficulties in self-assessment and emotion regulation in PD patients. In addition, individuals with PD often exhibit catastrophizing cognitions, characterized by excessive worry and negative interpretations of external stimuli.[16] This tendency may render them more susceptible to perceived threats, potentially triggering anxiety symptoms. The diminished DMN activity may further compound their challenges in processing emotions and affective states.

We observed increased spontaneous activity in the cerebellum, consistent with previous findings.[49] In addition, we noted reduced resting-state FC between the cerebellum and the precuneus. While traditionally associated with motor control and coordination, emerging research suggests the cerebellum's involvement in emotion regulation and processing.[50] Studies indicate that the cerebellum communicates with emotion-regulating regions in the brain, exerting a modulatory role in emotion generation and regulation through the adjustment of emotion-related neural circuits.[50,51] Similar abnormalities in the cerebellum and DMN have been observed in other emotion-regulation-related psychiatric disorders.[52] Therefore, the weakened connectivity between the cerebellar network and the DMN in PD patients may contribute to difficulties in effectively regulating emotions through adjustment of emotion-related neural circuits.

Limitations

There are several constraints in this study. First, the relatively small sample size calls for broader validation in a more diverse population. According to recent research,[53] small sample sizes in neuroimaging studies can increase the risk of unreliable and non-reproducible results, limiting the generalizability of our findings. Therefore, larger sample sizes are essential to enhance the robustness and reproducibility of the results. Second, the cross-sectional design limits causal inferences between catastrophizing emotion regulation and brain activity abnormalities. Future research, employing longitudinal designs, is warranted. Third, despite all participants abstaining from antipsychotic drugs for at least 2 weeks before the scan, individual medication differences in the patient group may still affect the results. In addition, variations in education, anxiety, depression, and CERQ scores among patients could influence outcomes. Given the small sample size, future research will expand the sample to further explore these variables' impact on brain activation results. Finally, assessing PD patients' spontaneous brain activity was solely based on resting-state fMRI data. Utilizing multimodal

fusion techniques like simultaneous Electroencephalography (EEG)-fMRI imaging[54] and brain-computer interfaces[55] in future studies could offer deeper insights.

Conclusion

Our study highlights the crucial role of the fronto-striatal-limbic circuits, especially the vmPFC-striatum-amygdala pathway, in the catastrophic style regulation of emotions in PD patients. The positive correlation between PerAF values in the vmPFC and amygdala and catastrophizing scores underscores the significance of this circuit in implicit emotion regulation in PD. In addition, weakened resting-state FC within the DMN and between the cerebellum and DMN may contribute to difficulties in emotion regulation. In summary, our research advances the understanding of implicit emotion regulation in PD by emphasizing the interplay between spontaneous neural activity and catastrophic cognition. These nuanced changes in regional activity and network connectivity provide a comprehensive model for PD emotion regulation and offer potential insights for targeted interventions, such as rTMS and cognitive behavioral therapy.

Declarations

Ethics approval and consent to participate

Ethics approval for this study was obtained from the Ethics Committee of the First Affiliated Hospital of Dalian Medical University (Approval Number: KY2014-30). Written informed consent was obtained from all participants or their legal guardians where applicable.

Consent for publication

Patients were included only if they or their legal representative provided written consent for the publication of patient-related data.

Author contributions

Hai-Yang Wang: Conceptualization; Data curation; Formal analysis; Funding acquisition; Writing – original draft; Writing – review & editing.

Bei-Yan Guan: Data curation; Investigation; Writing – review & editing.

Shi-Yao Wang: Data curation; Writing – review & editing.

Ming-Fei Ni: Data curation; Writing – review & editing.

Yan-Wei Miao: Data curation; Writing – review & editing.

Feng Tian: Funding acquisition; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The datasets used in this study can be made available upon reasonable request by contacting the corresponding author.

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Supplemental material

Supplemental material for this article is available online.

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