Alteration of prefrontal cortex and its associations with emotional and cognitive dysfunctions in adolescent borderline personality disorder

Qian Xiao
Central South University
Liying Shen
Central South University
Haoling He
First Affiliated Hospital of Guangxi Medical University
Xueying Wang
Central South University
Yan Fu
Central South University
Jun Ding
Shenzhen Kangning Hospital
Furong Jiang
Central South University
Jinfan Zhang
Central South University
Zhejia Zhang
Central South University
Xiaoping Yi
yixiaoping@csu.edu.cn
Central South University
Bihong T. Chen
City of Hope National Medical Center

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Abstract

Background

The neurobiological mechanism of borderline personality disorder (BPD) in adolescents remains unclear. The study aimed to assess the alterations in neural activity within prefrontal cortex in adolescents with BPD and investigate the relationship of prefrontal activity with cognitive function and emotional regulation.

Methods

This study enrolled 50 adolescents aged 12–17 years with BPD and 21 gender and age-matched healthy control (HC) participants. Study assessment for each participant included a brain resting-state functional MRI (rs-fMRI), cognitive testing with Stroop Color-Word Test (SCWT) and clinical assessment questionnaires such as Borderline Personality Features Scale (BPFS), Difficulties in Emotion Regulation Scale (DERS), Ottawa Self-Injury Inventory and Childhood Trauma Questionnaire (CTQ). Fractional amplitude of low-frequency fluctuations (fALFF) and seed-based functional connectivity (FC) were obtained from rs-fMRI analysis. Correlative analysis was also performed to evaluate the associations of the neuroimaging metrics such as fALFF and FC with cognitive testing scores and clinical assessment questionnaire scores.

Results

Adolescents with BPD showed increased fALFF values in the right inferior frontal gyrus and decreased activity in the left middle frontal gyrus as compared to the HC group ($p < 0.05$, cluster size ≥ 100, FWE correction). In adolescents with BPD, the reduced fALFF in the left middle frontal gyrus was associated with SCWT-A (reading characters) and SCWT-B (reading color). Increased fALFF in the right inferior frontal gyrus was related to BPFS, DERS-F and Ottawa Self-Injury Inventory-4C. Additionally, both the fALFF values in the left middle frontal gyrus and the right inferior frontal gyrus were related to the CTQ-D (emotional neglect) ($p < 0.05$). The left middle frontal gyrus exhibited increased FC with the right hippocampus, left inferior temporal gyrus and right inferior frontal gyrus (voxel $p < 0.001$, cluster $p < 0.05$, FWE correction). The increased FC between the left middle frontal gyrus and the right hippocampus was related to SCWT-C (cognitive flexibility).

Conclusions

We observed diverging changes in intrinsic brain activity in prefrontal cortex, and neural compensatory FC changes to maintain function in adolescents with BPD. In addition, increased neural function as indicated by brain activity and FC was associated with cognitive dysfunction, while decreased neural

function was closely associated with emotional dysregulation. These results indicated that alterations of intrinsic brain activity may be one of the underlying neurobiological markers for clinical symptoms in adolescents with BPD.

1. Introduction

Borderline personality disorder (BPD) is characterized by emotional instability, impulsive behavior and frequent non-suicidal self-injury (NSSI) [1]. BPD also exhibits cognitive impairments, which manifests as attention deficits, slow processing speed, difficulties in inhibiting responses, and impaired impulse control [2]. Additionally, childhood trauma may have long-term effects on both the cognitive functioning and emotional stability of individuals with BPD [3]. Emotional neglect is a type of childhood trauma that requires particular attention in Chinese children and adolescents, and it has been shown to be associated with social issues such as left-behind children phenomenon [4]. Adolescence is a high-risk period for developing BPD [5, 6] and it is also considered the optimal time for treatment [1]. However, the neurobiological mechanism underlying adolescent BPD remain unclear, which hinders development of targeted interventions and prevents prompt treatment of the vulnerable adolescents.

Prefrontal cortex consists of several functionally and structurally heterogeneous brain regions which are critical to cognitive functions and emotional regulation [7]. The dorsolateral prefrontal cortex contributes to working memory, goal-driven attention, and problem-solving. The ventrolateral prefrontal cortex is involved in inhibition, response selection, and monitoring; the medial prefrontal cortex in self-awareness, motivation, and emotional regulation; and the orbitofrontal cortex is involved in personality, inhibition, and emotional and social reasoning [7]. While executive dysfunction syndromes have traditionally been associated with injury to the dorsolateral prefrontal cortex in patients with BPD, these dysfunctions are also linked to damage in the parietal-temporal-frontal system, implicating a distinct neurobiological pattern for BPD[8]. Nevertheless, literature is limited regarding the activity patterns of various prefrontal cortex regions in adolescents with BPD.

Brain resting-state functional magnetic resonance imaging (rs-fMRI) can be used to assess intrinsic brain activity with a metric known as the amplitude of low-frequency fluctuation (ALFF) [9]. Previous rs-fMRI studies have shown abnormal brain activity in the prefrontal-limbic circuit in adults with BPD [10, 11]. Our team conducted the first rs-fMRI study in adolescents with BPD focusing on the ALFF parameter, and we found reduced ALFF values in the left superior frontal gyrus and right middle occipital gyrus, and increased ALFF in the limbic system such as the left hippocampus, insula and thalamus in adolescents with BPD, which was closely related to childhood trauma [12]. However, the ALFF method could be subject to interference from physiological noise, which may hinder the accuracy of research results.

Another metric from rs-fMRI analysis known as the fractional amplitude of low-frequency fluctuations (fALFF) has gained increasing attention in recent years [13]. The fALFF analysis examines the amplitude of the entire spectrum to evaluate the contribution of low-frequency amplitude relative to high-frequency amplitude in different brain regions, overcoming the challenge of physiological noise which has been an

issue for the ALFF metric [13, 14]. In the fALFF analysis, the low-frequency range is usually defined as 0.01–0.08 Hz, and the amplitude within this frequency range is believed to be associated with spontaneous activity of neurons in the brain [13]. Therefore, fALFF analysis provides information on the spontaneous activity level and connectivity of different brain regions, which has been informative for the pathophysiological mechanism of neuropsychiatric disorders such as schizophrenia [14]. So far, there was only one fALFF study on BPD but focused on adults, showing changes in activity in the default mode network such as the left middle temporal gyrus and right precuneus [15]. More studies need to be done to assess fALFF in adolescents with BPD, which may shed light on neural correlation for BPD in a younger population.

Functional connectivity (FC) derived from rs-fMRI has been used to evaluate neural circuits in individuals with neuropsychiatric disorders such as Alzheimer's disease, depression, and schizophrenia [16]. FC studies have revealed enhanced FC in the frontal-limbic circuit in adults with BPD as compared to the controls [17, 18]. Our own study showed an abnormal FC of cortical-limbic circuit in adolescents with BPD [12, 19, 20]. However, previous studies did not clarify the changes in FC of the prefrontal cortex. The FC between different areas of the prefrontal cortex in adolescent BPD remains unclear.

In this study, we recruited adolescents with BPD and gender- and age-matched healthy control (HC) participants. All study participants underwent rs-fMRI from which the fALFF and FC metrics within prefrontal cortex were obtained through imaging analysis. We hypothesized that there would be alterations in fALFF and FC in adolescents with BPD as compared to the HC participants, which would be correlated with cognitive testing scores and clinical assessment scores. The study results should further our understanding of neural changes in adolescents with BPD.

2. Methods

2.1. Participants

This study was approved by the institutional review board (IRB: 2022020227) at our hospital. Written informed consent was obtained from the parents or legal guardians of all adolescent participants. The adolescents with BPD were consecutively recruited from the Psychiatric Clinics at the Mental Health Center of Xiangya Hospital between October 2021 and February 2022. The HC participants, matched for age and gender, were recruited from local schools during the same study period.

The inclusion criteria for the patient group were as follows: (1) patients aged 12 to 17 years meeting the diagnostic criteria for BPD according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) [21], with at least 5 out of 9 criteria for diagnosis of BPD; (2) the patients' symptoms had been stable for more than 2 years, and these symptoms were not explained by a DSM-IV axis I psychiatric disorder or neurodevelopmental disorder. Additionally, their scores on the Borderline Personality Feature Scale (BPFS) for Children were higher than the designated score of 66. For the HC participants, the inclusion criteria were as follows: age between 12 and 17 years with no history of psychiatric disorder or

psychotropic medication. Exclusion criteria for all participants included a history of neurodevelopmental disorder, schizophrenia spectrum disorder, bipolar spectrum disorder, post-traumatic stress disorder, major depressive disorder, alcohol and/or drug dependence, attention-deficit hyperactivity disorder, neurological disorders, or an intelligence quotient (IQ) ≤ 80. All participants were right-handed, and their handedness was determined using the Edinburgh Handedness Inventory [22]. All participants were instructed to abstain from consuming alcohol or psychotropic substances for a 24-hour period preceding the brain rs-fMRI scan.

2.2. Structured interviews and symptom evaluation

We used the BPD section of the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II) for the structured interview for all participants [21]. Confirmation of BPD diagnosis required the presence of five or more of the nine diagnostic items. To assess the presence of Axis I mental disorders in the patients, we utilized the Schedule for Affective Disorders and Schizophrenia Scale for School-Age Children-Present and Lifetime version (K-SADS-PL) [23]. The same structured interviews were also conducted on the HC participants to rule out personality disorders and Axis I mental disorders. Both the adolescents and their parents or legal guardians were present during the structured interviews. A clinical team comprising of experienced psychiatrists (Q.X and F.J, with 10 and 8 years of subspecialty experience in adolescent psychiatry, respectively) performed a comprehensive clinical evaluation and made the final diagnosis. The information about psychiatric disorders in first-degree relatives was obtained from the participants and their parents/legal guardians.

The clinical assessments were conducted by the study psychiatrist (FJ) with 8 years of experience in psychiatric evaluation. The Abbreviated Wechsler Intelligence Scale was administered to evaluate the participants' IQ [24]. The Borderline Personality Features Scale for Children (BPFS) was employed to evaluate borderline personality features, using a cutoff score of 66 [25]. Scores above this threshold indicated a tendency towards borderline personality features. We employed the Ottawa Self-Injury Inventory to assess for emotional dysregulation and behavioral changes [26]. The functional subscale examined the underlying motivations and purposes of behavioral issues such as emotion dysregulation, lack of communication, or self-punishment. Subscale 4C of this Inventory examined the internal emotional regulation function such as using self-injurious behavior to alleviate negative emotions. Concurrently, emotional regulation abilities were assessed using the Difficulties in Emotion Regulation Scale (DERS) [27]. The DERS was a well-established and widely utilized assessment tool for measuring individuals' skills in managing and regulating their emotions. The Subscales “DERS-F” examined limited access to emotional regulation strategies, aiming to identify the extent to which individuals may have effective and diverse coping mechanisms for regulating their emotions. Childhood trauma experiences were assessed using the Childhood Trauma Questionnaire (CTQ) [28]. The questionnaire consisted of five subscales: emotional abuse (CTQ-A), physical abuse (CTQ-B), sexual abuse (CTQ-C), emotional neglect (CTQ-D), and physical neglect (CTQ-E). All assessments were conducted prior to the brain MRI scans, which were performed on the same day as the clinical assessments.

2.3. Cognitive testing

For cognitive testing, the Stroop Color-Word Test (SCWT) was utilized to evaluate participants' abilities in selective attention, processing speed, perceptual conversion, and response inhibition [29]. The test consisted of three subtasks: reading characters (SCWT-A), reading color (SCWT-B), and reading color interference (SCWT-C). SCWT-A and SCWT-B primarily reflected participants' abilities in selective attention and processing speed, while SCWT-C primarily assessed their response inhibition capabilities and perceptual conversion skills. For SCWT-A, participants were instructed to quickly identify and name the word printed on a white piece of paper, regardless of the ink color. For SCWT-B, participants were presented with the shape "X" printed in various colors, and they were asked to promptly identify and name the color of the ink used. The SCWT-C aimed to assess participants' response inhibition abilities and perceptual conversion. For this task, participants were required to promptly identify and name the ink color of words, even when the meaning of the word contradicted the ink color. Each test had a time limit of 45 seconds, and the scores were determined based on the number of correct answers they provided.

2.3. Brain rs-fMRI data acquisition and preprocessing

All brain rs-fMRI scans were conducted using the same Siemens MAGNETOM Prisma 3T MRI scanner. Echo-planar imaging sequence was employed to acquire the brain rs-fMRI data with the following parameters: repetition time (TR) = 2000 milliseconds (ms), echo time (TE) = 30 ms, matrix size = 64 × 64, flip angle = 90°, number of time points = 250, field of view (FOV) = 240 × 240 mm, slice thickness = 4 mm, gap = 0.4 mm, and 30 axial slices. Additionally, routine T2-weighted images and fluid attenuation inversion recovery (FLAIR) sequence were acquired. A senior neuroradiologist (ZH) with over 30 years of neuroimaging experience reviewed all brain MRI images to assess imaging quality and to identify any incidental brain abnormalities.

Spatial preprocessing of the rs-fMRI images was conducted using Statistical Parametric Mapping (SPM12, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Correction procedures were applied to address acquisition delays and head movement. Subjects with head movement exceeding 3 mm or rotation exceeding 3° during any period of the rs-fMRI scanning were excluded from further analysis. Normalization of the rs-fMRI data was performed according to the normative SPM12 echo planar imaging pattern, with a resampling resolution of 3 × 3 × 3 mm^3. To mitigate the influence of low-frequency drift and physiological high-frequency noise, a temporal band-pass filter was applied, specifically ranging from 0.01 to 0.08 Hz. The linear trend was removed, and head movement parameters were regressed out [30].

2.4. Brain fALFF analysis

We utilized the rs-fMRI Data Analysis Toolkit to analyze fALFF [31]. Through fast Fourier transform, the filtered time series data was transformed into the frequency domain with the following parameters: fast Fourier transform length set to the shortest and taper percent set to 0. In this study, we calculated the fALFF by dividing the amplitude within the frequency range of 0.01–0.08 Hz by the amplitude across the entire frequency range of 0-0.25 Hz. Subsequently, the computed fALFF index was normalized by

subtracting the mean and dividing it by the standard deviation to obtain a zfALFF map with a normal distribution [30, 32].

2.5. FC analysis

The FC analysis was performed on the rs-fMRI data with a region of interest (ROI) approach. The ROIs were identified from the fALFF analysis, which were selected as seeds to investigate their FC with the whole brain. The identified seed regions included the following: the right inferior frontal gyrus, opercular part (x=-36, y = 6, z = 30) and the left middle frontal gyrus (x=-36, y = 60, z = 21). The coordinates for the seed ROIs were determined based on the fALFF results. Pearson correlation coefficients were then calculated between each seed point and the entire brain, and Fisher-Z transform was applied.

2.6 Statistical analysis

Demographic and clinical information was analyzed using Statistical Package for the Social Sciences (SPSS) version 22.0. Continuous variables were analyzed using independent two-sample t-tests or the Mann-Whitney U test, while categorical variables were analyzed using the chi-square test. Mean values ± standard deviation (SD) were reported, and a significance level of $p < 0.05$ was used for two-tailed statistical tests.

For the fALFF analysis, a two-sample t-test was conducted to identify differences between the two groups. The statistical threshold was set at $p < 0.05$, and Family-Wise Error (FWE) correction with a cluster size of ≥ 100 was applied. Gender, age, and medication use were included as covariates for the fALFF analysis. For the FC analysis, gender and age were included as covariates. The statistical threshold was set at voxel $p < 0.001$ and cluster $p < 0.05$, with FWE correction applied for multiple comparisons. Correlation analysis between fALFF/FC values and clinical assessment scores for symptom features was performed using Spearman's rank correlation. The correlation analysis was controlled for age, gender, disease duration, age of onset, and medication use. A $p < 0.05$ was considered statistically significant.

3. Result

3.1. Demographic and symptom features

This study enrolled a total of 50 adolescents with BPD and 21 matched HC participants. The recruitment process for this study is presented in Fig. 1. Demographic and symptom features are summarized in Table 1. Among the adolescents with BPD, the median age was 14.6 ± 1.1 years, ranging from 12 to 17 years, and about half of the patients were female (n = 27, 54%). In our study, 80% of the patients were considered drug-naive, which meant they had not taken any psychotropic medication within the 2 months prior to enrollment. The remaining 20% of patients were taking psychotropic medications including antidepressants, antipsychotics, and/or mood stabilizers during the study period. Additionally, 10% of the patients had co-morbidities, with 1 case of compulsive-obsessive disorder and 4 cases of general anxiety disorder. The HC group had a mean age of 14.0 ± 1.2 years, with 66.6% of females. There

were no statistically significant differences in age (p = 0.617) or education (p = 0.738) between the two groups.

The total and subscales scores of BPFS, DERS, Ottawa Self-Injury Inventory and CTQ were all significantly higher in adolescents with BPD as compared to the HC group (p□0.001). The adolescents with BPD exhibited significantly more cognitive dysfunction than the HC group, as evidenced by between-group differences in SCWT-A, SCWT-B and SCWT-C scores (p□0.001) (Table 1).

3.2 Brain fALFF data

The adolescents with BPD showed increased fALFF values in the right inferior frontal gyrus, opercular part (x = 36, y = 6, z = 30, T = 10.34, cluster size = 519), but decreased fALFF in the left middle frontal gyrus (x=-36, y = 60, z = 21, T=-10.61, cluster size = 670) as compared to the HC group ($p < 0.05$) (Table 2 and Fig. 2).

3.3 FC data

The adolescents with BPD showed enhanced FC of the left middle frontal gyrus with the right inferior frontal gyrus (opercular part) (x = 33, y = 30, z=-18, T = 5.274, cluster size = 295), the right parahippocampal gyrus (x = 21, y=-12, z=-30, T = 5.517, cluster size = 102), right hippocampus(x = 42, y=-18, z=-15, T = 4.7357, cluster size = 241), left angular gyrus (x=-48, y=-57, z = 24, T = 4.5618, cluster size = 137), left inferior temporal gyrus(x=-57, y=-42, z=-21, T = 6.0435, cluster size = 743), the left superior frontal gyrus (x=-15, y = 57, z = 6, T = 5.6986, cluster size = 1054) and right postcentral gyrus (x = 27, y=-30, z = 48, T = 10.2265, cluster size = 2515) as compared to the HC group. In addition, the adolescents with BPD also had enhanced FC of the right inferior frontal gyrus (opercular part) with the left inferior occipital gyrus (x=-36, y=-87, z=-6, T = 5.6782, cluster size = 330), the right superior occipital gyrus (x = 21, y=-87, z = 3, T = 5.2021, cluster size = 244), and the right inferior temporal gyrus (x = 48, y=-18, z=-24, T = 6.6016, cluster size = 262) as compared to the HC group (voxel $p < 0.001$, cluster $p < 0.05$, FWE corrected) (Table 3 & Fig. 3).

3.4 Correlation analysis

In adolescents with BPD, the fALFF values of the right inferior frontal gyrus was positively correlated with the BPFS (r = 0.295, p = 0.038), DERS-F (r = 0.302, p = 0.033), and Ottawa Self-Injury Inventory-4C scores (r = 0.292, p = 0.040). The fALFF of the left middle frontal gyrus was positively correlated with the cognitive testing scores from SCWT-A (r = 0.335, p = 0.017) and SCWT-B (r = 0.374, p = 0.007). Notably, the enhanced FC between the left middle frontal gyrus and the right hippocampus was negatively associated with cognitive performance on SCWT-C (r=-0.321, p = 0.023) (Supplementary Fig. 1). Moreover, the fALFF values for both the left middle frontal gyrus (r=-0.424, p = 0.002) and the right inferior frontal gyrus (r = 291, p = 0.041) were correlated with the CTQ-D scores (Fig. 4).

4. Discussion

In this study, we observed a heterogeneous brain activity pattern in prefrontal cortex, i.e., increased activity in the right inferior frontal gyrus but decreased activity in the left middle frontal gyrus in adolescents with BPD, which was correlated with emotional regulation and cognitive functioning. These results implied a potential neural compensatory mechanism to maintain brain function in adolescents with BPD.

Our observation of increased activity in the right inferior frontal gyrus in adolescents with BPD is generally consistent with literature. The inferior frontal gyrus as a part of prefrontal cortex is known to be a core brain area for processing facial expression and has shown abnormal activity in patients with BPD [33]. In addition, the inferior frontal gyrus is involved in neural activity related to emotional expression and social interaction [34, 35]. Therefore, its correlation with emotional dysregulation and self-injurious behavior noted in the present study implied its potential role as a neural correlation underlying emotional issues in adolescents with BPD.

We found a decreased activity in the left middle frontal gyrus being correlated with deficits in attention and reaction speed as measured by the Stroop tests in our patient group. The left middle frontal gyrus as a part of prefrontal cortex is involved in cognitive processes [7], and therefore its decreased activity may predispose the patients to cognitive impairment in patients with BPD as shown in the literature [36]. On the other hand, the enhanced connectivity between the left middle frontal gyrus and the right hippocampus in our adolescents with BPD was found to be associated with impaired impulse control and response inhibition as measured by SCWT-C. Hippocampal activity has been shown to be associated with memory function in patients with BPD [37]. Our result suggested a potential role of the middle frontal gyrus in emotional control and memory in addition to cognitive function in adolescents with BPD.

We found both the left middle frontal gyrus as a cognitive region and the right inferior frontal gyrus as an emotional region had strong associations with a specific type of childhood trauma, namely emotional neglect. This indicated that the emotional neglect experienced during childhood may have a significant impact on the brain regions involved in cognitive function and emotional regulation [38, 39]. Our own work has identified the presence of early childhood trauma, particularly emotional neglect, in adolescents with BPD [12]. Emotional neglect may be linked to social factors such as the left-behind children in China suffering from prolonged parental separation as their parents left their village homes to make ends meet by working in the cites [40].

Our study identified the potential associations among the prefrontal cortical regions, cognitive function, emotional regulation, and childhood trauma experience in adolescents with BPD. These findings contributed to the growing body of literature assessing the neurobiological underpinnings of BPD and highlighted the importance of cognitive and emotional factors in adolescents with BPD. The enhanced FC between the right inferior frontal gyrus and the left middle frontal gyrus supported the notion of neural coordination and neuroplasticity within the prefrontal cortex. In addition, enhanced FC between the right inferior frontal gyrus and occipital/temporal gyri in adolescents with BPD indicated altered function among different brain regions, which was generally in agreement with our previous studies on

adolescent BPD [12, 19, 20]. Moreover, the left middle frontal gyrus showed enhanced FC in widespread areas, including the right limbic system, indicating it as an important neural hub in adolescents with BPD [41]. Taken together our study results and the data from literature [18], the enhanced FC within the cortical-limbic circuit may be a functional correlate for the cognitive and emotional issues in adolescents with BPD.

We also found a hemispheric difference in brain activity in adolescents with BPD. The decreased activity was noted in the middle frontal gyrus of the left hemisphere, while the increased activity was in the inferior frontal gyrus of the right hemisphere. Moreover, there was an enhanced FC between the left middle frontal gyrus and the right inferior frontal gyrus, as well as the right limbic system. Prior studies have reported that the individuals with left dominant hemisphere may have their executive function centered in the left hemisphere, and may have their emotional regulation centered on the right hemisphere [42]. In addition, the right limbic system responsible for emotional processing may provide a crucial contribution to implicit processing of fear [43], and an abnormality in the right frontal lobe has been found to be closely associated with emotional symptoms [44]. The hemispheric difference observed in our study was intriguing and more study is needed to confirm this finding.

The study had several limitations. First, there may have been potential case selection bias as our cohort may have included patients with more severe BPD. This is because our hospital has been known for providing higher-level psychiatric care and we routinely treat patients referred to us by the local hospitals. Second, the sample size was small, and we were unable to account for other confounding factors such as disease duration, medication use, family history, and treatment regimen, etc. Third, some patients in our cohort had co-morbid psychiatric disorder such as anxiety disorder, and obsessive-compulsive disorder, which may confound the study results. We could not exclude all patients with co-morbidities because these co-morbid conditions were also part of the features for BPD [45]. Nevertheless, we excluded patients with depression, bipolar disorder, and post-traumatic stress disorder because these co-morbidities have been reported in literature as potentially interfering with the results [46, 47].

5. Conclusion

We reported a diverging pattern of brain activity in various regions of prefrontal cortex in adolescents with BPD, which was associated with emotional and cognitive issues in adolescents with BPD. This study identified the prefrontal cortex being an important brain structural correlation of the clinical symptomatology in adolescents with BPD. Our study contributed new data to further our understanding of the neurobiological mechanism underlying BPD in vulnerable adolescents.

Declarations

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Conflict of Interest:

The authors declare no conflicts of interest.

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Author Contribution

The main contributors are Qian Xiao, Liying Shen, Haoling He, Xueying Wang, Yan Fu, Jun Ding, Furong Jiang, Jinfan Zhang, Zhejia Zhang, Xiaoping Yi, Bihong T. Chen. Q.X 's main contributions are the experimental design and paper writing. L.S 's main contributions are the collection of patients and control groups, data analysis and paper revision. H.H 's main contributions are magnetic resonance data collection, statistical analysis of demographic data. X.W 's main contributions are the collection of patients and control groups. Y.F 's main contributions is magnetic resonance data collection. J.D 's main contribution are the analysis of magnetic resonance data. F.J 's main contribution is scale assessment. J.Z 's main contribution is the analysis of magnetic resonance data. Z.Z 's main contribution is the guidance of magnetic resonance technology. X.Y 's main contributions are paper writing, experimental design, statistical analysis guidance and paper revision. Bihong T. Chen 's main contributions are the guidance of paper writing and revision. All authors reviewed the manuscript.

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Tables

Table 1. Demographic and clinical characteristics of the study cohort.

Characteristics	Adolescents with BPD (n=50)	HC group (n=21)	p-value
Gender			0.324
Male (n, %)	23 (46.0%)	7 (33.3%)	
Female (n, %)	27 (54.0%)	14 (66.6%)	
Age (years)	14.6 (1.1)	14.0 (1.2)	0.617
Education (years)	9.5 (1.1)	8.9 (1.1)	0.738
Age of onset (years)	12.0 (11.0-13.0)	-–	–
Illness duration (years)	3.0 (2.0-3.0)	–	–
IQ	110.0 (103.0-114.0)	106.0 (100.0-112.5)	0.075
Family history			<0.001***
Yes (n, %)	26 (52.0%)	0 (0.0%)	
Medication use			
Atypical antipsychotics (n, %)	5 (10.0%)	–	
Antidepressants (n, %)	10 (20.0%)	–	
Mood stabilizer (n, %)	4 (8.0%)	–	
Comorbidity			
OCD (n, %)	1 (2.0%)	–	
GAD (n, %)	4 (8.0%)	–	
GAF	55.0 (49.5-64.3)	87.0 (85.0-90.0)	<0.001***
SCWT-A	85.0 (76.0-100.0)	68.0 (57.0-75.5)	<0.001***
SCWT-B	59.38 ± 12.626	88.05 ± 8.558	<0.001***
SCWT-C	35.72 ± 9.769	43.0 ± 11.185	0.008**
DERS	126.5 (107.5-134.75)	54.0 (52.0-58.0)	<0.001***
DERS-A	18.5 (16.0-21.0)	8.0 (6.5-9.0)	<0.001***
DERS-B	14.5 (12.0-16.0)	9.0 (7.5-10.5)	<0.001***

DERS-C	19.0 (13.0-22.75)	8.0 (7.0-10.0)	<0.001***
DERS-D	21.5 (16.75-26.25)	8.0 (7.0-9.5)	<0.001***
DERS-E	21.5 (19.0-24.0)	10.0 (9.0-11.5)	<0.001***
DERS-F	30.5 (24.75-36.0)	12.0 (9.5-13.0)	<0.001***
BPFS	83.0 (74.75-96.25)	31.0 (29.5-35.5)	<0.001***
Ottawa Self-Injury Inventory	28.0 (20.0-35.25)	2.0 (1.0-3.0)	<0.001***
Ottawa Self-Injury Inventory-4A	4.5 (1.0-9.5)	1.0 (1.0-2.0)	<0.001***
Ottawa Self-Injury Inventory-4B	12.0 (8.0-16.0)	0.0 (0.0-1.0)	<0.001***
Ottawa Self-Injury Inventory-4C	10.0 (5.0-13.0)	0.0 (0.0-0.5)	<0.001***
Ottawa Self-Injury Inventory-5	7.5 (4.75-13.0)	0.0 (0.0-1.0)	<0.001***
CTQ	51.0 (40.75-60.0)	28.0 (26.5-31.0)	<0.001***
CTQ-A	11.5 (9.0-15.0)	5.0 (5.0-5.0)	<0.001***
CTQ-B	7.0 (5.0-9.0)	5.0 (5.0-6.0)	0.001**
CTQ-C	5.0 (5.0-6.0)	6.0 (5.0-6.5)	0.043*
CTQ-D	15.0 (10.0-20.0)	5.0 (5.0-6.0)	<0.001***
CTQ-E	9.0 (7.0-12.0)	6.0 (5.0-7.0)	<0.001***

Notes: Data was presented as median (IQR) or mean (SD)[#]. *p<0.05, **p<0.01 or ***p<0.001 indicates a significant difference between the two groups. Abbreviations: BPD, Borderline Personality disorder; HC, healthy control; IQ, Intelligence quotient; OCD, compulsive-obsessive disorder; GAD, general anxiety disorder; GAF, global assessment of functioning; SCWT, Stroop color-word test; DERS, Difficulties in Emotion Regulation Scale; BPFS, Borderline Personality Features Scale; CTQ, Childhood Trauma Questionnaire.

Table 2. Brain regions with significant alterations in fractional amplitude of low-frequency fluctuations (fALFF) between the adolescents with borderline personality disorder and the healthy control participants.

Brain region	MNI Peak coordinates			T value	Cluster Size
	X	Y	Z		
Right inferior frontal gyrus (opercular part)	36	6	30	10.3435	519
Left middle frontal gyrus	-36	60	21	-10.6098	670

Notes: MNI, Montreal Neurological Institute. $p < 0.05$, cluster size >= 100, family-wise error (FWE) corrected.

Table 3. Brain regions with significant alterations in seed-based functional connectivity between the adolescents with borderline personality disorder and the healthy control participants.

Seed	Brain region (gyrus)	MNI Peak coordinates			T value	Cluster Size
		X	Y	Z		
Right inferior frontal gyrus (opercular part)	Right inferior temporal	48	-18	-24	6.6016	262
	Left inferior occipital	-36	-87	-6	5.6782	330
	Right superior occipital	21	-87	3	5.2021	244
Left middle frontal gyrus	Right parahippocampal	21	-12	-30	5.517	102
	Left inferior temporal	-57	-42	-21	6.0435	743
	Right hippocampus	42	-18	-15	4.7357	241
	Right inferior frontal orbital	33	30	-18	5.274	295
	Left superior frontal	-15	57	6	5.6986	1054
	Right postcentral	27	-30	48	10.2265	2515
	Left angular	-48	-57	24	4.5618	137

Notes: MNI, Montreal Neurological Institute. voxel $p < 0.001$, cluster $p < 0.05$, family wise error corrected.

Figures

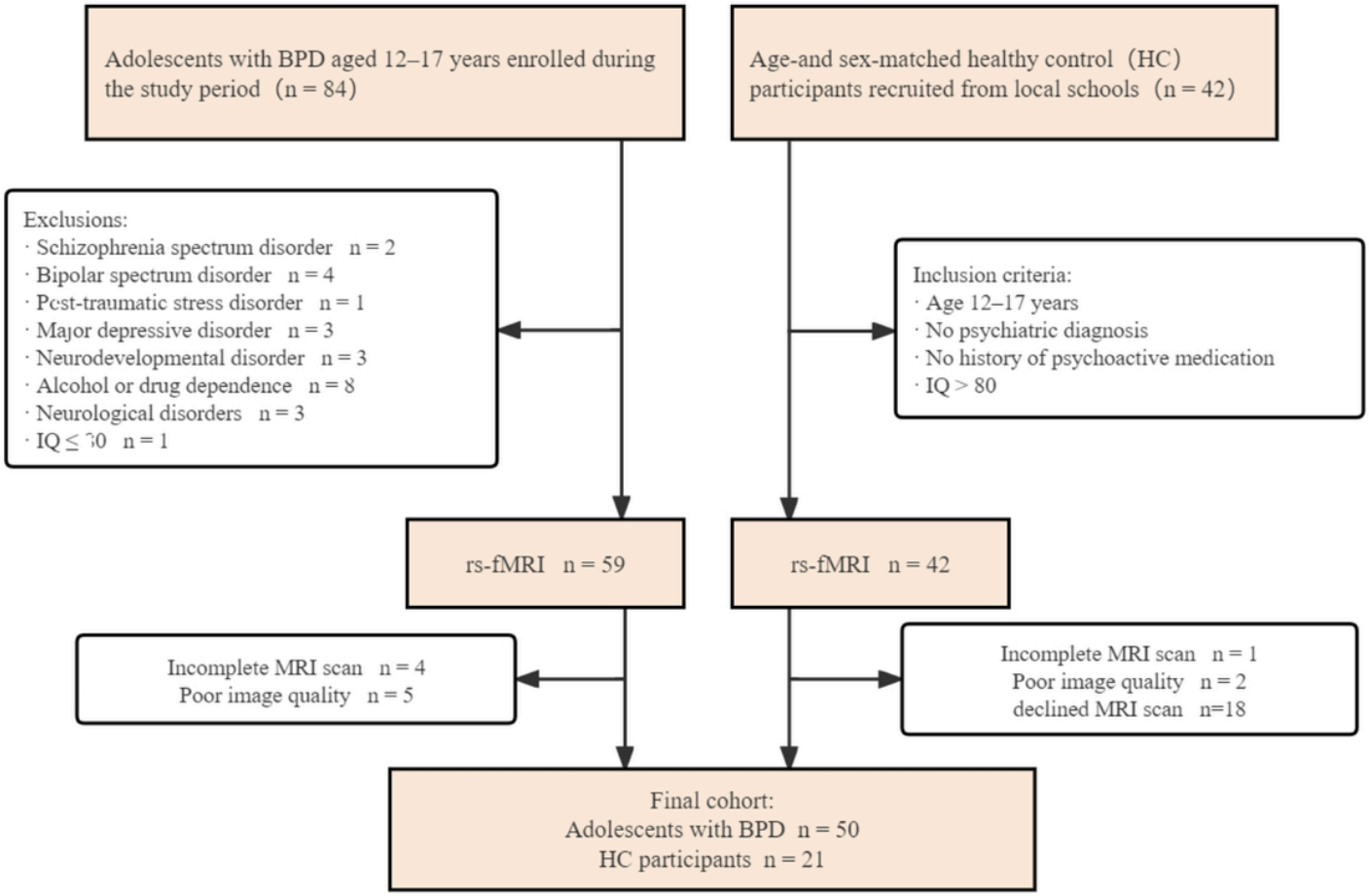

Figure 1

Flow-chart illustrating the enrollment process for adolescents with borderline personality disorder (BPD) and healthy control (HC) participants.

Abbreviations: IQ, intelligence quotient; rs-fMRI, resting-state functional magnetic resonance imaging.

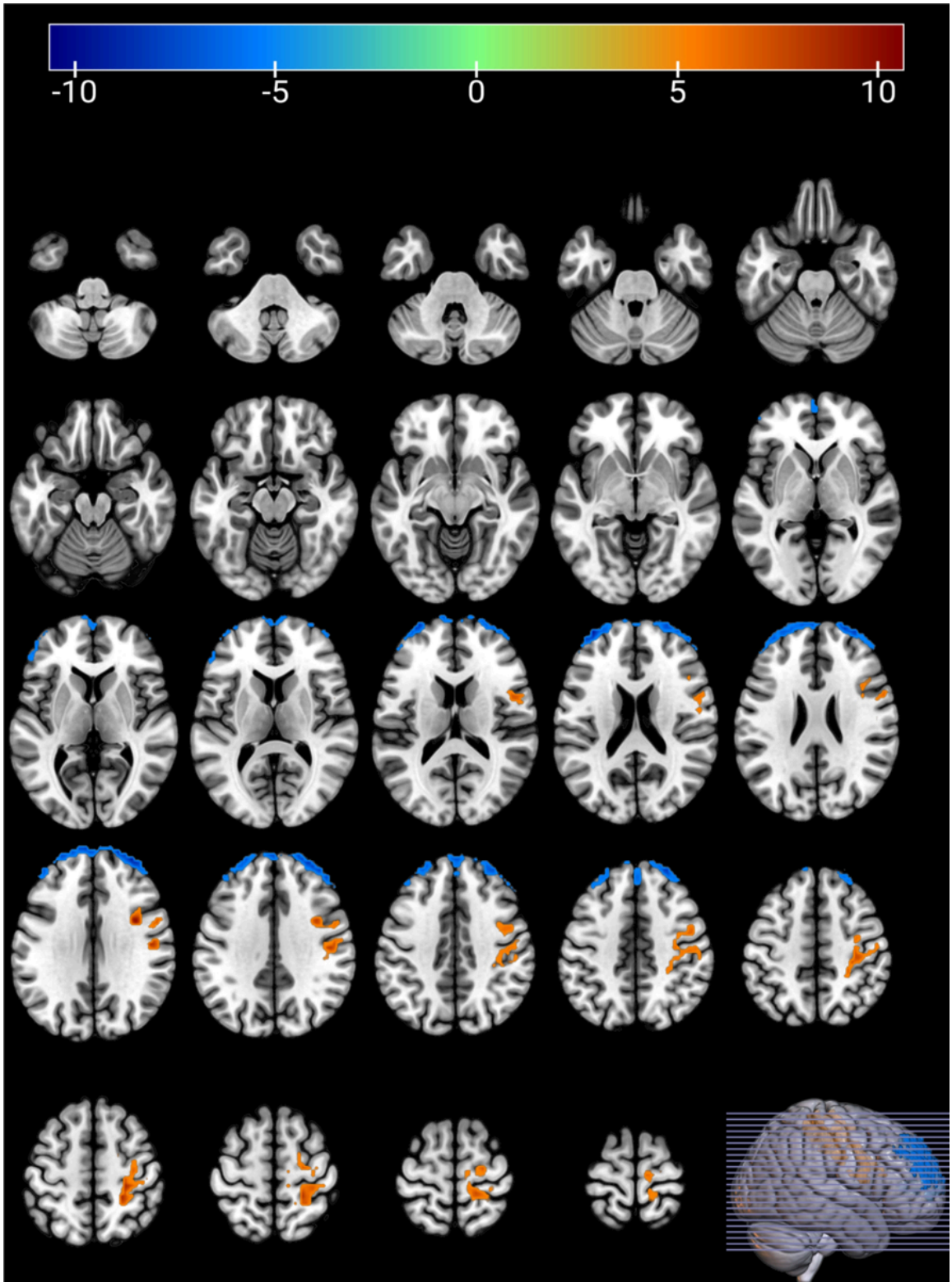

Figure 2

Brain regions showing increased fractional amplitude of low frequency fluctuations (fALFF) values (highlighted in orange) and reduced fALFF values (highlighted in blue) in adolescents with borderline personality disorder as compared to healthy control participants.

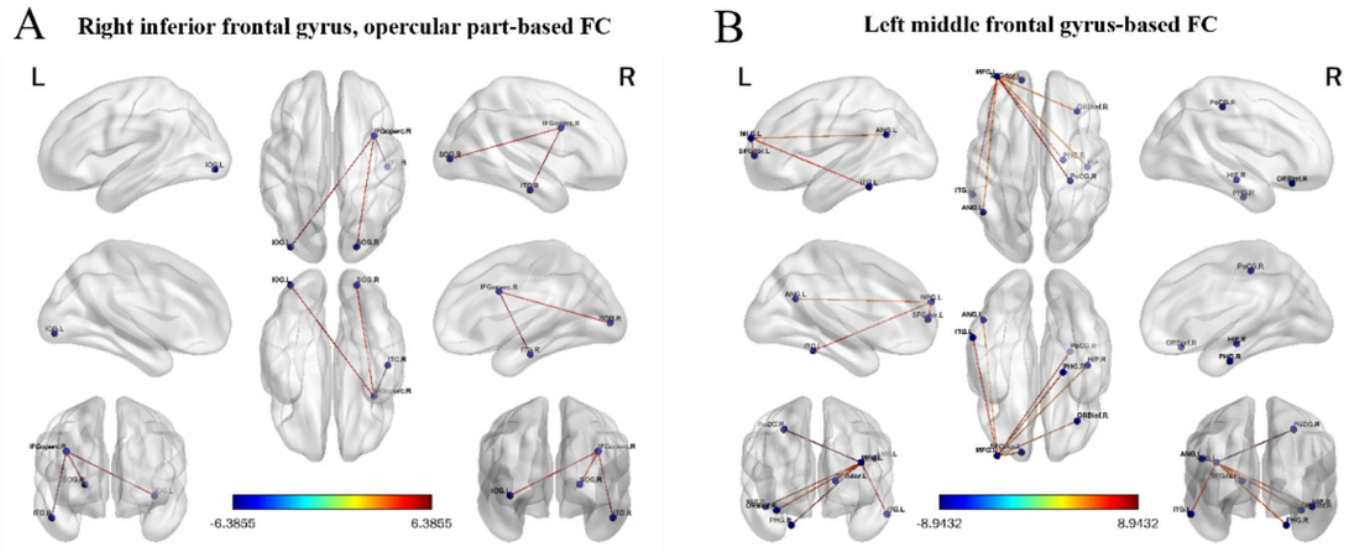

Figure 3

Significant alterations in functional connectivity (FC) in adolescents with borderline personality disorder as compared to the healthy control participants using the right inferior frontal gyrus (opercular part) and left middle frontal gyrus as the seed regions. **A.** Increased FC between the right inferior frontal gyrus (opercular part) and left inferior occipital gyrus, right superior occipital gyrus, and right inferior temporal gyrus. **B.** Increased FC between the left middle frontal gyrus and right inferior frontal gyrus (opercular part), right parahippocampal gyrus, right hippocampus, left angular gyrus, left inferior temporal gyrus, left superior frontal gyrus and right postcentral gyrus. $p < 0.001$ for voxels and $p < 0.05$ for clusters after family-wise error correction (FWE). Color bar indicates T scores. L, left; R, right.

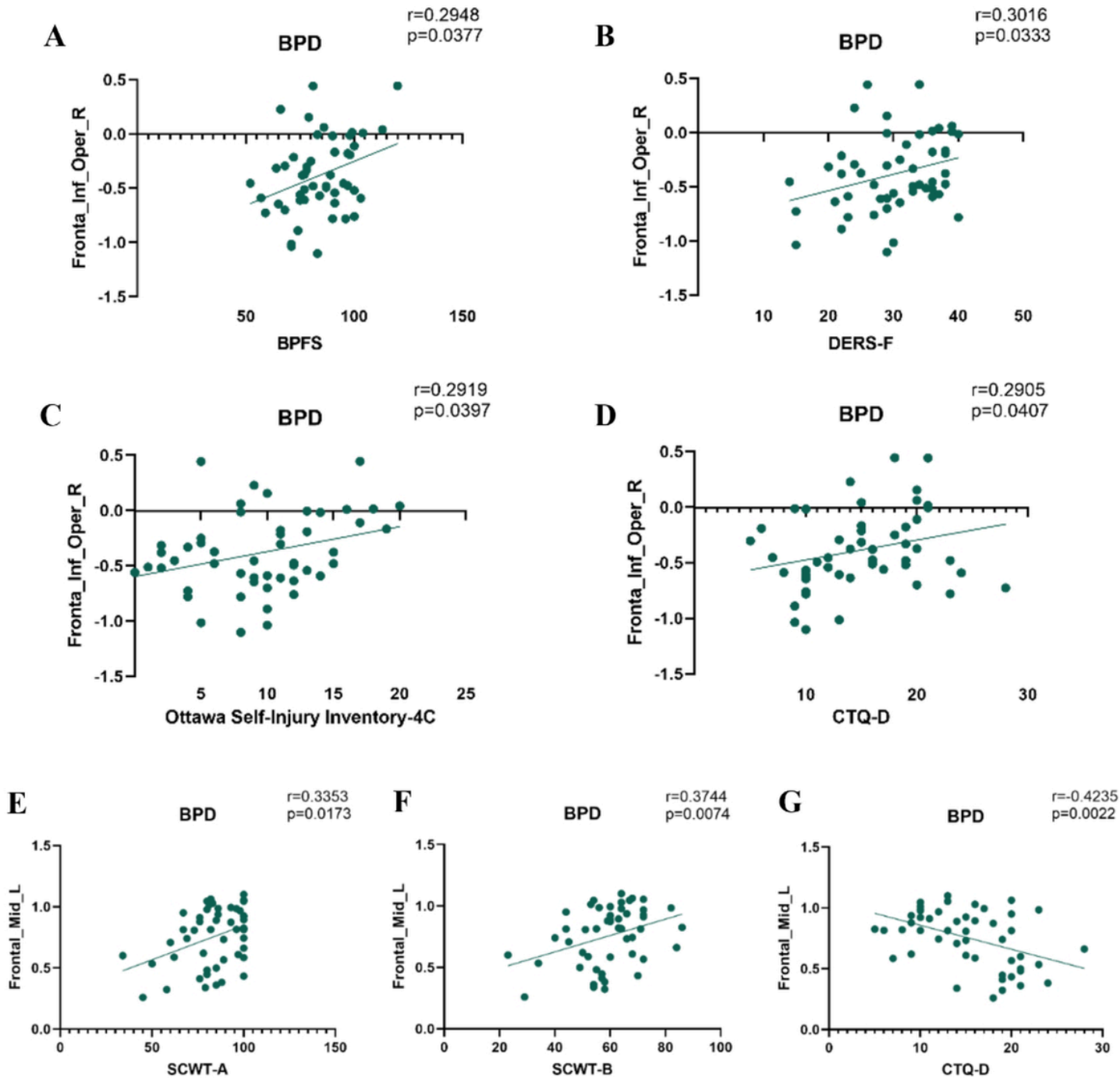

Figure 4

Correlation analyses of the alterations in fractional amplitude of low-frequency fluctuations (fALFF) values, or functional connectivity (FC) with cognitive testing scores, and emotional dysregulation scores in adolescents with borderline personality disorder. **A.**Positive correlation between the fALFF value of right inferior frontal gyrus and the BPFS score. **B.** Positive correlation between the fALFF value of right inferior frontal gyrus and the DERS-F score. **C.** Positive correlation between the fALFF value of right inferior frontal gyrus and the Ottawa Self-Injury Inventory-4C score. **D.** Positive correlation between the fALFF value of right inferior frontal gyrus and the CTQ-D score. **E.**Positive correlation between the fALFF of left middle frontal gyrus and the SCWT-A score. **F.** Positive correlation between the fALFF value of left

middle frontal gyrus and the SCWT-B score. **G.** Negative correlation between the fALFF value of left middle frontal gyrus and the CTQ-D score.

Abbreviations: BPFS, Borderline Personality Features Scale for Children; DERS, Difficulties in Emotion Regulation Scale; CTQ, Childhood Trauma Questionnaire; SCWT, Stroop color-word test; Fronta_inf_Oper_R, right inferior frontal gyrus: Frontal_Mid_L, left middle frontal gyrus.

Supplementary Files

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