Altered resting-state functional connectivity and its association with executive function in adolescents with borderline personality disorder

Xiaoping Yi
Central South University
Xueying Wang
Central South University
Yan Fu
Central South University
Furong Jiang
Central South University
Zhejia Zhang
Central South University
Jing Wang
Central South University
Zaide Han
Central South University
Qian Xiao (xiaoqian851112@126.com)
Central South University
Bihong T. Chen
City of Hope National Medical Center

Research Article

Keywords: MRI, adolescent borderline personality disorder, executive function, functional connectivity, limbic - cortical circuit, DMN

Posted Date: March 17th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2694170/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at European Child & Adolescent Psychiatry on August 9th, 2023. See the published version at https://doi.org/10.1007/s00787-023-02277-7.

Abstract

Background: Adolescents with borderline personality disorder (BPD) may have impaired executive functions such as impulse control and inattention. There are few functional MRI (fMRI) studies in adolescents with BPD and the neuroimaging markers of this disorder are unknown. The aim of this study was to investigate the functional connectivity (FC) of BPD in adolescents, and to explore the relationship between FC changes and executive function in adolescents with BPD.

Methods: 50 adolescents aged 12 to 17 years with BPD and 21 gender-and-age matched healthy controls (HC) were enrolled into the study. Brain MRI scan including a 3D-T1 weighted structural sequence and a resting-state fMRI was acquired. A seed-based FC analysis was performed. We used the Stroop color-word test (SCWT) and the trail making test (TMT) to evaluate the executive function of the participants. Correlative[xy1] [2] analysis of FC alterations with executive function and clinical symptoms were also performed.

Results: Compared to the HCs, adolescents with BPD showed increased FC in the limbic - cortical circuit, such as the FC between the left hippocampus and right parahippocampal gyrus, between the right middle occipital gyrus and the left middle temporal gyrus, and between the left medial superior frontal gyrus and the right inferior temporal gyrus. FC in the default mode network (DMN) was decreased between the left angular gyrus and the left precuneus but increased between the left angular gyrus and the right anterior cingulate cortex (voxel $P < 0.001$, cluster $P < 0.05$, FWE corrected). The BPD group demonstrated significantly lower cognitive testing scores than the HC group on the SCWT-A (P 0.001), SCWT-B (P 0.001), and SCWT-C ($P = 0.034$). The FC alterations between limbic system and cortical regions were associated with SCWT and TMT ($P < 0.05$).

Conclusions: FC alterations were noted in both limbic - cortical circuit and DMN in adolescents with BPD, which were associated with impaired executive function. This study implicated the FC alterations being the neural correlates of executive functioning in adolescents with BPD.

1. Introduction

Borderline personality disorder (BPD) is a severe mental disorder with a prevalence of 5 to 6% in a worldwide population[1]. Most patients develop BPD during adolescence, known as adolescent BPD[1, 2]. Adolescent BPD is at an early stage of this disorder for potential intervention to delay or reverse the disease progression[2, 3]. Adolescent BPD is characterized by executive dysfunction as the main clinical features including deficient impulse control, inattention, abnormal processing speed and loss of emotion regulation[4, 5]. However, the neural correlate of executive function in adolescents with BPD remains unclear.

Functional connectivity (FC) derived from resting-state functional MRI (rs-fMRI) A has been used to evaluate neural circuits underlying psychiatric disorders[6]. Exploring the FC features as well as the underline neural mechanism in BPD may help to improve the diagnosis and interventions[7]. Prior studies

in adult BPD have found altered FC in the salience network, default mode network (DMN), frontoparietal network and cognitive executive network, using independent component analysis method. Among the networks, the FC of FPN and CEN were reduced, while the FC of SN enhanced, and the FC of the DMN showed both decrease and increase between different seed regions[8–10]. A prior study analyzed the intrinsic functional neural circuits using graph theory method, and identified reduced FC in a subnetwork involving the prefrontal, occipital and limbic system in adults with BPD when compared to the controls[11]. Seed-based FC studies revealed the enhanced limbic - cortical circuit (prefrontal lobe, striatum, insula, anterior cingulate cortex and temporal cortex) in the adults with BPD compared to the controls[12, 13]. Similarly, adult BPD also had increased FC between the precuneus as the DMN node and inferior/middle frontal lobe, middle occipital lobe and superior parietal lobe[14]. However, all the resting - state FC studies were conducted in adults, and studies in adolescent BPD are limited.

The cognitive task-state fMRI studies have found the FC and the brain activity of the limbic - frontal network (frontal cortex, anterior cingulate gyrus, striatum, amygdala) being associated with deficits in impulse control in adult BPD[15–17]. Our prior studies have identified several brain regions with altered structure and function, and provided preliminarily evidence about abnormal FC of limbic - cortical circuit in adolescent BPD using seeds based rs-fMRI-FC analysis methods[18–20]. However, the relationship between abnormal FC and executive function, as well as the neural mechanism underline executive function impairment in adolescent BPD remains unclear.

In this study, we enrolled adolescents with BPD and the gender-and-age matched healthy control (HC) group, and assessed their executive function with cognitive testing and FC from rs-fMRI using a seed-based approach. We hypothesized that the FC of limbic - cortical circuit and between nodes within DMN would be altered, which may be correlated with executive dysfunction in adolescents with BPD.

2. Methods

2.1. Participants

A total of 50 adolescents diagnosed with BPD were enrolled from our psychiatric clinics between Oct. 2021 and Apr. 2022. Additionally, 21 HC participants were enrolled from local schools during the same study interval. The two groups were matched for age, sex, handedness, and education. Our institutional review board and ethics committee approved this study(IRB: 2022020227). All participant, as well as their parents and legal guardians provided written informed consents.

The inclusion criteria for adolescent BPD patients were as follows: (1) between the ages of 12 and 17, and met the diagnostic criteria for BPD according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV); (2) the core symptoms of BPD were stable for a minimum of 2 years and were not solely explained by Axis I mental disorders. In addition, the overall score on the Borderline Personality Feature Scale (BPFS) exceeded the threshold of 66[21]. (3) all patients were right-handed. The inclusion criteria for the HC group were: age between 12 and 17, with no history of psychiatric disorders

or psychoactive medication. Both groups shared the same exclusion criteria including the following: comorbidity with substance-related disorders, neurological or neurodevelopmental disorders, Intelligence Quotient (IQ) ≤ 80, bipolar spectrum disorder, schizophrenia spectrum disorder, major depressive disorder, and post-traumatic stress disorder. All participants abstained from alcohol and other abusive substances for 24 hours prior to the MRI scan.

2.2. Structured Interviews And Psychological Assessment

The BPD section of the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II) [22]was used for the structured interview. Confirmation of diagnosis required the presence of at least five of the nine diagnostic items. The Schedule for Affective Disorders and Schizophrenia Scale for School-Age Children-Present and Lifetime version (K-SADS-PL) was utilized to assess Axis I mental disorders[23]. Both the adolescents and their parents or legal guardians participated in the structured interviews. The same structured interviews were also carried out in the HC group to rule out personality disorders and Axis I mental disorders. The clinical team consisted of two senior psychiatrists (Q.X and F.J) with 10 and 8 years of subspecialty experience in adolescent psychiatry, respectively, and performed a comprehensive clinical evaluation and made the final diagnosis. Family history including history of psychiatric disorders in their first-degree relatives was obtained from both the participants and their parents or legal guardians.

A skilled psychiatrist with 8 years of experience in psychological assessment (F.J) conducted the psychological assessments. All interviews and evaluations were completed on the same day as the MRI scans. Handedness was evaluated using the Edinburgh Handedness Inventory[24], while IQ was measured by the Wechsler Abbreviated Intelligence Scale[25]. The Borderline Personality Features Scale for Children (BPFS)[21] was used to evaluate the core features of adolescent BPD. The assessment of emotion dysregulation was conducted using the Difficulties in Emotion Regulation Scale (DERS) and its six subscales[26]. These subscales include the lack of emotional awareness, lack of emotional clarity, nonacceptance of emotional responses, impulse control difficulties, difficulties in engaging in goal-directed activities, and limited access to emotion regulation strategies. The assessment of impulsive behavior was carried out using the Barratt Impulsiveness Scale 11th version (BIS-11)[27], which was composed of three subscales, namely attentional impulsiveness, motor impulsiveness, and non-planning impulsiveness. The Global Assessment of Functioning (GAF) was to rate the overall social, occupational, and psychological functioning of an individual[28].

2.3. Executive Function Testing

In our study, we selected executive function tests that effectively captured the key features of cognitive impairment in patients with BPD. These features included mainly reduced impulse control, slowed processing speed, and attention deficits. The following tests were utilized for this purpose:

We used the Stroop color-word test (SCWT) [29]to assess the attention and impulse control of participants. This test consisted of three subtasks. SCWT-A evaluated attention with reading characters, SCWT-B also evaluated attention with reading colors, and SCWT-C measured ability to impulse control through ignoring color disturbances. In addition, we employed the trail making test (TMT)[30] to measure attention and processing speed. TMT-A assessed the processing speed and attention, while TMT-B measured cognitive flexibility.

2.4. Mri Data Acquisition

All brain MRI scans were acquired on the same Siemens MAGNETOM Prisma 3T MRI scanner. Magnetization Prepared-Rapid Gradient Echo (MP-RAGE) sequence was used to acquire T1-weighted images of the entire brain[19]. The MPRAGE parameters were as follows: echo time = 2.03 ms, repetition time = 2300 ms, flip angle = 9°, acquisition matrix = 256 × 256 mm^2, voxel size = 1.0 × 1.0 × 1.0 mm^3, and 176 slices without gap. For, An echo-planar imaging sequence was used to acquire the rs-fMRI data with the following parameters[18]: echo time = 30 ms, repetition time = 2000 ms, matrix size = 64 × 64, flip angle = 90°, number of time points = 250, gap = 0.4 mm, FOV = 240 × 240 mm, 30 axial slices, and thickness = 4 mm. We also obtained additional MRI data, including fluid attenuation inversion recovery (FLAIR) and T2-weighted images, for assessing incidental brain abnormalities. A skilled neuroradiologist (Z.H, with over 30 years of experience in neuroimaging) reviewed all MRI data to ensure their quality and to rule out brain lesions.

2.5. Rs-fmri Pre-processing

The rs-fMRI preprocessing was performed in a similar fashion as our prior study[18, 20]. The dcm2niix was used to convert the functional and structural images of the original data into NIfTI format files. Using magnetic resonance data processing software (Matlab + SPM12 + DPABI), the pre-processing was performed as follows: (1) deleting the first five time points; (2) doing timing slice correction; (3) performing head movement correction with subsequent deletion of subjects with head movements exceeding 3 mm and 3°); (4) completing space normalization. (5) operating space smoothing with Full Width at Half Maximum (FWHM) as 6× 6× 6mm;(6) eliminating signal drift caused by machine heating or pulse; (7) regressing out noise covariables; (8) bandpass filtering on the data set with a frequency range of 0.01 to 0.08 Hz, and retaining the signals with physiological significance.

2.6 Fc Analysis

FC analysis was performed from the rs-fMRI data using the region of interest approach. Our previous study of the Amplitude of Low Frequency Fluctuation (ALFF) from the rs-fMRI in adolescent BPD identified alterations in four brain regions including the left hippocampus [x=-30, y=-18, z=-21], right middle occipital gyrus [x = 33, y=-87, z = 36], left superior medial frontal gyrus [x=-3, y = 66, z = 27] and left angular gyrus [x=-51, y=-69, z = 42][18], which were used as seed points for the FC analysis for the current

study. The four selected seed points represented the core node of limbic system, cortical region and DMN respectively. Subsequently, we calculated the Pearson correlation coefficient between each seed point and the overall brain, and Fisher-Z transform was performed.

2.7 Statistical Analysis

We used Statistical Package for the Social Sciences (SPSS) version 22.0 to analyze the demographic, psychological, and executive functional data. Continuous variables were tested using either the Mann-Whitney U test or independent two-sample T test, while the Chi-square test was used to analyze categorical variables.

FC analysis was performed using sex and age as covariates. The statistical threshold was set at cluster $P < 0.05$, voxel $P < 0.001$, and corrected for multiple comparisons with family-wise error (FWE) correction. Correlation analysis between FC value and executive function and emotional dysregulation was conducted using Spearman's rank correlation. The correlation analysis was adjusted for gender, age, age of onset, and disease duration. The data were presented as mean ± standard deviation (SD), and two-tailed statistical significance was set at $P < 0.05$.

3. Results

3.1 Clinical features

The demographic data, clinical features and executive function testing scores of adolescents with BPD and HCs are presented in Table 1. The median age of adolescents with BPD was 14.6 ± 1.1 years, while the mean age of the HCs was 14.0 ± 1.2 years. The onset of BPD was at 12 years of age, and the median duration of the disorder was 3 years. No significant differences were observed in terms of age, gender, intelligence, or education between the two groups ($P > 0.05$). However, the total scale and subscale scores of BPFS, DERS, BIS-11 and GAF in adolescents with BPD were significantly higher than those of the HCs ($P < 0.001$).

Only 20% of the adolescents with BPD was prescribed psychotropic medications, including antidepressants, antipsychotics, and mood stabilizers, in the two months preceding the MRI scan. Although we tried to enroll patients without comorbidities, 10% of the adolescents with BPD in our cohort had comorbidities, including four with general anxiety disorder and one with obsessive-compulsive disorder. Half of the adolescents with BPD had a family history of psychiatric illness (ten with general anxiety disorders, six with impulse control disorders, five with compulsive-obsessive disorders and four with major depressive disorders).

3.2 Executive Function

The adolescents with BPD had impaired attention as noted in the SCWT-A, SCWT-B and impulse control as noted in the SCWT-C when compared to the HCs. Specifically, the cognitive testing scores for the BPD group was significantly lower than the HC group including the SCWT-A (P 0.001), SCWT-B (P 0.001), and SCWT-C (P = 0.034). Conversely, the TMT-A and TMT-B scores showed no significant between-group differences (P 0.05) (Table 1).

3.3 Fc Alterations

Four significant regions including the left hippocampus, right middle occipital gyrus, left superior medial frontal gyrus and left angular gyrus identified from our prior rs-fMRI study of adolescent BPD were used as seed points for the FC analysis (36493941). The adolescents with BPD had mostly increased FC when compared to the HCs.

(1) Using the left hippocampus as a seed. There was significantly altered FC between this seed region and right parahippocampal gyrus (x = 27, y=-21, z=-21, T = 6.1814, cluster size = 845) and with bilateral inferior frontal gyrus (left, x=-36, y = 21, z = 12, T = 5.4793, cluster size = 100; right, x = 36, y = 30, z = 9, T = 6.4633, cluster size = 2092).

(2) Using the right middle occipital gyrus as a seed. There was significantly altered FC between this seed region and right inferior temporal gyrus (x = 48, y=-18, z=-24, T = 7.775, cluster size = 1230), with left middle temporal gyrus (x=-57, y=-6, z=-24, T = 5.562, cluster size = 311), with left insula (x=-39, y=-18, z = 24, T = 6.5456, cluster size = 609), with right anterior cingulate cortex (x = 12, y = 42, z = 24, T = 6.4796, cluster size = 528), with left superior frontal gyrus(x=-12, y = 39, z = 36, T = 6.4625, cluster size = 399), with left middle frontal gyrus(x=-33, y = 18, z = 45, T = 4.4159, cluster size = 89), and with left angular gyrus (x=-39, y=-60, z = 30, T = 6.4243, cluster size = 198).

(3) Using the left superior medial frontal gyrus as a seed. There was significantly altered FC between this seed region and right inferior temporal gyrus (x = 48, y=-18, z=-24, T = 6.4213, cluster size = 205), with right superior occipital gyrus (x = 21, y=-87, z = 3, T = 6.3149, cluster size = 555), with left inferior occipital gyrus (x=-36, y=-87, z=-6, T = 6.7099, cluster size = 574), and with right inferior frontal gyrus (x = 30, y = 6, z = 36, T = 6.0207, cluster size = 162).

(4) Using the left angular gyrus as a seed. There was significantly altered FC between this seed region and right middle temporal gyrus (x = 48, y=-3, z=-30, T = 7.5559, cluster size = 1225), and with right anterior cingulate cortex (x = 15, y = 42, z = 21, T = 5.8992, cluster size = 499). Of note, the FC between left angular gyrus and left precuneus was reduced (x = 0, y=-75, z = 54, T=-6.0971, cluster size = 164).

3.4 Correlation Analysis Of Fc Alterations With Executive Function And Clinical Features

The correlation analysis showed that the FC alterations that located in the core nodes of the limbic - cortical circuit and DMN were significantly associated with executive dysfunction, as well as with emotional dysregulation. Specifically, we found that (1) the FC between the left hippocampus and right parahippocampal gyrus was correlated with the attention test score (SCWT-A)(R=-0.296, P = 0.037), impulse control test score (SCWT-C) (R=-0.347, P = 0.014) and functional impairment test score (GAF) (R=-0.296, P = 0.037); (2) the FC between the right middle occipital gyrus and left middle temporal gyrus was correlated with the SCWT-A score (R=-0.283, P = 0.047) and the attentional impulsiveness test score (BIS-11-A) (R = 0.286, P = 0.044); (3) the FC between the left superior medial frontal gyrus and right inferior temporal gyrus was correlated with the SCWT-C test score (R=-0.313, P = 0.027) and difficulties in engaging in goal-directed activities (DERS-E) test score (R = 0.293, P = 0.039); (4) the FC between the left angular gyrus and with right anterior cingulate cortex was correlated with the SCWT-A (R=-0.369, P = 0.008), SCWT-B (R=-0.331, P = 0.019), SCWT-C (R=-0.402, P = 0.004) and processing speed (TMT-A) test score (R = 0.343, P = 0.015); (5) the FC between the left angular gyrus and right middle temporal gyrus was correlated with DERS-E test score (R = 0.294, P = 0.038).

4. Discussion

In this study, we found extensive altered FC within the limbic - cortical circuit as well as DMN, which was significantly associated with the executive dysfunction in adolescents with BPD. To our knowledge, this study was the first study assessing FC alterations in rs-fMRI and its association with the cognitive dysfunction in adolescents with BPD.

Our results showed increased FC between the left hippocampus and right parahippocampal gyrus, which was negatively associated with attention (SCWT-A) and impulse control (SCWT-C) and also with the overall functional level of the patients (GAF). The hippocampus and parahippocampal gyrus are important memory and emotion regulation areas in the limbic system, and their FC is crucial for maintaining healthy emotional and cognitive function[31]. Our study suggests that enhanced FC between the hippocampus and parahippocampal gyrus may be the underlying neural correlates for executive function in adolescents with BPD.

We also found an increased FC between the right middle occipital gyrus and the limbic - frontal network. Prior studies have shown the middle occipital gyrus being closely related to higher cognitive functions, such as controlling attention and behavioral responses[32]. In our previous studies, we found abnormal volume and activity of bilateral middle occipital gyrus in adolescents with BPD as compared to the HCs[19]. In addition, this study also showed the FC between the right middle occipital gyrus and left middle temporal gyrus being associated with attention (SCWT-A) and attentional impulsiveness (BIS-11-A). Impulsivity can manifest in a variety of ways in BPD, including risky behaviors, substance abuse, binge eating, self-harm, and impulsive spending[5]. Attentional impulsiveness refers to difficulty in inhibiting prepotent responses and sustaining attention over time[33]. Overall, the association between the FC in the middle occipital gyrus and middle temporal gyrus with attention and attentional

impulsiveness highlighted the importance of these brain regions for executive function in adolescents with BPD.

We observed an increased FC between the left superior medial frontal gyrus and right inferior temporal gyrus, right superior occipital gyrus, left inferior occipital gyrus, and right inferior frontal gyrus. The superior medial frontal gyrus is a central node for the regulation and processing of emotional information[34]. Our results are generally in line with prior studies showing dysfunctional FC of limbic - frontal circuit in adults with BPD[12–14].

The study also revealed a correlation between the FC of the left superior medial frontal gyrus and the right inferior temporal gyrus and impulse control (SCWT-C) as well as difficulties in engaging in goal-directed activities (DERS-E). Impulsive behavior can be a way for individuals with BPD to cope with intense emotional distress or to try to regulate their emotions, but it can also have negative consequences and may exacerbate their symptoms[5]. Difficulties in engaging in goal-directed activities is a subscale of the DERS, which assesses an individual's ability to regulate their emotions effectively in various situations[26]. Adolescents with BPD who experience difficulties in engaging in goal-directed activities may find it hard to maintain their focus and motivation to complete tasks, particularly when they are experiencing intense negative emotions such as anxiety, sadness, or anger[1]. The finding implied that the FC alterations between the left superior medial frontal gyrus and the right inferior temporal gyrus may be a potential mechanism underlying impulsivity and emotional dysregulation in adolescents with BPD.

The brain regions within the DMN also showed altered FC in our study. Abnormal FC of DMN have been reported in adults with BPD[14, 35]. However, there was limited information on DMN in adolescents with BPD. We chose the left angular gyrus as a region of interest because it was found to have enhanced activity in our previous ALFF rs-fMRI study in adolescents with BPD[18], this region played a crucial role in DMN for various function such as rumination, self-related information processing and empathy[36]. This study found an enhanced FC between the left angular gyrus and the right middle temporal gyrus and the right anterior cingulate cortex. In addition, we found that adolescents with BPD exhibited reduced FC between the left angular gyrus and the left precuneus, both of which were located within the DMN[36]. Our study contributed the first evidence to show altered FC between important nodes in the DMN in adolescent BPD patients. In relation to executive function, the FC between the left angular gyrus and the right anterior cingulate cortex was found to be correlated with attention (SCWT-A, SCWT-B, TMT-A), impulse control (SCWT-C), and processing speed (TMT-A). Taken together, the adolescents with BPD may have altered FC in the DMN, which may be the mechanism of executive dysfunctions of adolescent BPD.

There are several limitations in this study. First, the adolescent with BPD in our cohort may have more severe symptoms with higher frequency of self-harm and psychotic symptoms than other studies. This might be due to our hospital being an established center for psychiatric care and we care for sicker patients referred from community hospitals. Second, although our sample size was larger than previous studies[37], it was still modes. We could not take into consideration of all potential confounding variables such as psychotic symptoms, comorbidities, and medication use in the analysis. Third, although this

study excluded several comorbidities that might affect FC, 10% of the adolescent with BPD in our cohort had anxiety related disorders. The comorbidity issue was challenging because BPD was known to have comorbid mental disorders[38].

5. Conclusion

This study showed extensive FC alterations involving the limbic - cortical circuit and DMN in adolescents with BPD, which was correlated with executive function. Our study results implicated potential neural correlates of cognitive function in adolescents with BPD.

Declarations

Funding: This research was funded by the Youth Fund of National Natural Science Foundation of China (82201702), National Natural Science Foundation of China (U22A20377), the Youth Science Foundation of Xiangya Hospital: 2020Q20, Natural Science Foundation of Hunan Province (2022JJ30979, 2020JJ4925), and China Post-Doctoral Science Foundation (2022M713536).

Conflict of Interest:

The authors declare no conflicts of interest.

References

1. M. Bohus, J. Stoffers-Winterling, C. Sharp, A. Krause-Utz, C. Schmahl, K. Lieb, Borderline personality disorder, Lancet 398(10310) (2021) 1528-1540.
2. M. Kaess, R. Brunner, A. Chanen, Borderline personality disorder in adolescence, Pediatrics 134(4) (2014) 782-93.
3. A.C. Videler, J. Hutsebaut, J.E.M. Schulkens, S. Sobczak, S.P.J. van Alphen, A Life Span Perspective on Borderline Personality Disorder, Curr Psychiatry Rep 21(7) (2019) 51.
4. A. Kalpakci, C. Ha, C. Sharp, Differential relations of executive functioning to borderline personality disorder presentations in adolescents, Personal Ment Health 12(2) (2018) 93-106.
5. P. Linhartova, A. Latalova, R. Bartecek, J. Sirucek, P. Theiner, A. Ejova, P. Hlavata, B. Kosa, B. Jerabkova, M. Bares, T. Kasparek, Impulsivity in patients with borderline personality disorder: a comprehensive profile compared with healthy people and patients with ADHD, Psychol Med 50(11) (2020) 1829-1838.
6. M. Greicius, Resting-state functional connectivity in neuropsychiatric disorders, Curr Opin Neurol 21(4) (2008) 424-30.
7. A. Amad, J. Radua, Resting-state meta-analysis in Borderline Personality Disorder: Is the fronto-limbic hypothesis still valid?, J Affect Disord 212 (2017) 7-9.

8. P. Das, V. Calhoun, G.S. Malhi, Bipolar and borderline patients display differential patterns of functional connectivity among resting state networks, Neuroimage 98 (2014) 73-81.
9. A. Doll, C. Sorg, A. Manoliu, A. Woller, C. Meng, H. Forstl, C. Zimmer, A.M. Wohlschlager, V. Riedl, Shifted intrinsic connectivity of central executive and salience network in borderline personality disorder, Front Hum Neurosci 7 (2013) 727.
10. R.C. Wolf, F. Sambataro, N. Vasic, M. Schmid, P.A. Thomann, S.D. Bienentreu, N.D. Wolf, Aberrant connectivity of resting-state networks in borderline personality disorder, J Psychiatry Neurosci 36(6) (2011) 402-11.
11. T. Xu, K.R. Cullen, B. Mueller, M.W. Schreiner, K.O. Lim, S.C. Schulz, K.K. Parhi, Network analysis of functional brain connectivity in borderline personality disorder using resting-state fMRI, Neuroimage Clin 11 (2016) 302-315.
12. X. Lei, M. Zhong, Y. Liu, X. Jin, Q. Zhou, C. Xi, C. Tan, X. Zhu, S. Yao, J. Yi, A resting-state fMRI study in borderline personality disorder combining amplitude of low frequency fluctuation, regional homogeneity and seed based functional connectivity, J Affect Disord 218 (2017) 299-305.
13. P. Sarkheil, C.N. Ibrahim, F. Schneider, K. Mathiak, M. Klasen, Aberrant functional connectivity profiles of brain regions associated with salience and reward processing in female patients with borderline personality disorder, Brain Imaging Behav 14(2) (2020) 485-495.
14. A. O'Neill, A. D'Souza, A.C. Samson, A. Carballedo, C. Kerskens, T. Frodl, Dysregulation between emotion and theory of mind networks in borderline personality disorder, Psychiatry Res 231(1) (2015) 25-32.
15. P.H. Soloff, K. Abraham, K. Ramaseshan, A. Burgess, V.A. Diwadkar, Hyper-modulation of brain networks by the amygdala among women with Borderline Personality Disorder: Network signatures of affective interference during cognitive processing, J Psychiatr Res 88 (2017) 56-63.
16. P.H. Soloff, R. White, A. Omari, K. Ramaseshan, V.A. Diwadkar, Affective context interferes with brain responses during cognitive processing in borderline personality disorder: fMRI evidence, Psychiatry Res 233(1) (2015) 23-35.
17. G.Y. Wang, J. van Eijk, T. Demirakca, M. Sack, A. Krause-Utz, S. Cackowski, C. Schmahl, G. Ende, ACC GABA levels are associated with functional activation and connectivity in the fronto-striatal network during interference inhibition in patients with borderline personality disorder, Neuroimage 147 (2017) 164-174.
18. Q. Xiao, X. Yi, Y. Fu, F. Jiang, Z. Zhang, Q. Huang, Z. Han, B.T. Chen, Altered brain activity and childhood trauma in Chinese adolescents with borderline personality disorder, J Affect Disord 323 (2023) 435-443.
19. X. Yi, Y. Fu, J. Ding, F. Jiang, Z. Han, Y. Zhang, Z. Zhang, Q. Xiao, B.T. Chen, Altered gray matter volume and functional connectivity in adolescent borderline personality disorder with non-suicidal self-injury behavior, Eur Child Adolesc Psychiatry (2023).
20. X. Yi, Y. Fu, Z. Zhang, F. Jiang, Q. Xiao, B.T. Chen, Altered regional homogeneity and its association with cognitive function in adolescents with borderline personality disorder, J Psychiatry Neurosci

48(1) (2023) E1-E10.

21. P. Liu, X. Wang, Evaluation of Reliability and Validity of Chinese-Version Borderline Personality Features Scale for Children, Med Sci Monit 25 (2019) 3476-3484.
22. H.M. Wong, L.Y. Chow, Borderline personality disorder subscale (Chinese version) of the structured clinical interview for DSM-IV axis II personality disorders: a validation study in Cantonese-speaking Hong Kong Chinese, East Asian Arch Psychiatry 21(2) (2011) 52-7.
23. J. Kaufman, B. Birmaher, D. Brent, U. Rao, C. Flynn, P. Moreci, D. Williamson, N. Ryan, Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data, J Am Acad Child Adolesc Psychiatry 36(7) (1997) 980-8.
24. R.C. Oldfield, The assessment and analysis of handedness: the Edinburgh inventory, Neuropsychologia 9(1) (1971) 97-113.
25. D. Li, Y. Jin, S.G. Vandenberg, Y.M. Zhu, C.H. Tang, Report on Shanghai norms for the Chinese translation of the Wechsler Intelligence Scale for Children-Revised, Psychol Rep 67(2) (1990) 531-41.
26. J. Li, Z.R. Han, M.M. Gao, X. Sun, N. Ahemaitijiang, Psychometric properties of the Chinese version of the Difficulties in Emotion Regulation Scale (DERS): Factor structure, reliability, and validity, Psychol Assess 30(5) (2018) e1-e9.
27. C.F. Lu, C.X. Jia, A.Q. Xu, A.Y. Dai, P. Qin, Psychometric characteristics of Chinese version of Barratt Impulsiveness Scale-11 in suicides and living controls of rural China, Omega (Westport) 66(3) (2012) 215-29.
28. I.H. Aas, Guidelines for rating Global Assessment of Functioning (GAF), Ann Gen Psychiatry 10 (2011) 2.
29. F. Scarpina, S. Tagini, The Stroop Color and Word Test, Front Psychol 8 (2017) 557.
30. G.J. Demakis, Frontal lobe damage and tests of executive processing: a meta-analysis of the category test, stroop test, and trail-making test, J Clin Exp Neuropsychol 26(3) (2004) 441-50.
31. D. Carcone, A.C.H. Lee, A.C. Ruocco, Disrupted Relationship between Hippocampal Activation and Subsequent Memory Performance in Borderline Personality Disorder, J Affect Disord 274 (2020) 1041-1048.
32. S. Tu, J. Qiu, U. Martens, Q. Zhang, Category-selective attention modulates unconscious processes in the middle occipital gyrus, Conscious Cogn 22(2) (2013) 479-85.
33. L. Schulze, C. Schmahl, I. Niedtfeld, Neural Correlates of Disturbed Emotion Processing in Borderline Personality Disorder: A Multimodal Meta-Analysis, Biol Psychiatry 79(2) (2016) 97-106.
34. A. Henri-Bhargava, D.T. Stuss, M. Freedman, Clinical Assessment of Prefrontal Lobe Functions, Continuum (Minneap Minn) 24(3, BEHAVIORAL NEUROLOGY AND PSYCHIATRY) (2018) 704-726.
35. R.C. Kluetsch, C. Schmahl, I. Niedtfeld, M. Densmore, V.D. Calhoun, J. Daniels, A. Kraus, P. Ludaescher, M. Bohus, R.A. Lanius, Alterations in default mode network connectivity during pain processing in borderline personality disorder, Arch Gen Psychiatry 69(10) (2012) 993-1002.
36. M.E. Raichle, The brain's default mode network, Annu Rev Neurosci 38 (2015) 433-47.

37. K. Safar, J. Sato, A.C. Ruocco, M.S. Korenblum, H. O'Halpin, B.T. Dunkley, Disrupted emotional neural circuitry in adolescents with borderline personality traits, Neurosci Lett 701 (2019) 112-118.
38. A.M. Choate, H. Fatimah, M.A. Bornovalova, Comorbidity in borderline personality: understanding dynamics in development, Curr Opin Psychol 37 (2021) 104-108.

Tables

Table 1. Demographic and clinical characteristics of the study cohort			
Characteristics	Adolescent BPD (n=50)	HC (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
Onset age (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
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	60.0 (53.8-68.0)	89.0 (82.0-93.5)	<0.001***
SCWT-C	35.5 (30.0-42.0)	41.0 (32.5-51.0)	0.034*
TMT-A	31.5 (24.8-46.3)	30.0 (25.0-34.5)	0.281
TMT-B	81.5 (56.8-104.3)	75.0 (63.0-92.5)	0.664
DERS	126.5 (107.5-134.8)	54.0 (51.0-56.5)	<0.001***
DERS-Lack of emotional awareness	18.5 (16.0-21.0)	8.0 (6.0-9.0)	<0.001***
DERS-Lack of emotional clarity	14.5 (12.0-16.0)	9.0 (7.0-10.0)	<0.001***
DERS-Nonacceptance of emotional responses	19.0 (13.0-22.8)	8.0 (7.0-9.5)	<0.001***
DERS-Impulse control difficulties	21.5 (16.8-26.3)	8.0 (7.0-10.0)	<0.001***
DERS-Difficulties in engaging in goal-directed activities	21.5 (19.0-24.0)	10.0 (9.0-11.0)	<0.001***
DERS-Limited emotion regulation strategies	30.5 (24.8-36.0)	11.0 (9.0-12.5)	<0.001***
BIS-11	67.5 (60.8-72.0)	26.0 (25.0-28.0)	<0.001***
BIS-11_Attentional impulsivity	17.0 (15.0-19.0)	7.0 (6.0-8.0)	<0.001***

BIS-11_Motor impulsivity	20.5 (18.8-23.3)	9.0 (9.0-10.0)	<0.001***
BIS-11_Nonplanning impulsivity	27.0 (23.5-30.0)	10.0 (9.0-11.0)	<0.001***
BPFS	83.0 (74.8-96.3)	31.0 (28.5-35.5)	<0.001***
Familial history			<0.001***
Yes (n, %)	26 (52.0%)	0 (0.0%)	
Medications			
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%)	–	

Notes: Data was presented as median (IQR) or mean (SD)[#]. *P<0.05, **P<0.01 and ***P<0.001 suggest a significant difference between the characteristics in the two cohorts. Abbreviations: BIS-11, Barratt Impulsiveness Scale 11th; BPD, Borderline Personality disorders; BPFS, Borderline Personality Features Scale; DERS, Difficulties in Emotion Regulation Scale; GAD, general anxiety disorders; GAF, global assessment of functioning; HC, healthy controls; IQ, Intelligence quotient; OCD, compulsive-obsessive disorders; SCWT, Stroop color-word test; TMT, trail making test.

Table 2. Brain regions with significant alterations in seed-based functional connectivity between the adolescents with borderline personality disorders (BPD) and the healthy controls (HCs) (voxel P < 0.001, cluster P < 0.05, FWE corrected)

Seed	Brain region	MNI Peak coordinates			T value	Cluster Size
		X	Y	Z		
The left hippocampus	Right parahippocampal gyrus	27	-21	-21	6.1814	845
	Right triangular inferior frontal gyrus	36	30	9	6.4633	2092
	Left triangular inferior frontal gyrus	-36	21	12	5.4793	100
	Right thalamus	21	-27	6	5.9613	168
	Left superior parietal gyrus	-24	-60	69	-5.1317	138
The right middle occipital gyrus	Right inferior temporal gyrus	48	-18	-24	7.775	1230
	Left middle temporal gyrus	-57	-6	-24	5.562	311
	Left insula	-39	-18	24	6.5456	609
	Left superior frontal gyrus	-12	39	36	6.4625	399
	Right anterior cingulum	12	42	24	6.4796	528
	Right opercular rolandic area	42	-9	24	5.4254	96
	Left angular gyrus	-39	-60	30	6.4243	198
	Left middle frontal gyrus	-33	18	45	4.4159	89
The left superior frontal gyrus	The right inferior temporal gyrus	48	-18	-24	6.4213	205
	Right superior occipital gyrus	21	-87	3	6.3149	555
	Left inferior	-36	-87	-6	6.7099	574

	occipital gyrus					
	Right inferior opercular frontal gyrus	30	6	36	6.0207	162
The left angular	The right middle temporal gyrus	48	-3	-30	7.5559	1225
	Right anterior cingulum	15	42	21	5.8992	499
	Left precuneus	0	-75	54	-6.0971	164
Abbreviations: FWE, Family Wise Error correction; MNI, Montreal Neurological Institute;						

Figures

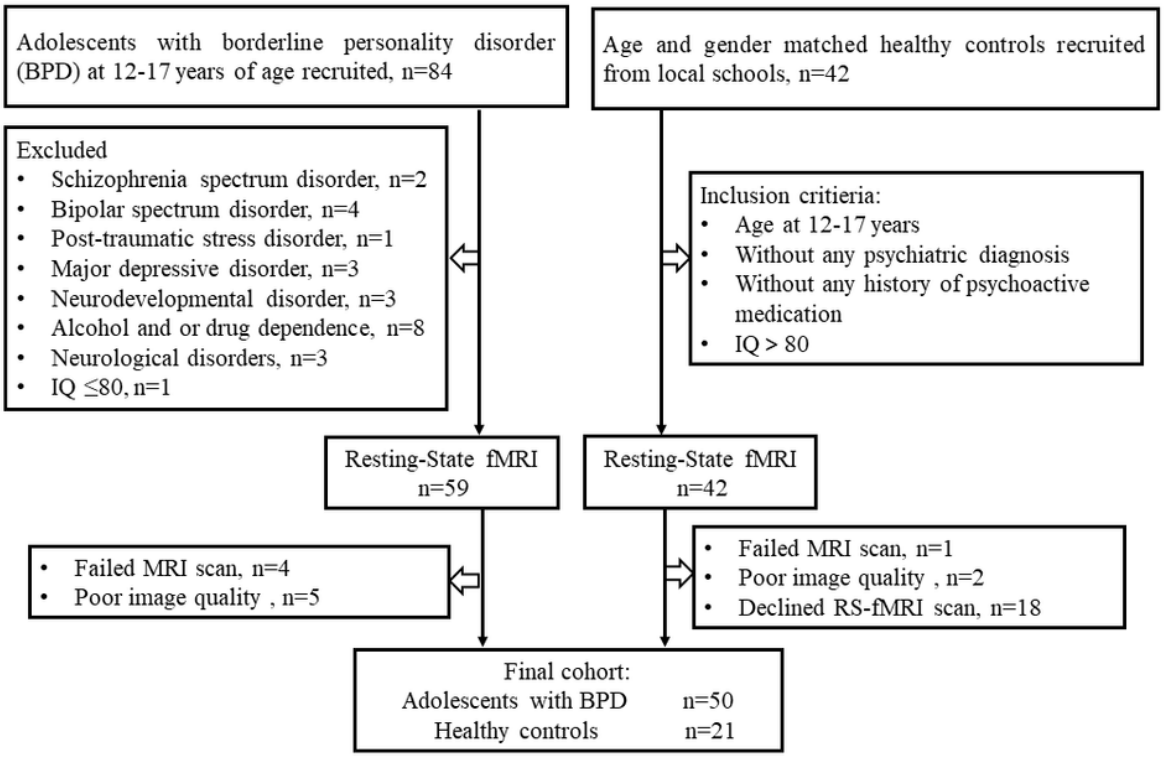

Figure 1

Flow chart illustrating the enrolment process.

Abbreviations: fMRI, functional MRI; IQ, intelligence quotient.

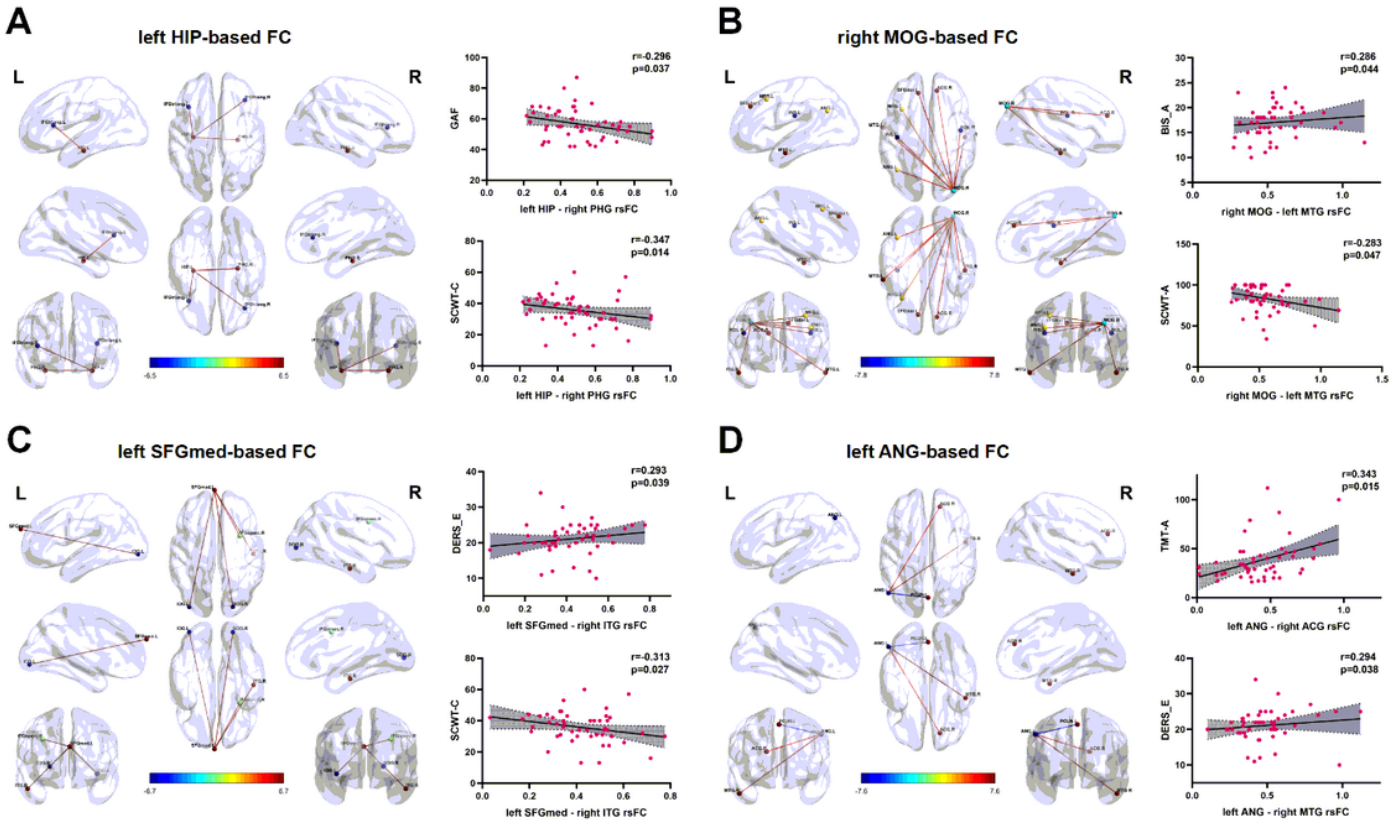

Figure 2

Functional Connectivity (FC) changes and the correlations between FC and executive function and clinical features. (A). Correlation between the FC between the left hippocampus and right parahippocampal gyrus with the impulse control (SCWT-C) (R=-0.347, P=0.014) and functional impairment (GAF) (R=-0.296, P=0.037); (B). Correlation between the FC between the right middle occipital gyrus and left middle temporal gyrus with SCWT-A (R=-0.283, P=0.047) and attentional impulsiveness (BIS-11-A) (R=0.286, P=0.044); (C). Correlation between the FC between the left superior medial frontal gyrus and right inferior temporal gyrus with the SCWT-C (R=-0.313, P=0.027) and difficulties in goal-directed activities (DERS-E) (R=0.293, P=0.039); (D). Correlation between the FC between the left angular gyrus and with right anterior cingulate cortex with the TMT-A (R=0.343, P=0.015), and correlation between the FC between the left angular gyrus and right middle temporal gyrus with DERS-E (R=0.294, P=0.038).

Abbreviations: ACG, anterior cingulum; ANG, angular gyrus; BIS-A, Attentional impulsivity of Barratt Impulsiveness Scale 11th; BPD, Borderline Personality disorders; DERS-E, Difficulties in engaging in goal-directed activities of Difficulties in Emotion Regulation Scale; GAF, global assessment of functioning; HIP, hippocampus gyrus; ITG, inferior temporal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; PHG, parahippocampal gyrus; rsFC, resting functional connectivity; SCWT-A, attention of Stroop color-word test; SCWT-C, impulse control of Stroop color-word test; SFGmed, superior medial frontal gyrus; TMT-A, trail making test.