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CLINICAL RESEARCH ARTICLE

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Altered cortical thickness and emotional dysregulation in adolescents with borderline personality disorder

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ABSTRACT

Background: Emotional dysregulation is a core feature of borderline personality disorder (BPD). Previous studies have reported that abnormal grey matter volume is associated with the limbic–cortical circuit and default mode network (DMN) in patients with BPD. However, alterations of cortical thickness in adolescents with BPD have not been well evaluated.

Objective: The aim of this study was to assess cortical thickness and its association with emotional dysregulation in adolescents with BPD.

Method: This prospective study enrolled 52 adolescents with BPD and 39 age- and sex-matched healthy controls (HCs). Assessments included brain magnetic resonance imaging (MRI) acquisition with structural and resting-state functional MRI data, and clinical assessment for emotional dysregulation using the Difficulties in Emotion Regulation Scale (DERS). Cortical thickness and seed-based functional connectivity were analysed with FreeSurfer 7.2 software. Correlation analysis between cortical thickness and the scores from emotional assessment was performed with Spearman analysis.

Results: Compared to HCs, there was altered cortical thickness in the DMN and limbic–cortical circuit in adolescents with BPD (Monte Carlo correction, all $p < .05$). These regions with altered cortical thickness were significantly associated with emotional dysregulation (all $p < .05$). There were also alterations of functional connectivity, i.e. with increased connectivity of the right prefrontal cortex with bilateral occipital lobes, or with the limbic system, and with decreased connectivity among the DMN regions (voxel $p < .001$, cluster $p < .05$, family-wise error corrected).

Conclusions: Our results suggest that the altered cortical thickness and altered functional connectivity in the limbic–cortical circuit and DMN may be involved in emotional dysregulation in adolescents with BPD.

Grosor cortical alterado y desregulacion emocional en adolescentes con trastorno de personalidad limitrofe

Antecedentes: La desregulación emocional es una característica central del trastorno de personalidad limítrofe (TLP). Estudios previos han reportado que el volumen anormal de sustancia gris esta asociado con el circuito límbico-cortical y la red de modo predeterminado (DMN) en pacientes con TLP. Sin embargo, las alteraciones del grosor cortical en adolescentes con TLP no han sido bien evaluadas.

Objetivo: El objetivo de este estudio fue evaluar el grosor cortical y su asociación con la desregulación emocional en adolescentes con TLP.

Método: Este estudio prospectivo recluto 52 adolescentes con TLP y 39 controles sanos (CSs) emparejados por edad y sexo. La evaluación del estudio incluyo la realización de RNM cerebral con datos de RNM estructural y funcional en estado de reposo (RNMf) y evaluaciones clínicas para la desregulación emocional utilizando la Escala de Dificultades en la Regulación

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MRI; adolescent borderline personality disorder; emotional dysregulation; cortical thickness; functional connectivity; limbic–cortical circuit; default mode network

PALABRAS CLAVE
RNM; adolescentes con trastorno de personalidad limítrofe; desregulación emocional; grosor cortical; conectividad funcional; circuito límbico-cortical; red de modo predeterminado.

关键词
MRI; 青少年边缘性人格障碍; 情绪失调; 皮层厚度; 功能连接; 边缘-皮层回路; 默认模式网络。

HIGHLIGHTS

- Emotional dysregulation is a core feature of borderline personality disorder, but the underlying neural correlates are not well known.
- There was altered cortical thickness and functional connectivity in the DMN and limbic–cortical circuit in adolescents with borderline personality disorder.
- Altered cortical thickness

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Emocional (DERS). El grosor cortical y la conectividad funcional basadas en semillas se analizaron con el software FreeSurfer 7.2. El análisis correlativo entre el grosor cortical y los puntajes de la evaluación emocional se realizó con el análisis de Spearman.
Resultados: En comparación con los CSs, hubo un grosor cortical alterado en la DMN y el circuito límbico-cortical en los adolescentes con TLP (corrección de Monte Carlo, todos $p < .05$). Estas regiones con el grosor cortical alterado se asociaron significativamente con desregulación emocional (todos $p < .05$). Tambien hubo alteraciones en la conectividad funcional, es decir, con conectividad aumentada de la corteza prefrontal derecha con los lóbulos occipitales bilaterales**,** o con el sistema límbico y con conectividad disminuida entre las regiones DMN (p de voxel < .001, cluster $p < .05$, FWE corregido).
Conclusiones: Nuestro resultados sugieren que el grosor cortical alterado y la conectividad funcional alterada en el sistema límbico-cortical y DMN pueden estar involucrados en la desregulación emocional en adolescentes con TLP.

边缘性人格障碍青少年的皮层厚度改变和情绪失调

目的：情绪失调是边缘性人格障碍 (BPD) 的核心特征。 先前的研究报道了 BPD 患者的异常灰质体积与边缘-皮层回路和默认模式网络 (DMN) 相关。 然而，BPD 青少年的皮层厚度变化尚未得到很好的评估。 本研究旨在评估 BPD 青少年皮层厚度及其与情绪失调的关系。
方法：本前瞻性研究招募了 52 名 BPD 青少年和 39 名年龄和性别匹配的健康对照者 (HC)。研究评估包括使用结构和静息状态功能 MRI (fMRI) 数据的脑部 MRI 采集，以及使用情绪调节困难量表 (DERS) 对情绪失调进行临床评估。 使用 FreeSurfer 7.2 软件分析皮层厚度和基于种子的功能连接。 使用斯皮尔曼分析进行皮层厚度与情绪评估分数之间的相关性分析。
结果：与HC相比，BPD青少年的DMN和边缘-皮层回路的皮层厚度发生改变（蒙特卡罗校正，均$p < .05$＝。 这些皮层厚度改变的区域与情绪失调显著相关（全部$p < .05$）。 功能连通性也发生了变化，即右前额叶皮层与双侧枕叶或边缘系统的连通性增加，DMN 区域之间的连通性降低（体素 $p < .001$，簇 $p < .05$，FWE 校正）。
结论：我们的结果表明，皮层厚度的改变以及边缘-皮层回路和 DMN 中功能连接的改变可能与 BPD 青少年的情绪失调有关。

was associated with emotional dysregulation in adolescents with borderline personality disorder.

1. Introduction

Borderline personality disorder (BPD) is characterized by a persistent pattern of emotional dysregulation, marked impulsivity, interpersonal disturbances, and identity instability (Bohus et al., 2021), which often begins during adolescence (Ibraheim et al., 2017). The incidence of BPD is approximately 1.6–5.9% in the general population (Ellison et al., 2018). The core characteristics of adolescent BPD are derived from emotional dysregulation, including emotional awareness deficiency, poor emotional acceptance, undirected goal behaviour, and impulse control deficiency (Mirkovic et al., 2021). Adolescents with BPD may have severe symptoms (Ibraheim et al., 2017) but they may also be at too early a stage of the disease for effective treatment to improve prognosis (Bohus et al., 2021). However, previous studies of adolescent BPD were focused on the psychological aspects of the disorder and risk factors, with limited information on the neural mechanisms of BPD. Neuroimaging may uncover brain structural and functional alterations and their association with emotional dysregulation in patients with BPD, which could potentially assist in the early diagnosis and treatment of this disorder (Boen et al., 2014; Bruehl et al., 2013; de Araujo et al., 2014).

Computation of cortical thickness through surface-based morphometry analysis of brain magnetic resonance imaging (MRI) is an important method to assess brain structural changes (de Araujo et al., 2014; Depping et al., 2016; Vatheuer et al., 2021). Cortical thickness has been studied in various disorders such as autism and Parkinson's disease, and its alterations may reflect underlying genetic and neurobiological processes (Ecker et al., 2010; Pereira et al., 2012). In addition, cortical thickness has been recognized as a brain surface morphological measure to assess structural alterations in adolescents with BPD (Richter et al., 2014). Altered cortical thickness in both the limbic–frontal circuit and the default mode network (DMN), such as prefrontal cortex, orbitofrontal cortex, temporoparietal junction, bilateral temporal poles, and bilateral paracentral lobules, has been noted in in adults with BPD (Boen et al., 2014; Bruehl et al., 2013; de Araujo et al., 2014). In addition, previous studies have suggested that structural integrity of the amygdala, insula, and prefrontal cortex plays a crucial role in the failure of emotional regulation in BPD (Bruehl et al., 2013). However, no between-group differences in cortical thickness were revealed in a cohort of female adolescents with BPD compared with controls (Richter et al., 2014). It is largely unknown whether alterations of cortical thickness may occur in adolescents with BPD or may be associated with emotional dysregulation.

In this prospective study, we enrolled a group of adolescents with BPD and a group of healthy controls (HCs) matched by age and gender. All participants underwent brain MRI scans and clinical assessment

for emotional dysregulation. We hypothesized that there were alterations in cortical thickness in the adolescents with BPD, which may be associated with the scores for emotional assessment.

2. Method

2.1. Participants

This study was approved by the institutional review board in our hospital (IRB: 2022020227). Written informed consent was obtained from the parents or legal guardians of all participants.

All adolescents with BPD were enrolled from the outpatient clinics at the Mental Health Center of Xiangya Hospital, P. R. China, from October 2021 to April 2022. During the same study interval, age- and gender-matched HCs were enrolled from local schools. All subjects were evaluated with a structured clinical interview tool to assess whether they had any personality disorders or other Axis I psychiatric disorders.

Inclusion criteria for the adolescents with BPD included the following: (1) patients aged between 12 and 17 years fulfilling the diagnostic criteria for BPD in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (Wong & Chow, 2011), having at least five out of nine criteria; (2) patients in whom symptoms had been stable for at least 2 years, and the symptoms could not be completely interpreted by the criteria for DSM-IV Axis I psychiatric disorders; and for whom the total score on the Borderline Personality Feature Scale for Children (BPFS) was greater than the demarcated score of 66; and (3) patients who were right-handed. For the HC group, inclusion criteria included the following: age between 12 and 17 years with intelligence quotient (IQ) >80, and no history of psychiatric disorders or psychoactive medication. Exclusion criteria for both groups included the following: schizophrenia spectrum disorder, bipolar spectrum disorder, post-traumatic stress disorder, neurodevelopmental disorders, major depressive disorder, alcohol and/or drug dependence, neurological disorders, IQ ≤ 80, and left-handedness. All participants were required to avoid alcohol and psychoactive substances for at least 24 h before the brain MRI scan.

BPD was a formal exclusion criterion for the HCs, which was determined through the following assessments. First, all HCs underwent the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) to exclude BPD (Wong & Chow, 2011). Secondly, all HCs were assessed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL) to exclude Axis I psychiatric disorders (Kaufman et al., 1997). Thirdly, all HCs were evaluated with the BPFS to ensure that their BPFS score was lower than the demarcated score of 66. The BPD symptoms reported on the BPFS self-report measure as listed in Table 1 were used as part of the assessment to exclude BPD in the HCs. BPD was ruled out in the HCs through a combination of the diagnostic interview (SCID-II), the assessment with the K-SADS-PL, and evaluation with the BPFS.

Table 1. Demographic and clinical characteristics of the sample.

Characteristics	Adolescents with BPD ($n = 52$)	HCs ($n = 39$)	p
Gender			.808
Male	24 (46.2)	17 (43.6)	
Female	28 (53.8)	22 (56.4)	
Age (years)	14.0 (14.0–15.0)	15.0 (14.0–16.0)	.723
Education (years)	9.0 (9.0–10.0)	9.0 (8.0–11.0)	.850
Onset age (years)	12.0 (11.0–13.0)	–	–
Illness duration (years)	3.0 (1.3–3.0)	–	–
IQ	110 (103–114)	108 (103–113)	.585
GAF	55.0 (48.5–63.8)	86.0 (84.0–88.0)	< .001***
DERS	122.5 (109.0–133.5)	55.0 (52.0–59.0)	< .001***
DERS-A	19.0 (16.0–21.0)	8.0 (7.0–9.0)	< .001***
DERS-B	14.5 (12.0–16.8)	9.0 (7.0–11.0)	< .001***
DERS-C	18.5 (13.0–22.0)	9.0 (7.0–10.0)	< .001***
DERS-D	20.5 (16.3–25.0)	8.0 (7.0–10.0)	< .001***
DERS-E	21.0 (19.0–24.0)	10.0 (9.0–12.0)	< .001***
DERS-F	30.0 (25.0–35.8)	11.0 (9.0–13.0)	< .001***
BPFS	81.0 (75.0–95.8)	32.0 (30.0–35.0)	< .001***
BPFS-A	22.0 (19.0–26.0)	8.0 (7.0–9.0)	< .001***
BPFS-B	21.0 (17.0–24.0)	8.0 (7.0–10.0)	< .001***
BPFS-C	19.0 (17.0–23.0)	8.0 (7.0–10.0)	< .001***
BPFS-D	20.0 (18.0–24.0)	7.0 (6.0–9.0)	< .001***
BIS-11	68.0 (61.3–72.8)	26.0 (25.0–28.0)	< .001***
BIS-11-A	17.0 (15.0–19.0)	7.0 (6.0–8.0)	< .001***
BIS-11-B	21.0 (19.0–24.8)	9.0 (9.0–10.0)	< .001***
BIS-11-C	27.0 (24.0–30.0)	10.0 (9.0–11.0)	< .001***
Family history			< .001***
Yes	28 (53.8)	0 (0)	
No	24 (46.2)	39 (100)	
Medication			–
Atypical antipsychotics	6 (11.5)	–	
Antidepressants	12 (23.1)	–	
Mood stabilizer	4 (7.7)	–	
Comorbidity			–
OCD	1 (1.9)	–	
GAD	4 (7.7)	–	

Note: Data are presented as n (%) or median (interquartile range). *$p < .05$, **$p < .01$, and ***$p < .001$ indicate a significant difference between the BPD group and the HC group.

BIS-11, Barratt Impulsiveness Scale, 11th version; BIS-11-A, attentional impulsiveness; BIS-11-B, motor impulsiveness; BIS-11-C, non-planning impulsiveness; BPD, borderline personality disorder; BPFS, Borderline Personality Features Scale for Children; BPFS-A, score for emotional instability; BPFS-B, score for identity recognition issues; BPFS-C, score for negative interpersonal relationships; BPFS-D, score for impulse control impairment; DERS, Difficulties in Emotion Regulation Scale; DERS-A, score for lack of emotional awareness; DERS-B, score for lack of emotional clarity; DERS-C, score for non-acceptance of emotional responses; DERS-D, score for impulse control difficulties; DERS-E, score for difficulties engaging in goal-directed activity; DERS-F, score for limited access to emotion regulation strategies; GAD, generalized anxiety disorder; GAF, Global Assessment Function; HC, healthy control; IQ, intelligence quotient; OCD, compulsive–obsessive disorder.

2.2. Structured interviews and psychological assessment

Both the adolescents and their parents or guardian underwent structured interviews. The clinical team, which consisted of senior psychiatrists (Q. X. and F. J., with, respectively, 10 and 8 years of experience in adolescent psychiatry), performed a comprehensive clinical evaluation and made the final diagnosis. The diagnostic criteria for family history were used to collect information about psychiatric disorders in first-degree relatives, and were provided by the adolescents and their parents or legal guardians.

Psychological assessment was performed by another study psychiatrist (F. J., with 8 years of experience in psychiatry). Handedness was evaluated by the Edinburgh Handedness Inventory (Oldfield, 1971) and IQ was measured by the Wechsler Abbreviated Intelligence Scale (Wechsler, 1999). Emotional assessment was evaluated with the Difficulties in Emotion Regulation Scale (DERS) (Li et al., 2018) and its six subscales, comprising scales for lack of emotional awareness, lack of emotional clarity, non-acceptance of emotional responses, impulse control difficulties, difficulties engaging in goal-directed activity, and limited emotional regulation strategies. The BPFS was used to assess the core symptoms of borderline personality in adolescents, including scales for emotional instability, identity problems, negative relationships, and impulse control problems (Liu & Wang, 2019). The Barratt Impulsiveness Scale, 11th version (BIS-11) was used to assess impulsivity, including three subscales for attentional impulsiveness, motor impulsivity, and unplanned impulsivity (Lu et al., 2012). The Global Assessment Function (GAF) scale had only one score and was used to assess the adolescents' psychological, social, and occupational functioning (Aas, 2011). All interviews and assessments were performed on the same day as the brain MRI scan.

2.3. Brain MRI data acquisition

All brain MRI data were acquired on the same Siemens MAGNETOM Prisma 3 T MRI scanner. Both structural and functional brain MRI data were acquired for each participant. Structural imaging with a T1-weighted magnetization prepared–rapid gradient echo (MPRAGE) sequence for whole-brain coverage was acquired, with the following parameters: voxel size = 1.0 × 1.0 × 1.0 mm^3, acquisition matrix = 256 × 256 mm^2, repetition time = 2300 ms, echo time = 2.03 ms, flip angle = 9°, and 176 slices with no gap. Resting-state functional magnetic resonance imaging (fMRI) data were acquired with an echo-planar imaging sequence, with the following parameters: echo time = 30 ms, repetition time = 2000 ms, matrix size = 64 × 64, flip angle = 90°, number of time points = 250, field of view = 240 × 240 mm, slice thickness = 4 mm, gap = 0.4 mm, and 30 axial slices. Additional imaging data, such as the T2-weighted sequence and fluid attenuation inversion recovery (FLAIR) sequence, were obtained for the evaluation of incidental brain abnormalities. All brain MRI data were reviewed by a senior neuroradiologist (Z. H., with more than 30 years of experience in neuroimaging) to ensure imaging quality and to rule out incidental brain pathology.

2.4. Cortical thickness analysis

Cortical surface reconstruction and segmentation on the T1-weighted images were performed with the FreeSurfer 7.2 software package to automate image processing as per the recon-all command recommended by the software (Fischl, 2012). The calculations took an average of about 10 h for each participant. In brief, imaging data processing included the following steps (Dale et al., 1999; Fischl et al., 1999): (1) converting the original DICOM (Digital Imaging and Communications in Medicine) images for T1-weighted data to the NIFTI (Neuroimaging Informatics Technology Initiative) format and then to MGZ format, and performing head movement correction; (2) completing the affine transformation from the original volume to the Montreal Neurological Institute (MNI) 305 atlas and carrying out the Talairach coordinate system transformation; (3) standardizing the signal strength of the original volume, performing the strength correction, and removing the deviation of the signal strength; (4) generating the original curved surface and performing automatic local anatomical correction; (5) expanding the generated cortical image and converting it to the spherical distribution template; (6) using 10 mm full-width half-height smoothing to check the image for Gaussian smoothing; and (7) calculating the cortical thickness index for the whole brain. The results from the automatic image processing for each subject were checked manually to assess whether the brain surface reconstruction was consistent with the grey matter boundary and whether the subcortical nucleus segmentation was consistent with the intensity boundary. If errors were detected, manual correction was performed. The measurement of cortical thickness was obtained on the shortest linear distance between the pia meningeal surface and the interface between grey matter and white matter.

2.5. Functional connectivity analysis

Functional connectivity analysis was performed on the resting-state fMRI data using a region of interest approach. The seeds for assessing functional connectivity to the whole brain were placed in the specific regions showing altered cortical thickness that were

correlated with emotional dysregulation in the adolescents with BPD. To assess functional connectivity, the brain surface clusters with altered cortical thickness mapped on the MNI 305 standard space were transformed to the MNI 152 standard space. The Pearson correlation coefficient between each seed point and the whole brain was calculated, and the Fisher *Z*-transform was performed.

2.6. Statistical analysis

We used SPSS version 22 to analyse the demographic and clinical data. The independent two-sample *t*-test or the Mann–Whitney *U*-test was used to analyse the continuous variables, and the chi-squared test was used to test the categorical variables.

Statistical analysis of cortical thickness was performed with the MRI glmfit in the FreeSurfer 7.2 software package. The differences in cortical thickness were compared by the different offset, same slope (DOSS) analysis model. Age, gender, and total intracranial volume were considered as covariables. The significance level for the peak was set as $p < .001$, Monte-Carlo *Z*-correction was adopted for multiple comparison correction, and the significance level for cluster was set as $p < .05$.

Correlation analysis between the reduced cortical thickness and the scores from the clinical assessment of emotional dysregulation was performed with the Spearman's rank correlation. The correlation analysis was controlled for age, gender, duration of illness, and age of onset. Two-tailed statistical significance was set at $p < .05$.

The functional connectivity analysis included age and gender as covariables. The statistical threshold was set at voxel $p < .001$, cluster $p < .05$, corrected for multiple comparisons with family-wise error (FWE) correction.

3. Results

3.1. Demographic and clinical characteristics

Details of the recruitment process for this cohort are presented in Figure 1. Demographic and emotional assessment data for all participants are presented in Table 1. In total, 52 adolescents with BPD and 39 matched HCs were enrolled. There were no significant differences in age, sex, intelligence, or education between the adolescents with BPD and the HCs ($p > .05$). The scores for BPD symptom features (BPFS), dysregulation of emotion (DERS), impulsivity (BIS-11), and global social function (GAF) were all significantly higher in the adolescents with BPD than in the HCs ($p < .001$). In addition, 53.8% (28/52) of the adolescents with BPD had a family history of mental disorders. In the 2 months prior to the study assessment, 19.2% of patients reported taking psychoactive medications, including antidepressants and mood stabilizers. Furthermore, 9.6% of the patients had

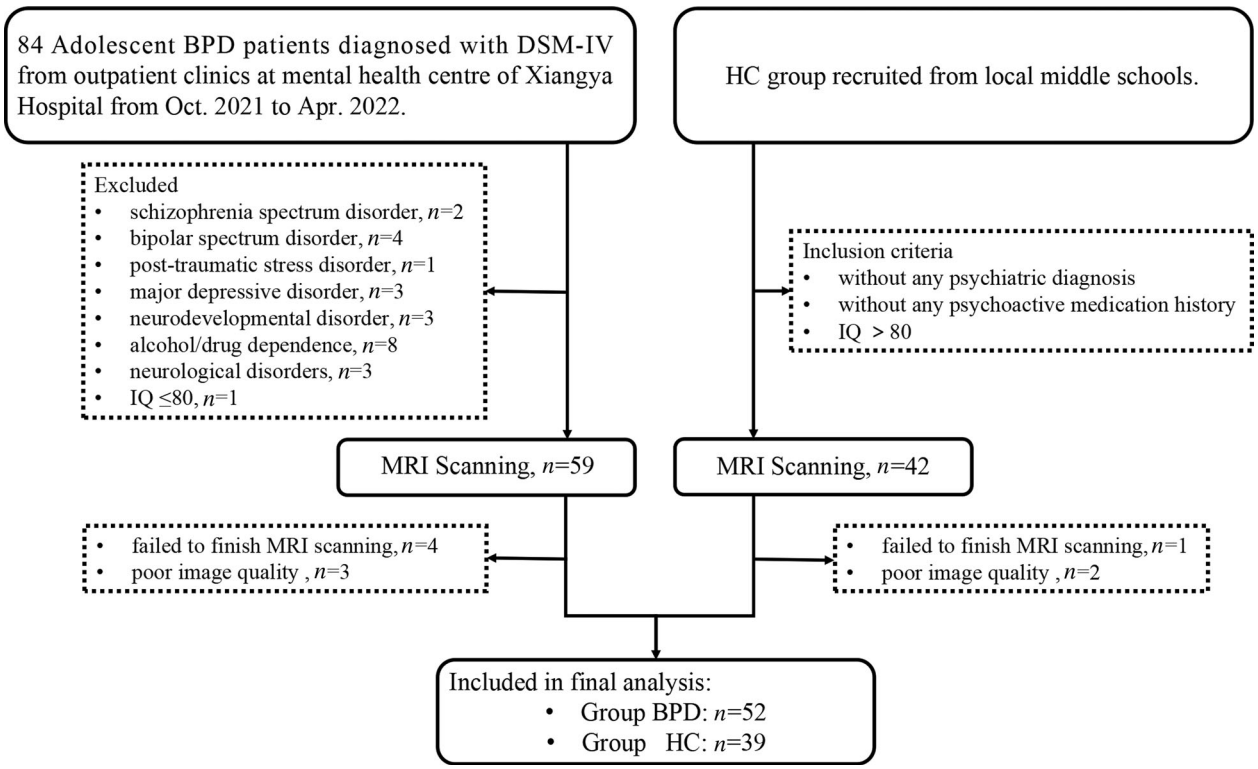

Figure 1. Flowchart illustrating the enrolment process for the adolescents with borderline personality disorder (BPD) and healthy controls (HCs). DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; IQ, intelligence quotient; MRI, magnetic resonance imaging.

comorbidities (four with general anxiety disorders and one with obsessive–compulsive disorder).

3.2. Cortical thickness alterations

There was altered cortical thickness involving the DMN regions in the adolescents with BPD compared with the HCs, which included the following: (1) decreased cortical thickness in the right precuneus ($x = 24.2$, $y = -63.1$, $z = 8.1$, $T = -7.172$, cluster size = 550.41) and right supramarginal gyrus ($x = 48.4$, $y = -37.8$, $z = 21.7$, $T = -5.061$, cluster size = 238.8); and (2) increased cortical thickness in the bilateral parahippocampal gyrus (left, $x = -33.3$, $y = -39.8$, $z = -10.6$, $T = 10.077$, cluster size = 474.28; right, $x = 35.1$, $y = -40.5$, $z = -9.8$, $T = 6.858$, cluster size = 451.5) and left medial orbitofrontal cortex ($x = -6.2$, $y = 7.6$, $z = -11.5$, $T = 11.384$, cluster size = 353.26).

Decreased cortical thickness was also noted in the limbic–cortical circuit in the adolescents with BPD compared with the HCs, involving the bilateral occipital gyrus (left, $x = -12.4$, $y = -102.3$, $z = -0.2$, $T = -15.948$, cluster size = 2629.81; right, $x = 18.9$, $y = -96.5$, $z = 15.5$, $T = -10.429$, cluster size = 1421.92; right, $x = 19$, $y = -87.5$, $z = -6.7$, $T = -5.151$, cluster size = 151.85), left lingual gyrus ($x = -23.2$, $y = -68.1$, $z = 1.1$, $T = -7.108$, cluster size = 304.92), right superior frontal gyrus ($x = 21$, $y = 16$, $z = 56.8$, $T = -3.998$, cluster size = 152.68), bilateral inferior temporal lobe (left, $x = -48.4$, $y = -24.2$, $z = -28.5$, $T = -5.904$, cluster size = 178.5; right, $x = 49.1$, $y = -23.2$, $z = -27.4$, $T = -5.595$, cluster size = 237.72), and left fusiform gyrus ($x = -34.4$ $y = -14.3$, $z = -31.6.$, $T = 4.593$, cluster size = 151.98). The significance level for the peak was set as $p < .001$, and the significance level for cluster was set as $p < .05$ (Figure 2 and Table 2).

3.3. Correlation between cortical thickness and scores for emotional dysregulation

The scores for clinical assessment of emotional dysregulation, as measured by the DERS, BPFS, BIS-11, and GAF scales, were significantly associated with cortical thickness measurements in the brain regions of the limbic–cortical circuit and DMN. Specifically, lack of emotional awareness (DERS-A) was negatively correlated with the bilateral parahippocampal gyrus (left, $r = -0.461$, $p = .001$; right, $r = -0.521$, $p < .001$), left inferior temporal gyrus ($r = -0.368$, $p = .007$), and right precuneus ($r = -0.403$, $p = .003$). There was a negative correlation between lack of emotional clarity (DERS-B) and the left inferior temporal gyrus ($r = -0.394$, $p = .004$). There was a positive correlation between non-acceptance of emotional responses (DERS-C) and the right inferior temporal gyrus ($r = 0.353$, $p = .01$). There was a negative correlation between the right lateral occipital gyrus and engaging in goal-directed activity score (DERS-E) ($r = -0.2968$, $p = .033$). The score for impulse control impairment

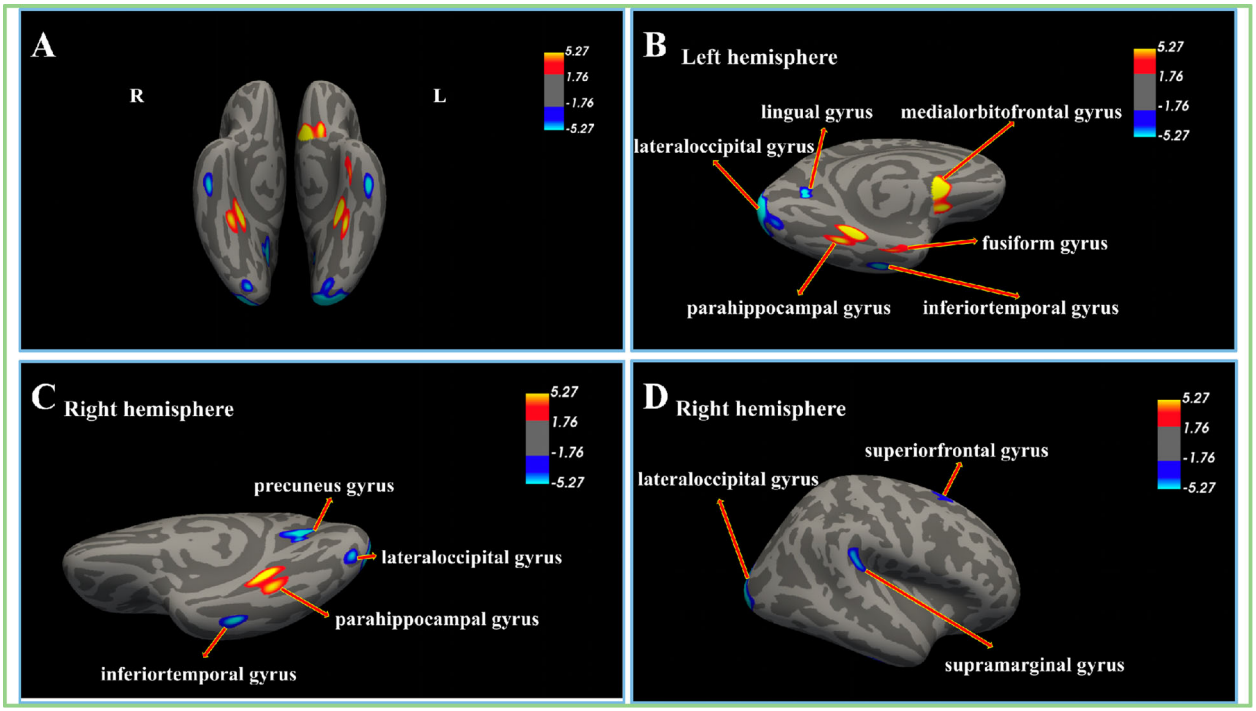

Figure 2. Brain regions with increased (highlighted in orange) and decreased cortical thickness (highlighted in blue) in the limbic–cortical circuit and default mode network (DMN) of adolescents with borderline personality disorder (BPD) compared with healthy controls (HCs). (A) Cortical thickness alterations in bilateral hemispheres. (B) Cortical thickness alterations in the left hemisphere. (C) Cortical thickness alterations in the medial surface of the right hemisphere. (D) Cortical thickness alterations in the lateral surface of the right hemisphere.

Table 2. Brain regions with altered cortical thickness in adolescents with borderline personality disorder (BPD) compared with healthy controls (HCs).

No.	Location	Size (mm^2)	No. of vertices	Mean cortical thickness of BPD (*SD*)	Mean cortical thickness of HCs (*SD*)	*p* (FWE)
	Left hemisphere					
1	Lateral occipital[a]	2629.81	3221	1.76 (0.11)	2.00 (0.13)	.0001
2	Parahippocampal[a]	474.28	999	2.66 (0.14)	2.43 (0.16)	.0001
3	Medial orbitofrontal	353.26	753	3.06 (0.23)	2.65 (0.26)	.0003
4	Lingual	304.92	689	1.73 (0.17)	1.96 (0.23)	.0009
5	Inferior temporal[a]	178.5	300	2.80 (0.38)	3.20 (0.38)	.0171
6	Fusiform	151.98	320	2.95 (0.24)	2.62 (0.25)	.0343
	Right hemisphere					
7	Lateral occipital[a]	1421.92	1815	1.87 (0.15)	2.12 (0.14)	.0001
8	Precuneus[a]	550.41	1135	1.90 (0.18)	2.14 (0.20)	.0001
9	Parahippocampal	451.5	913	2.61 (0.13)	2.43 (0.16)	.0001
10	Supramarginal	238.8	588	2.28 (0.19)	2.50 (0.21)	.0031
11	Inferior temporal[a]	237.72	377	2.82 (0.38)	3.20 (0.37)	.0031
12	Superior frontal	152.68	292	2.70 (0.30)	2.93 (0.25)	.0312
13	Lateral occipital	151.85	192	1.67 (0.17)	1.86 (0.22)	.0321

Note: All clusters were corrected with multiple comparisons using family-wise error (FWE) correction (Monte Carlo, cluster-wise corrected *p*-values < .05).
[a]Clusters were selected from region of interest (ROI) analysis.

(BPFS-D) was negatively correlated with the bilateral occipital gyrus ($r = -0.280$, $p = .044$). Attentional impulsiveness (BIS-11-A) was negatively correlated with the left inferior temporal gyrus ($r = -0.484$, $p = .0003$). Overall functional impairment, as measured by the GAF, was significantly correlated with the left inferior temporal gyrus ($r = 0.336$, $p < .001$) ($p < .05$) (Figure 3 and Supplementary Figure 1).

3.4. Functional connectivity alterations

The adolescents with BPD showed increased functional connectivity compared with the HCs, involving the following regions: (1) between the left lateral occipital gyrus and right superior frontal gyrus ($x = 24$, $y = 36$, $z = -12$, $T = 5.0159$, cluster size = 331); (2) from the right lateral occipital gyrus to the right inferior orbitofrontal gyrus ($x = 36$, $y = 27$, $z = -21$, $T = 10.1480$, cluster size = 767), or to the right inferior frontal gyrus ($x = 48$, $y = 30$, $z = 0$, $T = 5.3920$, cluster size = 593), or to the right anterior cingulate gyrus ($x = -12$, $y = 42$, $z = 9$, $T = 4.4318$, cluster size = 135); (3) from the left inferior temporal gyrus to the right inferior temporal gyrus ($x = 48$, $y = -12$, $z = -33$, $T = 6.6611$, cluster size = 253) or to the right inferior orbitofrontal gyrus ($x = 51$, $y = 24$, $z = -6$, $T = 4.9926$, cluster size = 126); and (4) from the right inferior temporal gyrus to the right inferior orbitofrontal gyrus ($x = 36$, $y = 30$, $z = -21$, $T = 7.1943$, cluster size = 2802, or to the left inferior temporal gyrus ($x = -51$, $y = -12$, $z = -30$, $T = 6.498$, cluster size = 285).

The adolescents with BPD showed decreased functional connectivity compared with the HCs, involving the following regions: (1) between the left parahippocampal gyrus and the left superior parietal gyrus ($x = -18$, $y = -75$, $z = 57$, $T = -4.6591$, cluster size = 129); and (2) from the right precuneus to the left middle frontal gyrus ($x = -33$, $y = 0$, $z = 66$, $T = -5.7415$,

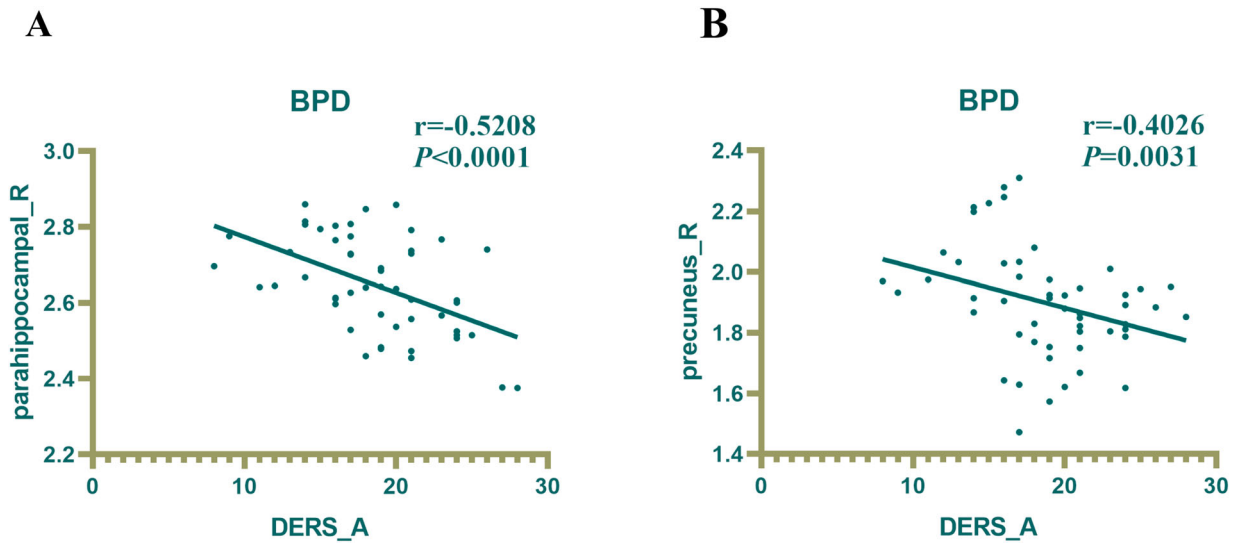

Figure 3. Correlation analysis between cortical thickness and the scores on the Difficulties in Emotion Regulation Scale (DERS-A for lack of emotional awareness) in adolescents with borderline personality disorder (BPD). (A) Negative correlation between the cortical thickness of the right parahippocampal gyrus and the DERS-A score. (B) Negative correlation between the cortical thickness of the right precuneus gyrus and the DERS-A score.

cluster size = 173) or to the left superior parietal gyrus ($x = -27$, $y = -57$, $z = 69$, $T = -4.833$, cluster size = 168) (Table 3, Figure 4, and Supplementary Figure 2).

4. Discussion

In this study, we found altered cortical thickness in both the DMN regions and the limbic–cortical circuit in the adolescents with BPD, which was associated with emotional dysregulation. In addition, there were changes in the functional connectivity of the brain regions with altered cortical thickness in the adolescents with BPD. To the best of our knowledge, this is the first study of cortical thickness and its association with emotional dysregulation in adolescents with BPD.

We found alterations in cortical thickness in two key nodes of DMN, i.e. the left medial orbitofrontal cortex and the right precuneus, in our cohort of adolescents with BPD. These two regions have been implicated in emotional dysregulation with impaired mentalization (Raichle, 2015). The medial orbitofrontal cortex plays an important role in regulating mood reactivity, impulsivity, and social behaviour, which have been considered the core symptoms of BPD (Dusi et al., 2021; Wolf et al., 2012). Our observation of reduced cortical thickness in the left medial orbitofrontal cortex was consistent with a similar finding of cortical thinning in the same region in female adults with BPD (de Araujo et al., 2014). In addition, a positron emission tomography (PET) study identified diminished glucose metabolism in the medial orbitofrontal cortex of patients with BPD (Soloff et al., 2005), which may be related to cortical thinning. As a crucial node in DMN, the precuneus has been suggested to be involved in reflective and self-related processing (Cavanna & Trimble, 2006), empathy, awareness, and conscious information processing.

Table 3. Brain regions with significant alterations in seed-based functional connectivity between adolescents with borderline personality disorder (BPD) and healthy controls (HCs) (voxel $p < .001$, cluster $p < .05$, FWE corrected).

		MNI peak coordinates				
Seed point	Brain region	*X*	*Y*	*Z*	*T*	Cluster size
Left lateral occipital	Frontal_Sup_R	24	36	−12	5.0159	331
Right lateral occipital	Frontal_Inf_Orb_R	36	27	−21	10.148	767
	Frontal_Inf_Tri_R	48	30	0	5.392	593
	Cingulum_Ant_R	−12	42	9	4.4318	135
Left inferior temporal	Temporal_Inf_R	48	−12	−33	6.6611	253
	Frontal_Inf_Orb_R	51	24	−6	4.9926	126
Right inferior temporal	Frontal_Inf_Orb_R	36	30	−21	7.1943	2802
	Temporal_Inf_L	−51	−12	−30	6.498	285
Left parahippocampal	Parietal_Sup_L	−18	−75	57	−4.6591	129
Right precuneus	Frontal_Mid_L	−33	0	66	−5.7415	173
	Parietal_Sup_L	−27	−57	69	−4.833	168

Note: Ant, anterior; FWE, family-wise error; Inf, inferior; L, left; Mid, middle; MNI, Montreal Neurological Institute; Orb, orbital; R, right; Sup, superior; Tri, triangular.

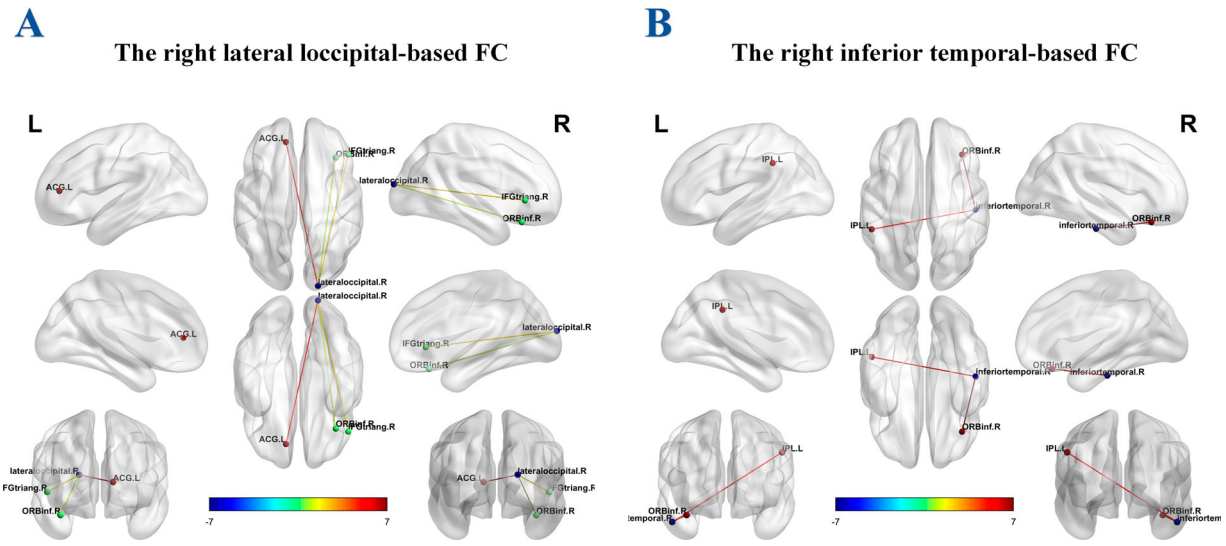

Figure 4. Significant alterations of functional connectivity (FC) in adolescents with borderline personality disorder (BPD) compared with healthy controls (HCs), using the right lateral occipital and right inferior temporal regions as seed points. (A) Increased FC of the right lateral occipital gyrus with the right inferior orbitofrontal gyrus, right inferior frontal gyrus, and right anterior cingulate gyrus. (B) Increased FC of the right inferior temporal gyrus with the right inferior orbitofrontal gyrus and left inferior temporal gyrus. Voxel $p < .001$, cluster $p < .05$, family-wise error (FWE) corrected. The colour bar indicates the *T* score.

Cortical thinning in the precuneus, as noted in our study, may have implications in terms of extensive processing of internal thoughts and self-referential information in adolescents with BPD. However, increased grey matter in the precuneus and increased connectivity between the precuneus and the frontal cortex have been noted in adults with BPD (O'Neill et al., 2015; Yang et al., 2016). We speculate that cortical thinning of the precuneus may be unique in adolescents with BPD, and the precuneus may increase in size with cortical thickening in adulthood in compensation for cortical loss during the adolescent stage.

Our finding of cortical thinning involving the limbic–cortical circuit and its association with emotional dysregulation supports the notion of linking this neural circuit to emotional instability in adolescents with BPD. It has been suggested that emotional disorders in BPD may be caused by limbic system alterations and prefrontal lobe deficits (Sicorello & Schmahl, 2021). In this study, we observed significantly decreased ability to regulate emotions in adolescents with BPD, which was associated with this neural circuit. Our study added new data for adolescent BPD and suggested that cortical thinning in the limbic–cortical circuit may be involved in emotional control in adolescents with BPD, similarly to adults with BPD (Boen et al., 2014). In addition, we found that an emotional awareness deficit was significantly correlated with the core nodes of DMN, including the bilateral parahippocampal gyrus and right precuneus. We also identified global functional impairment and its significant correlation with cortical thickness of the left lingual gyrus and left inferior temporal gyrus. Taking these findings together, this study identified new specific involvement of the limbic–cortical circuit and DMN in emotional disorders of BPD during the adolescent stage.

Our study showed a positive correlation between cortical thickness in the right inferior temporal gyrus and DERS-C scores (non-acceptance of emotional responses). This correlation may be associated with the neuronal structure underlying emotional regulation. Non-acceptance of emotional responses, as indicated by the DERS-C scores, may illicit more brain activation than the innate acceptance of emotional responses, which may promote more neuronal synaptogenesis. This process may lead to an increase in cortical thickness, and thus a positive correlation. In addition, our study showed increased functional connectivity between the right inferior temporal gyrus and right inferior orbitofrontal gyrus, and both brain regions were critical for emotional regulation. We speculate that the increased functional connectivity may be the neural correlate for the increased DERS-C scores in our cohort of adolescents with BPD.

Our findings of altered functional connectivity complemented the observations of changes in cortical thickness in this study. We found an increased functional connectivity between the right prefrontal cortex and bilateral occipital lobes, implying that the prefrontal–occipital circuit may be involved in adolescent BPD (Kimmel et al., 2016). We also identified increased functional connectivity between the bilateral inferior temporal gyrus and right orbitofrontal gyrus. The inferior temporal gyrus is an important brain region of the limbic system (Sicorello & Schmahl, 2021), and the increased connectivity with the orbitofrontal cortex implied potential pathological changes in the limbic–frontal circuit in adolescent BPD (Silbersweig et al., 2007). Cortical thickness changes were also noted in the limbic–frontal circuit in our cohort of adolescents with BPD. However, we also noted decreased functional connectivity within the DMN, such as between the precuneus and middle frontal gyrus. The DMN is involved in emotional regulation, and it is related to rumination and self-negative evaluation in adolescents with BPD (Aguilar-Ortiz et al., 2020). The decreased functional connectivity between DMN nodes may lead to unstable self-image and impaired emotional regulation in adolescents with BPD (Kluetsch et al., 2012; Yang et al., 2016). The decrease in connectivity between the left superior parietal gyrus and the limbic system, such as the parahippocampal gyrus and the lingual gyrus, suggested insufficient regulation of the left superior parietal lobe to the limbic system, which has been shown to be closely related to impaired emotional regulation (Irle et al., 2007; Richter et al., 2014).

There were several limitations to the study. First, there may be case selection bias in our cohort, which may have included patients with more severe symptoms of BPD. Our hospital is known for tertiary psychiatric care in China and we take care of sicker patients transferred from community hospitals. Secondly, although our sample size was larger than in previous studies, it was still a modest cohort. We did not have the statistical power to test the effects of confounding factors, such as education, duration of illness, or different medications, on cortical thickness. Thirdly, we excluded multiple comorbidities such as depression, post-traumatic stress disorder, bipolar spectrum disorders, neurodevelopmental disorder, schizophrenia spectrum disorders, and substance use disorder in our study. Although prior reports have shown potentially different pathological mechanisms between these disorders and BPD (Reich et al., 2019; Villarreal et al., 2021), these disorders may confound our study results and therefore should be excluded. Nevertheless, 10% of our patients had comorbidities such as anxiety disorder and obsessive–compulsive disorder. BPD is known to have a high comorbidity rate and is often accompanied by high anxiety. It

was challenging to enrol patients without any psychiatric illness as these comorbidities were inseparable from features of BPD and some are characteristics of BPD (Choate et al., 2021).

5. Conclusion

In this study, we found altered cortical thickness and functional connectivity in the limbic–cortical circuit and DMN, which could be underlying neural correlates for emotional dysregulation in adolescents with BPD. This study identified novel information on potential neural mechanisms specifically for BPD during the adolescent stage, which should contribute to the early diagnosis and prompt treatment of this disorder in vulnerable adolescents.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability statement

The data that support the findings of this study are available from the corresponding author (X. Y.), upon reasonable request. The data are not publicly available owing to privacy and ethical restrictions.

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