Common and Specific Characteristics of Adolescent Bipolar Disorder Types I and II: A Combined Cortical Thickness and Structural Covariance Analysis

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Background: By calculating cortical thickness (CT) and cortical structural covariance (SC), we aimed to investigate cortical morphology and cortical inter-regional correlation alterations in adolescent bipolar disorder type I (BD-I) and type II (BD-II) patients.

Methods: T1-weighted images from 36 BD-I and 22 BD-II patients and 19 healthy controls (HCs) were processed to estimate CT. CT values of the whole brain were compared among three groups. Cortical regions showing CT differences in groups were regarded as seeds for analyzing cortical SC differences between groups. The relationship between CT and clinical indices was further assessed.

Results: Both BD groups showed cortical thinning in several frontal and temporal areas vs. HCs, and CT showed no significant difference between two BD subtypes. Compared to HCs, both BD groups exhibited reduced SC connections between left superior frontal gyrus (SFG) and right postcentral gyrus (PCG), left superior temporal gyrus (STG) and right pars opercularis, and left STG and right PCG. Compared with HCs, decreased SC connections between left STG and right inferior parietal gyrus (IPG) and right pars opercularis and right STG were only observed in the BD-I group, and left PCG and left SFG only in the BD-II group. CT of right middle temporal gyrus was negatively correlated with number of episodes in BD-II patients.

Conclusions: Adolescent BD-I and BD-II showed commonly decreased CT while presenting commonly and distinctly declined SC connections. This study provides a better understanding of cortical morphology and cortical inter-regional correlation alterations in BD and crucial insights into neuroanatomical mechanisms and pathophysiology of different BD subtypes.

Keywords: bipolar disorder, MRI, neuroimaging, cortical thickness, structural covariance, subtype
INTRODUCTION

Bipolar disorder (BD) is a common mental disorder featuring violent emotional fluctuations (1). BD can be divided into two subtypes, type I (BD-I) and type II (BD-II). BD-I is characterized by at least one full-blown manic episode, and BD-II is defined as alternating episodes of depression and hypomania. The disorder is associated not only with premature death, severe disability, and psychosocial impairment (2), but also with impaired cognition (3). The diagnosis of BD is mainly through clinical history, interview, and behavioral observations, which may lead to misdiagnosis, improper treatment, and eventually poorer outcomes (4). So far, the pathophysiology underlying BD is still unclear. Fortunately, brain imaging provides a non-invasive approach for exploring the brain structure, making it a hot spot in the study of the pathological mechanism of mood disorders (5). Anatomical brain abnormalities in BD are confirmed by imaging studies, which may help in the development of neuroimaging markers (6). For better understanding the underlying mechanisms of BD, investigating neural structural changes may contribute to improving treatment and diagnosis of individuals with BD. Although the neural underpinnings of BD progression remain unclear, research suggests that mood episodes could cause lasting neurobiological changes (7). Individuals with BD-I and BD-II exhibit different symptoms, which partly indicates different neurobiological mechanisms and pathophysiology of the two BD subtypes (8). However, little is known about common and special structural abnormalities of BD-I and BD-II (9).

Cortical thickness (CT) is beneficial for identifying biological markers of BD, which has been found in prior review (10). CT thinning is a consistent neuroimaging finding in BD patients, primarily in frontal and temporal cortex and then in anterior cingulate and parietal regions (11–16). Clinical evidence shows that the course of disease and related health problems in BD-II patients are as severe as in BD-I patients (1). Nevertheless, the majority of studies in BD focus on individuals with BD-I or a combination of BD-I and BD-II. Thus far, there are relatively few studies paying attention to probing CT changes in BD-I, BD-II patients, and healthy controls (HCs). In these studies, region-of-interest (ROI)–based and data-driven methods were used to analyze CT in some regions and whole brain areas, respectively. In an ROI–based study, combining BD in adolescents and young adults, uncorrected results show that BD-II patients had reduced CT in anterior cingulate cortex compared with BD-I patients (17). Using data-driven methods, a study reports that both adult BD-I and BD-II shared lower CT in several frontal regions, but only the BD-I group showed thinner cortices in medial prefrontal and temporal regions relative to HCs (8). However, a recent study, also employing a data-driven approach, focuses on adult (age ≥25 years) and adolescents/young adults (age <25 years) with BD and reports no significant differences in CT between BD-I and BD-II groups, and whole adult BD subjects showed CT reductions in left par opercularis, left fusiform gyrus, and left rostral middle frontal gyrus (MFG) compared with HCs, whereas whole adolescent/young adult subjects with BD presented cortical thinning in right supramarginal gyrus (18).

Taken together, although these findings of CT alterations in two subtypes of BD remain controversial, these alterations exert an effect on neural processing in BD (19). Hence, it is meaningful to understand the pathophysiology of BD by characterizing thickness of cortex in BD patients. Relative to an ROI–based CT analytic method, data-driven analysis of CT is beneficial for comprehensive understanding of cortical structure alterations. The whole-brain CT alterations of adolescent BD-I and BD-II were needed for further investigation.

In recent years, cortical morphology study is not only limited to CT of one brain region, but also attracted growing interest in cortico-cortical correlations. Structural covariance (SC) describes a phenomenon by which gray matter properties of one brain area may change together with those of other widely distributed cortical areas (20). It could uncover intracortical similarities and be described as the coordinated change in brain morphological measurements (e.g., cortical thickness) (21), showing partial agreement with functional connectivity (22) and white matter connections (23). Recently, an increasing number of studies have confirmed the alterations of cortical SC in various mood disorders (24–26). However, only a few studies investigate cortical SC in individuals with BD. Comparing cortical SC between schizophrenia and BD-I patients, study observes that BD patients presented decreased cortical SC between left superior occipital gyrus and its neighbor anatomic structures and right insular cortex and its adjacent anatomic regions (27). One study compared SC in nucleus accumbens (NAc) in BD and major depressive disorder (MDD) and reports that, compared with HCs, BD groups displayed decreased volumetric SC connections between NAc and prefrontal gyrus, bilateral anterior insula, and bilateral striatum and increased NAc connections between NAc and left hippocampus extending to thalamus (28).

When comparing cortical and subcortical volumetric SC in BD and MDD, another study found BD patients showed distinct anatomical relationships of the connections between striatum and dorsolateral prefrontal cortex (DLPFC) and putamen and caudate nuclei vs. HCs (29). In summary, the above evidence accumulated supports the crucial role of structural SC in BD. The SC of brain regions could be interpreted to support the existence of coordinated neurodevelopmental and maturational alteration in distributed cortical regions (20). Given that adolescence is a period for the onset and coordinated neurodevelopment of mental disorders (30), abnormal cortical SC may play a vital role in the pathophysiology of psychiatric disorders. Thus, in brain regions showing CT alterations, evaluating cortical SC abnormalities in adolescent BD-I and BD-II may offer novel insights given that brain cortical regions do not function in isolation.

Herein, we sought to analyze whole-brain CT differences among the adolescent BD-I, BD-II, and HCs and seed-based cortical SC differences. Specifically, CT values of whole brain were compared among the three groups and subgroups. Subsequently, cortical regions showing between-group CT differences were regarded as seeds. Correlation coefficients between each seed and other cortical regions were compared between groups. In addition, we also analyzed the relationship between cortical region thickness and clinical index. According to
previous evidence, we hypothesized that patients with BD-I and BD-II would show great CT reductions in frontal and temporal regions compared with HCs and that cortical SC connections among frontal, temporal, and parietal regions would be abnormal in BD-I and BD-II groups.

MATERIALS AND METHODS

Participants

The subjects enrolled were 77 adolescents (BD-I patients, N = 36; BD-II patients, N = 22; HCs, N = 19). All BD patients were outpatients from the clinical psychiatric department in the Second Xiangya Hospital of Central South University, and HCs were recruited by advertisements in local schools. All the BD patients met the criteria of Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV). The inclusion criteria for all subjects were (a) 12–18 years old, (b) right-handed, and (c) able to hold their head still to finish the MRI scanning. Exclusion criteria of all participants were (a) score of full-scale intelligence quotient (IQ) ≤ 80; (b) pregnancy; (c) contraindications of MRI scanning, including claustrophobia or foreign metallic substances in the body; (d) history of alcohol or drug abuse; (e) history of electroconvulsive therapy; (f) other psychiatric disorders, such as autism, schizophrenia, bulimia nervosa or anorexia, and learning disabilities; (g) active medical psychiatric disorders, such as autism, schizophrenia, bulimia nervosa or anorexia, and learning disabilities; (g) active medical or neurological diseases. In addition, HCs were required to be without a history of mental disorder in their first-degree relatives. The study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University. Informed consent documents were obtained from all participants and at least one legal guardian.

Demographic and Clinical Evaluation

The diagnoses were determined through consensus between two broad-certified child psychiatrists based on clinical interviews and administrations of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADSPL) (31). Demographic and clinical information of all subjects were collected on the day of MRI scanning. Intellectual ability of all the subjects was assessed by the Wechsler Abbreviated Scale of Intelligence (WASI). The Young Mania Rating Scale (YMRS) (32) and Mood and Feelings Questionnaire (MFQ) (33) were adopted to assess the current mood state of every participant. The information of onset age, illness duration, number of episodes, psychotic symptom, familial BD history, medications, and comorbidity of patients were collected. Four BD patients were in the first episode. Twenty-three patients had not been treated with medication.

IBM SPSS (version 25.0, Armonk, NY, United States) was used for statistical analysis of demographic and clinical data. Categorical variables were compared by Pearson chi-square test. Continuous variables were compared by one-way analysis of variance among the three groups and two-sample t-test between two groups. Statistical power was calculated by G*Power (version 3.1) (https://www.psychologie.hhu.de/arbeitgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower.html).

MRI Data Acquisition

Siemens 3 Tesla Trio scanner (Siemens, Munich, Germany) was used for MRI scanning. T1-weighted images were acquired by employing a three-dimensional magnetization-prepared rapid acquisition gradient echo (3D MPRAGE) protocol. Sequence parameters were the following: repetition time = 2,300 ms, echo time = 2.03 ms, inversion time = 900 ms, slice thickness = 1 mm, field of view (FOV) = 256 × 256 mm², matrix = 256 × 256, flip angle = 9°, voxel size = 1 × 1 × 1 mm³, and 176 axial slices. During MRI scanning, a foam pad placed on two sides of each subject's head was to restrict the subjects’ head motion and cotton earplugs reduced the noise and protected subjects' hearing.

MRI Data Processing

The cortical reconstruction and segmentation were automatically finished employing a FreeSurfer version 6.0 software (https://surfer.nmr.mgh.harvard.edu) longitudinal stream. In brief, this process mainly included motion correction, automated Talairach transformation, intensity normalization, skull stripping, reconstruction of the white and gray matter boundary and the cortical surface, estimation of brain surfaces and surface segmentation. CT values were extracted from 68 (34 regions per hemisphere) cortical gray matter regions based on Desikan–Killiany atlas (34). Cortical reconstructions and segmentations of all subjects were visually inspected by experienced researchers and manually corrected if needed.

Cortical Thickness Analysis

Age and gender were included as covariates in all comparisons of CT. Analysis of covariance (ANCOVA) was used to analyze CT changes among the three groups. The main effects comparisons of CT were corrected by false discovery rate (FDR) correction (35). For the cortical regions showing significant CT differences among the three groups after FDR correction, post hoc comparisons were further conducted with FDR correction for multiple comparisons. Because the relationship between total intracranial volume (TIV) and CT is controversial (36), TIV was not regarded as a covariate in CT analysis. Moreover, using analysis of covariance with age and gender as covariates, no significant difference (F = 0.504, p = 0.606, Power = 0.137) of TIV was found among the three groups.

Structural Covariation Analysis

SC analysis between subgroups was conducted employing a seed-based approach on the basis of post hoc comparison results from CT analysis. If cortical regions showed significant intergroup differences of CT between groups (BD-I vs. HCs, BD-II vs. HC, BD-I vs. BD-II), these cortical regions were regarded as seeds to analyze the intergroup difference of SC. According to previous study of SC (37), the detailed analysis steps of SC were as follows. First, to construct seed-base cortical SC network of each population (BD-I, BD-II, HCs), partial correlation analysis was separately used to calculate the CT correlation coefficient between each seed and all other cortices with age and gender as

Kuang et al. Cortical Alterations in Bipolar Disorder
TABLE 1 | Demographic and clinical data of all participants.

| Characteristics                        | BD-I (n = 36) | BD-II (n = 22) | HCs (n = 19) | Statistic | p    | Power |
|----------------------------------------|---------------|---------------|--------------|-----------|------|-------|
| Gender (male/female)                   | 20/16         | 9/13          | 7/12         | χ² = 2.172 | 0.338| 0.243 |
| Age (years)                            | 15.31 (1.93)  | 14.64 (1.50)  | 14.16 (1.57) | F = 2.935  | 0.059| 0.535 |
| Education (years)                      | 8.33 (1.90)   | 7.64 (1.47)   | 7.47 (2.22)  | F = 1.667  | 0.196| 0.335 |
| IQ                                     | 102.67 (13.60)| 105.32 (12.12)| 105.32 (7.51)| F = 0.471  | 0.626| 0.125 |
| YMRS scores                            | 18.15 (15.25) | 9.50 (11.10)  | 3.63 (2.06)  | F = 9.690  | <0.001| 0.946 |
| MFQ scores                             | 12.44 (12.30) | 15.41 (12.59) | 6.11 (3.33)  | F = 3.849  | 0.026| 0.647 |
| Onset age (year)                       | 13.83 (1.81)  | 13.55 (1.99)  | –            | t = 0.565  | 0.574| 0.085 |
| Illness duration (months)              | 19.08 (13.33) | 11.73 (14.00) | –            | t = 2.001  | 0.050| 0.497 |
| Number of episodes                     | 3.58 (2.27)   | 2.91 (1.19)   | –            | t = 1.285  | 0.204| 0.268 |
| Psychotic symptoms (yes/no)            | 17/19         | 13/9          | –            | χ² = 0.770 | 0.380| 0.142 |
| Familial BD history (yes/no)           | 18/18         | 11/11         | –            | χ² = 0.000 | 1.000| 0.050 |

Values are presented as mean (standard deviation).
BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; HCs, healthy subject controls; IQ, intelligence quotient; YMRS, Young Manic Rating Scale; MFQ, Mood and Feelings Questionnaire; ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional defiant disorder; OCD, obsessive–compulsive disorder; TIC, tic.
χ², value for Pearson chi-square test; F, value for one-way analysis of variance; t, value for two-sample two-tailed t-test.
Bold values indicate significant differences with p < 0.05.

covariates. Second, a partial correlation coefficient $r$ value was Fisher-transformed to a $z$ value as follows:

$$Z_i = \frac{1}{2} \log_e \left[ \frac{1 + r_i}{1 - r_i} \right],$$

where $r_i$ is the partial correlation coefficient $r$ value between each seed and each other cortical region, and $i$ is each population. Finally, a $z$-test was used to assess intergroup difference of cortical SC network as follows:

$$z = \frac{Z_1 - Z_2}{\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}.$$

The sample distribution of $Z_i$ is approximately normal with a variance equal $1/(n-3)$, and $n$ refers to the sample size of each population. The standard error of the difference between the two independent $Z_i$ is the square root of that sum of variance, and the standard error is employed as the denominator in the $z$-test. The $z$ value was converted to the $p$-value using a normal cumulative distribution function. The $p$-value of this test was corrected using FDR correction at $p < 0.05$.

Cortical Thickness Correlation Analysis

Exploratory correlation analysis between CT and clinical indices was performed. Pearson correlation analysis was used to analyze the residual relationship between CT and clinical indices with age and gender regressed.

RESULTS

Demographic and Clinical Data

As shown in Table 1, three groups did not significantly differ in gender, age, education, and IQ distribution. YMRS and MFQ scores showed significant differences among the three groups. There was no significant difference between BD-I and BD-II groups in onset age, illness duration, number of episodes, first episode, psychotic symptoms, and familial history.

Cortical Thickness Analysis

As shown in Table 2, the CT of seven cortical regions showed significant differences among the three groups. Compared with HCs, both BD-I and BD II groups exhibited decreased CT in seven cortical regions, involving left inferior temporal gyrus (ITG), left rostral MFG, left superior frontal gyrus (SFG), left transverse temporal gyrus (TTG), right middle temporal gyrus (MTG), and bilateral superior temporal gyrus (STG). There was no significant difference of CT between BD-I and BD-II groups. The results of all CT analyses are shown in the Supplementary Table S1.
| Brain region thickness | EMN (SE) | BD-I | BD-II | HCs | Main effecta | BD-I vs. HCs | BD-II vs. HCs | BD-I vs. BD-II |
|-----------------------|----------|------|-------|-----|--------------|--------------|---------------|----------------|
| | | t | p | Power | t | p | Power | t | p | Power |
| Left inferior temporal gyrus | 2.84 (0.02) | 2.81 (0.03) | 2.94 (0.03) | 6.57 | 0.027 | 0.917 | 2.83 | 0.013 | 0.808 | 3.47 | 0.003 | 0.930 | 1.00 | 0.336 | 0.173 |
| Left rostral middle frontal gyrus | 2.34 (0.02) | 2.30 (0.02) | 2.40 (0.02) | 6.20 | 0.034 | 0.902 | 2.30 | 0.036 | 0.657 | 3.45 | 0.003 | 0.931 | 1.52 | 0.159 | 0.338 |
| Left superior frontal gyrus | 2.83 (0.02) | 2.77 (0.03) | 2.93 (0.03) | 6.59 | 0.027 | 0.919 | 2.53 | 0.023 | 0.712 | 3.62 | 0.003 | 0.909 | 1.38 | 0.200 | 0.272 |
| Left superior temporal gyrus | 2.83 (0.02) | 2.77 (0.03) | 2.96 (0.03) | 8.92 | <0.001 | 0.977 | 2.95 | 0.009 | 0.847 | 4.23 | <0.001 | 0.982 | 1.59 | 0.150 | 0.353 |
| Left transverse temporal gyrus | 2.52 (0.03) | 2.46 (0.04) | 2.65 (0.04) | 5.81 | 0.049 | 0.881 | 2.44 | 0.026 | 0.707 | 3.36 | 0.003 | 0.906 | 1.18 | 0.264 | 0.219 |
| Right middle temporal gyrus | 2.92 (0.03) | 2.91 (0.03) | 3.07 (0.04) | 7.76 | 0.023 | 0.955 | 3.52 | 0.003 | 0.944 | 3.47 | 0.003 | 0.918 | 0.22 | 0.835 | 0.054 |
| Right superior temporal gyrus | 2.90 (0.02) | 2.82 (0.03) | 3.01 (0.03) | 9.70 | <0.001 | 0.985 | 2.81 | 0.013 | 0.810 | 4.43 | <0.001 | 0.989 | 1.97 | 0.071 | 0.501 |

EEM, estimated marginal means; SE, standard error; BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; HCs, healthy subject controls.

aTwo-sample t-test controlling for age and gender.

bFDR correction was used for main effect comparisons and post hoc comparisons; p-values are presented after FDR correction.

Bold values indicate significant differences with p < 0.05.

**Table 3** Significant between-group differences (BD-I vs. HCs; BD-II vs. HCs) in structural covariance analysis.

**Structural Covariance Analysis**

According to the above results of CT analysis, seven cortical regions were regarded as seeds of ROI to analyze SC differences between groups (BD-I vs. HCs, BD-II vs. HCs) (Table 3; Figure 1). Compared with HCs, both BD-I and BD-II groups showed significantly reduced cortical SC connections between left SFG and right postcentral gyrus (PCG), left STG and right pars opercularis, and left STG and right PCG. Apart from these regions, the BD-I group displayed specifically reduced SC connections between left STG and right inferior parietal gyrus (IPG), and right pars opercularis and right STG compared with HCs. Compared with HCs, a significantly decreased cortical SC connection between left PCG and left SFG was only observed in the BD-II group. Interestingly, there was no significant difference in CT between BD-I and BD-II groups, but significant differences of some SC connections were found between BD-I and BD-II groups. The results of all SC analyses are shown in the Supplementary Tables S2, S3 and Supplementary Figure S1.

**Cortical Thickness Correlation Analysis**

As shown in Figure 2, BD-II group showed negative correlation (r = –0.503, p = 0.017, Power = 0.695) between CT in the right MTG and number of episodes.

**DISCUSSION**

By calculating CT and cortical SC, the present study probed cortical morphology differences among adolescent BD-I, BD-II, and HCs. The findings of this study were 3-fold: (a) Both BD-I and BD-II groups showed reduced CT in seven cortical regions, including left ITG, left rostral MFG, left SFG, left TTG, right MTG, and bilateral STG. No significant CT difference was found between two BD subtypes. (b) BD-I and BD-II groups shared similarly decreased inter-hemispheric SC connections, including SC connections between left SFG and right PCG, left STG and right pars opercularis, and left STG and right PCG. When comparing with HCs, significantly decreased SC connections between left STG and right IPG and right pars opercularis and right STG were only observed in the BD-I group, and significantly declined SC connection between left SFG and right PCG was only found in the BD-II group. (c) An increase of number of episodes was negatively associated with a thinner right MTG in BD-II patients. Therefore, the discovery of common and specific characteristics in BD-I and BD-II is essential for understanding the neuroanatomy pathophysiology of two BD subtypes though combined CT and cortical SC analysis.

**Common Alteration in CT in BD-I and BD-II**

CT is thought to mainly reflect the morphological characteristics of gray matter, such as density, size, and arrangement of cells (38). Our results show that both BD-I and BD-II patients had CT reductions in left rostral MFG and left SFG, which
Kuang et al. Cortical Alterations in Bipolar Disorder

**FIGURE 1** | Significant between-group differences of cortical structural covariance. Brain regions are expressed with colored balls, and decreased structural covariance connections between brain regions are represented by solid black lines. (A) BD-I group presents significantly decreased structural covariance connections relative to HCs after FDR correction; (B) BD-II group shows significantly declined structural covariance connections compared with HCs after FDR correction. BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; HCs, healthy subject controls.

**FIGURE 2** | Scatterplots show correlation between cortical thickness in right MTG and number of episodes in adolescent bipolar disorder type II subjects. Asterisk (*) represents the residuals removing the effect of age and gender. The horizontal and vertical axes represent residuals of number of episodes and right MTG thickness, respectively. Bipolar disorder type II group showed significantly negative correlations ($r = -0.503, p = 0.017, Power = 0.695$) between cortical thickness in right MTG and number of episodes. MTG stands for middle temporal gyrus.

are representative of a functionally defined area DLPFC (39). This result is consistent with a previous neuropathological study, in which declined neuronal and glial density were reported in DLPFC in BD patients (40). Similarly, another review also reported declined density of glia and neurons and decreased size of neurons in frontal areas of BD (41). In addition, in our study, extensive cortical thinning of the temporal gyrus was also found in both BD-I and BD-II patients compared with HCs, including left ITG, left TTG, right MTG, and bilateral STG. Decreased density of neurons in ITG and declined neuronal clustering in the auditory association region in STG and reduced neuronal integrity in TTG were found in BD (42–44). Thus, our findings were in keeping with the neuropathological studies, and decreased density or size of neurons in frontal and temporal regions may be the reasons for its reductions of CT in BD relative to HCs.

These cortical regions showing significant CT differences between groups have different functions. To be specific, rostral MFG and SFG are responsible for generating emotional responses (45) and cognitive control (27), respectively. STG is a critical structure in auditory and language processing and social cognition (46). ITG and MTG participated in high-order visual processing (47), and TTG is involved in auditory information processing (48). Based on previous investigations, the frontal and temporal regions with significant CT differences in the present study were involved in symptoms of emotional (49), cognitive (50), auditory processing (51), and visual impairment (52) in individuals with BD. Moreover, when performing memory, language, cognitive, and affective tasks, BD patients exhibited abnormalities in frontal or temporal regions vs. HCs (53–56). Therefore, we infer that the cortical thinning of several frontal and temporal regions may be associated with memory, emotional, and cognitive dysregulation in adolescent BD-I and BD-II subjects.

In our study, there was no significant difference in CT between BD-I and BD-II groups, possibly because of the small sample size. The result of another study with a relatively small sample size was similar to our finding with no significant difference between two BD subtypes on CT (57). However, a previous study with a large sample size of BD patients found significant differences in CT between BD subtypes. In that study, the CT of right temporal lobe of BD-I patients was significantly lower than that of BD-II patients (8). Lack of significant difference might arise from the small sample size of our study. In future research, we would further study CT with a larger sample size of BD patients. In addition, most BD-I patients had been treated with medication, whereas a relatively small number of BD-II patients had received medication treatment. Previous studies suggest that alterations of brain structure can
be normalized in response to medication treatment (58–60). Therefore, medication treatment may also contribute to the finding of no significant difference in CT between BD-I group and BD-II group.

**Common Alteration in SC Connections in BD-I and BD-II**

It has been suggested that structural associations are due to a mutual-trophic effect of axonal connection (21). Therefore, changes in axon connections may directly affect cortical morphology, deciding changed patterns of SC (61). In our study, both BD-I and BD-II groups shared decreased SC in left SFG and right PCG, left STG and right pars opercularis of inferior frontal gyrus (IFG), and left STG and right PCG. These decreased inter-hemispheric SC connections are similar with results of a diffusion tensor imaging (DTI) study in adult BD. Fractional anisotropy (FA) is a white matter integrity index which reflects axonal coherence (62). Both adult BD-I and BD-II groups showed decreased FA in the corpus callosum relative to HCs, indicating fiber impairments of corpus callosum in both BD subtypes (63). Moreover, adolescent BD with combining BD-I and BD-II subjects were found to show decreased FA in corpus callosum (64). Corpus callosum is a major interhemispheric commissure, which connects most of the neocortical regions (64). Therefore, abnormal changes in axon of corpus callosum in two BD subtype patients may result in the shared decreased inter-hemispheric SC connections in BD-I and BD-II patients.

**Specific Alteration in SC Connections Between BD-I and HCs**

In our study, BD-I patients showed a decrease of SC connection between right pars opercularis of IFG and right STG relative to HC. This result is also similar to two previous DTI studies in which declined FA in right uncinate fasciculus was found in BD-I patients but not in BD-II patients (65, 66). Uncinate fasciculus, an infrahemispheric fronto-temporal fiber, connects ventral and orbital parts of the prefrontal cortex and anterior part of temporal gyrus (67). It is a crucial tract of emotion regulation and memory network (68). Thus, this ipsilateral decrease of SC connection may be related to the emotion and memory deficits of BD-I patients. In addition, our study also found a lower SC connection between left STG and right IPG in BD-I subjects relative to HCs. Interestingly, in our study, this decreased inter-hemispheric SC was only in BD-I patients but not in BD-II patients, which was not found in most DTI studies that only found abnormal interhemispheric (decreased FA in corpus callosum) connection in both adult BD-I and BD-II patients. A potential reason may be that the sample in these DTI studies was mostly adult individuals with BD. Besides this, the DTI method is difficult to distinguish the cross fiber and too small tracts at current scanning resolutions (69). Therefore, we infer that SC could be a complimentary method, which provide unique information about the cortico-cortical connection.

**Specific Alteration in SC Connection Between BD-II and HCs**

In our study, BD-II patients had a weaker SC connection between left PCG and left SFG vs. HCs. Studies regarding BD-I and BD-II as a whole found that FA in superior longitudinal fasciculus (SLF) was decreased in BD patients relative to HCs (70, 71). SLF, as a major long association fiber tract, ipsilaterally connects parietal, frontal, temporal, and occipital cortices (67). Declined FA in SLF indicated axonal abnormality in BD, which may contribute to our findings of a decrease of cortical SC connection between left PCG and left SFG in BD-II patients. Moreover, prior study indicated that the strength of frontal-parietal correlation was correlated with performance of schizophrenia in recall memory task (72). This study suggests frontal-parietal correlation may be associated with cognitive symptoms. Recent neurobiological research supports that BD and schizophrenia share neurocognitive (73) and genetic characteristics (74), which indicate that two mental diseases are related at the etiological level. Poorer recognition of facial expressions was reported in BD-II patients but not in BD-I patients (75). This cognitive task study results were in accordance with our results. Thus, we infer that the decreased SC connection between left PCG and left SFG may be associated with cognitive impairment in BD-II patients.

**Specific Relationship Between CT and Clinical Variables in BD-II**

Correlation analysis results provide evidence that the thickness of right MTG is negatively correlated with the number of episodes in BD-II patients. This finding may indicate that the CT defect in right MTG was more obvious with an increase in the number of episodes in BD-II patients. This result is similar to a longitudinal study focused on adult BD-II patients. This study observed that adult BD-II patients with more depressive number of episodes between baseline and follow-up periods had more severe thinning of the left temporal cortex than patients with fewer depressive numbers of episodes (76). Hence, our finding further supported the association between increased cortical thinning and the number of mood episodes.

**LIMITATION**

In the current study, there are some limitations. First, the sample size of the study is relatively small, especially the number of BD-II patients and HCs. In future work, study needs to be conducted in a broader population of patients and HCs to make the study more convincing. Second, our study is cross-sectional, so we do not know the detailed process of cortical thinning alterations over time in BD patients. Hence, for a better understanding of the corticall changes in BD disease, longitudinal research is needed to help identify the neurodevelopmental process of adolescent BD and understand the procession of abnormalities and the factors that lead to them. Third, because some patients were under medication treatment, medication may have potential influences in our findings. However, influences of medication are unlikely to account for our results as our findings of decreased CT and declined SC connections represent
brain structural abnormalities, whereas previous studies prove that changes of brain structure can be normalized in response to medication treatment (58–60). In addition, a previous study found that depressive/manic episodes may have a different effect on brain structure in BD (77). Our study did not collect the type of episodes, so future work needs to further explore the relationship between different type of number of episodes and cortical thickness.

CONCLUSION

In short, we estimate cortical morphology differences among the adolescent BD-I, BD-II, and HCs by calculating CT and cortical SC. Cortical thinning in frontal and temporal cortices was common to adolescent BD-I and BD-II, therefore, which was not sensitive to differences in BD subtype. However, decreased SC connections among frontal, temporal, and parietal regions were common or specific to BD-I and BD-II subjects. The findings of common and specific patterns of cortical morphology alterations may not only be useful for understanding neuroanatomical mechanisms and pathophysiology of two BD subtypes, but also treatment and diagnose of BD-I and BD-II. In addition, the negative correlation between CT in right MTG and number of episodes in BD-II patients suggests that, with an increase of number of episodes, the CT defect of right MTG was more obvious.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of The Second Xiangya Hospital of Central South University. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

QJ and GL: conception and study design. WG and LS: magnetic resonance data acquisition and clinical support. ZL, DC, and LK: statistical analysis and data interpretation. YG and JQ: interpretation of results. LK and WC: paper writing and important revision of the article. All authors: approval of final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.750798/full#supplementary-material

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