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ORIGINAL RESEARCH

Cortical thickness and subcortical volumes alterations in euthymic bipolar I patients treated with different mood stabilizers

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Abstract

Reported structural abnormalities of patients with bipolar disorder (BD) are inconsistent and the use of psychotropic medication is one of the sources of heterogeneity. A fairly small number of morphometric studies have involved comparison of BD on different mood stabilizers. Here in this study, we aimed to investigate the cortical thickness and subcortical volumes in euthymic BD patients on lithium and valproate and healthy controls (HC), and to elucidate the relationship between the use of medication and brain structure variations. We acquired structural magnetic resonance imaging data from 35 BD patients (19/valproate;16/lithium) and 30 HC subjects. Cortical thickness was compared in multiple locations across the continuous cortical surface, and subcortical volumes were compared on a structure-by-structure basis. Group analyses revealed widespread thinning of the prefrontal cortex in BD. Compared with BD on valproate, BD on lithium showed significant increased cortical thickness of the left rostral middle frontal cortex and right superior frontal cortex, while cortical thickness was not significantly different between BD on lithium and HC in the bilateral rostral middle frontal cortex. Moreover, no significant difference was observed in subcortical volume. Limitations of this study comprise the possible effect of other psychotropic drugs, small sample size and the cross-sectional design. Therefore, the results suggest medication-related neurobiological difference between BD patients on different mood stabilizers, but no casual role can be proposed. Our findings provided new evidence about the effects of psychotropic medication upon neuroanatomy in BD, and could help to explain the inconsistency of existing studies as well as contribute to the extraction of reliable neuroimaging biomarkers in BD.

Keywords Bipolar disorder · Euthymia · Mood stabilizers · MRI · Prefrontal cortex

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Introduction

Bipolar disorder (BD) is a chronic and disabling disease, which affects >1% of the global population and has both high morbidity and mortality rates, especially for type I of BD (Vieta et al. 2018). Advanced neuroimaging analytics have made it possible to obtain automatic measurements of cortical thickness across cortical surface and segmented volumes of subcortical structures (Dale et al. 1999; B. Fischl et al. 1999; Bruce Fischl et al. 2002). The psychopathology of BD is associated with structural abnormalities in the brain, but results from morphometric imaging studies are inconsistent. Having summarized previous region-of-interest (ROI) and whole-brain cortical thickness studies of patients with BD, one review article concluded that BD patients exhibited reduced cortical thickness primarily in several key regions involved in emotional processing and regulatory: the bilateral prefrontal, left cingulate and left temporal cortices (Hanford et al. 2016). According to one meta-analyses of published studies using structural magnetic resonance imaging (MRI) to compare brain structure in BD patients and healthy controls (HC) (investigations using voxel-based morphometry were excluded), the prefrontal lobe volume reductions, the enlargement of the globus pallidus and lateral ventricular are the most consistent volumetric differences (Kempton et al. 2008; Arnone et al. 2009). Recently, Hibar and colleagues performed the largest sample study to date of cortical thickness and subcortical volume measures from MRI scans and they observed thinner cortical gray matter in the frontal, temporal and parietal regions of both brain hemispheres and volumetric reductions in the hippocampus and thalamus (Hibar et al. 2018; Hibar et al. 2016).

The use of psychotropic medication, such as antidepressants, antipsychotics and mood stabilizers, is arguably one of the most widely debated sources of heterogeneity in the results of morphological neuroimaging studies mentioned above (Phillips and Swartz 2014). Therefore, it is possible that the structural differences observed between BD patients and HC are partly due to exposure of BD patients to psychotropic medications (Hafeman et al. 2012). Lithium and valproate are prescribed widely for stabilizing mood and reducing the risk of relapse into manic and depressive states of BD (Ahearn et al. 2013). Among the studies of effects of medication on neuroimaging, lithium is the most widely examined medication. Cross-sectional and longitudinal studies using voxel-based morphometry and volumetric measures showed fronto-limbic volumetric increases during lithium treatment in patients with BD (Lopez-Jaramillo et al. 2017; Zung et al. 2016; Moore et al. 2009). However, according to recent large sample studies measuring cortical thickness and subcortical volume, they reported significant evidence of increased cortical thickness in the left paracentral gyrus and bilateral superior parietal gyrus and larger thalamic volumes in BD patients taking lithium (Hibar et al. 2018; Hibar et al. 2016). Only a small number of prospective studies have focused on the grey matter metrics associated with other mood stabilizers, such as valproate, and part of them reported that medicated adult and pediatric patients had increased gray matter volume of limbic and frontal areas compared with those who were not (Atmaca et al. 2007; K. Chang et al. 2005; Baloch et al. 2010), but some other reported no significant changes in gray matter volume (Kiki Chang et al. 2009; Lyoo et al. 2010). Therefore, in this study, we examined both cortical thickness and subcortical volumes between euthymic BD patients and HC. Furthermore, we performed comparison among BD patients on valproate, BD patients on lithium and HC in order to elucidate the relationship between the use of different mood stabilizers and brain structure variation in BD. Our findings could observe mood-stabilizer class-specific effects on brain structure and may help to explain previous inconsistencies in the bipolar literature.

Methods

Participants

All patients were recruited from outpatient departments and inpatient units for affective disorders at Shenzhen Mental Health Centre, from June 2016 to May 2017. Healthy controls (HC) were recruited by poster or advertisement. All study procedures were approved by the Human Research Ethics Committee of the Shenzhen Mental Health Centre, and were conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent.

All the patients were interviewed and diagnosed by experienced psychiatrists (Erni Ji and Haichen Yang). Euthymia was defined as the absence of any episode of depression or hypo-mania for two months before scanning (Caseras et al. 2015; First et al. 1997). The inclusion criteria for patients with BD were: (1) age ≥ 18 and ≤ 60 years and ability to give voluntary informed consent; and that they (2) met the DSM-IV criteria for bipolar I disorder according to the diagnostic assessment by the SCID (Structured Clinical Interview for DSM-IV) criteria (First et al. 2002; First et al. 1997); (3) satisfied criteria for undergoing magnetic resonance imaging (MRI) scanning based on a screening questionnaire. Exclusion criteria for BD patients included: (1) current depressive, manic or hypomanic episode according to the SCID; (2) changes in psychotropic medications or mood state within 3 months prior to or during the study; (3) history of hospitalization within 6 months. Patients were assessed using the SCID, Young Mania Rating Scale (YMARS) (Young et al. 1978) and Hamilton Depression Scale (HAMD) (Hamilton 1967). All BD patients were euthymic for at least three months before participation in this study and all had an YMARS and HAMD of less than 6. In total, 35 euthymic BD patients were

enrolled in this study and they were further grouped according to different kinds of mood stabilizers. Without a randomized controlled design, results of this study could not be used to infer causality of observed medication effect.

Exclusion criteria for HC included: (1) a current or past psychiatric diagnosis; (2) any organic brain disease; (3) a history of head trauma resulting in loss of consciousness longer than 10 min; (4) a history of substance or alcohol dependence within the 12 months before assessment; (5) a first-degree family history of any major psychiatric disorders, dementia, or mental retardation. The non-patient version of the SCID was used to ensure that the healthy controls had no history of psychiatric or neurologic illness (First et al. 2002). In total, 30 healthy subjects were enrolled in this study.

MRI data acquisition

Magnetic resonance images were acquired using a 3.0 Tesla Siemens Trio scanner (Siemens Medical, Erlangen, Germany) at Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences. To reduce head movement and scanner noise, each subject's head was fixed by foam pads in a standard 12-channel birdcage head coil. For cortical thickness and subcortical volume measurements, high resolution T1-weighted images were collected with a volumetric three-dimensional spoiled gradient recall sequence with the following parameters: TR/TE = 2000/30 ms, FOV = 240 × 240 mm^2, matrix size = 256 × 256, flip angle = 90°, slice number = 176, voxel size = 0.9 × 0.9 × 1 mm^3.

MRI data analysis

Structural T1 images were analyzed using FreeSurfer (version 6.0.0, http://surfer.nmr.mgh.harvard.edu) to perform cortical reconstruction and volumetric segmentation of the whole brain according to procedures described in previous studies (Dale et al. 1999; B. Fischl et al. 1999). For each participant, the procedure included the correction of small head motions and signal intensity non-uniformity in the structural T1 images, the removal of non-brain tissue, segmenting the brain into gray matter (GM) and white matter (WM), labeling the subcortical structures, a surface tessellation was formed to generate triangular cortical meshes in the GM/WM boundary and GM/CSF (cerebrospinal fluid) boundary, the cortical surface data were smoothed and inflated, topological defects were removed or fixed (Dale et al. 1999; B. Fischl et al. 1999; B. Fischl and Dale 2000; B. Fischl et al. 2004). Then, cortical thickness at each vertex was measured as the average of two shortest distances, from the GM/WM boundary to the GM/CSF boundary and from the GM/CSF boundary to the GM/WM boundary. The reconstructed brain was registered to an average spherical surface and the thickness measurement at each vertex was mapped on a common spherical coordinate system. Finally, we used a 10 mm full-width half maximum (FWHM) Gaussian smoothing kernel. For the record, the FreeSurfer-generated pial and white surfaces (directly used to calculate cortical thickness and surface area, and divide cortical and subcortical domains for label propagation) were visually inspected and manual corrections were made if necessary (Li et al. 2015; Iscan et al. 2015).

Subcortical volumes were obtained from the automated procedure performed in FreeSurfer. According to a recent review, the volumes of eight subcortical structures (including the nucleus accumbens, amygdala, caudate, hippocampus, globus pallidus, putamen, thalamus, lateral ventricles), which are critically related to distinguishing features of brain structure and functions in BD patients, were extracted from each hemisphere for further statistical analysis (Hibar et al. 2016; C. H. Chen et al. 2011).

Statistical analysis

Demographics and questionnaires

Demographic, clinical, and medication regimen information are summarized in Table 1. Subject groups were compared for demographic and, where applicable, clinical characteristics, including gender, age, scale ratings, the presence or absence of medications prescribed (anticonvulsants, antipsychotics, mood stabilizers, antidepressants, anxiolytics and prescribed antipsychotic dose in chlorpromazine equivalents). Subjective characteristics were analyzed by SPSS software (SPSS Statistics, IBM, Armonk, NY). Repeated Shapiro-Wilk tests were applied for normality test. Clinical domains were analyzed using Chi-square test, two-sample t-test, one-way ANOVA or Mann–Whitney U test with a confidence interval of 95% where applicable. A P value <0.05 was considered significant.

Group analysis of cortical thickness and subcortical volume

For group analysis, a general linear model was used at each vertex in the whole brain to identify the brain regions where all BD patients showed significant cortical thickness difference relative to HC, or where significant cortical thickness difference exists among BD on valproate, BD on lithium and HC. Age, gender, and education were included as covariates of no interest. We used an uncorrected threshold of $P < 0.001$ for initial vertex-wise comparisons. To correct for multiple comparisons, a Monte-Carlo permutation cluster analysis was adopted and only clusters with a significant threshold of $P < 0.05$ were reported. Besides, P values were adjusted for two hemispheres using Bonferroni correction.

Table 1 Demographic characteristics of the bipolar disorder (BD) patients and healthy controls (HC) in this study

	HC	BD	BD^1	BD^2	P value		
					BD vs. HC	BD^1 vs. BD^2	BD^1 vs. BD^2 vs. HC
No. of subjects (male/female)	30 (15/15)	35 (13/22)	19 (9/10)	16 (4/12)	0.297[a]	0.172[a]	0.239[a]
Age, years, mean (SD)	31.5 (8.17)	28.9 (7.25)	32.2 (7.80)	30.7 (8.77)	0.180[d]	0.603[d]	0.351[b]
Education, years, mean (SD)	13.4 (2.93)	14.4 (2.88)	12.2 (2.91)	14.9 (2.25)	0.159[d]	0.005[d*]	0.007[b*]
HAMD, mean (SD)	—		0.6 (0.90)	0.8 (0.98)	—	0.511[c]	—
YMARS, mean (SD)	—		1.2 (1.26)	1.1 (1.44)	—	0.777[c]	—
Duration of illness, years, mean (SD)	—		10.0 (5.77)	6.74 (6.96)	—	0.139[d]	—
No. of manic episodes, mean (SD)	—		2.9 (1.68)	2.1 (1.39)	—	0.119 [c]	—
No. of depressive episodes, mean (SD)	—		1.8 (1.86)	1.3 (0.87)	—	0.497 [c]	—
Medication							
Anticonvulsants	—	2/35	0/19	2/16	—	0.112[a]	—
Antipsychotics	—	35/35	19/19	16/16	—	—	—
CPZ equivalents, mean (SD)	—		213.2 (110.36)	242.2 (129.65)	—	0.479[d]	—
Mood stabilizers	—	35/35	19/19	16/16	—	—	—
Antidepressants	—	2/35	1/19	1/16	—	0.900[a]	—
Anxiolytics	—	1/35	1/19	0/16	—	0.352[a]	—

Abbreviations: *HC,* healthy controls; *BD*, bipolar disorder; *BD^1* , *BD* on valproate; *BD^2* , BD on lithium; *SD*, standard deviation; *HAMD*, Hamilton Depression Scale; *YMRS*, young mania rating scale; *CPZ*, chlorpromazine

a: P values for Pearson Chi-square test

b: P values for one-way ANOVA

c: P values for independent two-sample Mann-Whitney U test

d: *P* values for independent two-sample t-test

*: Significant difference of education was observed

For clusters with significant difference among three groups, their cortical thicknesses were extracted and post-hoc tests were performed.

The group analysis of subcortical volumes was performed with SPSS software (SPSS Statistics, IBM, Armonk, NY). For each structure, a general linear model was fitted with volume as the dependent variable, groups as the categorical predictor, and age, gender, education and intracranial volume were included as covariates of no interest. Multiple comparisons were controlled using the false discovery rate of 0.05 (Benjamini and Hochberg 1995).

Relationship between structural differences and clinical variables

For BD patients, we extracted the average cortical thickness for each cluster showing a significant between-group difference. And then we calculated the partial Pearson's correlation coefficients between the average cortical thickness in each cluster and each of the clinical variables (onset age, illness duration, HAMD and YMARS scores, numbers of manic and depressive episodes) for the BD patients. In the correlation calculations, we regressed out the confounding factors of age, gender and education.

Results

Demographic and behavioral results

BD patients were grouped according to their treatment of mood stabilizers: 19 BD patients were defined as BD on valproate and 16 BD patients were defined as BD on lithium. The demographic and clinical characteristics of all subjects included in the data analysis are presented in Table 1. The two BD subgroups and HC group did not differ significantly in gender and age. Group of BD patients on valproate had lower educational level than other two groups, thus education was added as covariate in all group-level analyses. There was no significant difference of HAMD, YMARS, illness duration, number of manic and depressive episodes, presence or absence of prescribed medications and antipsychotic dose between two subgroups of BD patients.

Abnormalities of cortical thickness in BD

Controlling for age, gender, education and multiple comparisons, significant reduced cortical thickness in all BD patients was found in the lateral orbital frontal cortex and superior frontal cortex of both right and left hemispheres, and rostral

middle frontal cortex of the left hemisphere ($P < 0.05$, cluster-wise corrected, Table 2 and Fig.1).

Table 3 and Fig. 2 (top panel) show the clusters with a significant difference in the cortical thickness between three groups (BD on valproate, BD on lithium and HC), and these clusters include the left lateral orbital frontal cortex, bilateral rostral middle frontal cortex and right superior frontal cortex ($P < 0.05$, cluster-wise corrected). Compared with BD on valproate, BD on lithium shows significant increased cortical thickness in the left rostral middle frontal cortex and right superior frontal cortex. Besides, cortical thickness difference was not significant between BD on lithium and HC in the bilateral rostral middle frontal cortex (bottom panel of Fig. 2).

Abnormalities of subcortical volume in BD

After controlling for age, gender, educational level and intracranial volume, no significant difference was observed in subcortical volume between two or three groups (see Table S1 and Table S2 in the supplementary material).

Relationship between structural differences and clinical variables

For the euthymic BD group, no significant correlation was found between the cortical thickness and any of the clinical characteristics.

Discussion

In this study, we compared cortical thickness and subcortical volume of euthymic BD patients on two kinds of widely used mood stabilizers, lithium and valproate. We observed both disease-related and treatment-related between-group differences in regional cortical thickness, but no significant difference of subcortical volume was found.

Cortical thickness is proposed to be a localized measure of neuron numbers within a cortical region (Pasko Rakic 2007; P Rakic 1988; Pontious et al. 2008). Compared with HC, BD patients showed widespread reduction in cortical thickness over the prefrontal cortex. This result is partly consistent with several previous studies which observed cortical thinning associated with BD in the frontal cortex and other brain regions, such as the temporal cortex (Niu et al. 2017; Elvsåshagen et al. 2013; Foland-Ross et al. 2011). A recent review of cortical thickness in BD identified cortical thinning in the bilateral prefrontal regions as robust differences between BD and HC groups (Hanford et al. 2016). The results of our study demonstrated widespread cortical thinning across prefrontal regions implicated in the dorsal and orbital prefrontal cortices which are responsible for regulation of emotion and processing of internal mood state (Yamasaki et al. 2002). The prefrontal cortex is part of the fronto-limbic functional neuroanatomical network which is typically disturbed in bipolar patients (Townsend and Altshuler 2012). Therefore, morphological changes of the prefrontal cortex may be linked with the emotional dysregulation in BD. Besides, in keeping with the functional and structural imaging results, neuropathological studies of BD have already implicated these brain regions because they have found reduced neuronal size and deficits in glial cell numbers and density in the dorsolateral prefrontal cortex and orbito-frontal cortex (Behan and Cotter 2006).

The mood stabilizers lithium and valproate are traditionally used to treat BD (Chiu et al. 2013). According to existed preclinical researches of rodents and human cell lines, neurotrophic and neuroprotective properties have been attributed to lithium. Specifically, the mechanism may be related to inhibiting proapoptotic pathways, such as regulating the neurotrophic intracellular signaling cascade involving brain-derived neurotrophic factor (BDNF), and increasing levels of the neuroprotective B cell lymphoma protein-2 (bcl-2) (Quiroz et al. 2010). For valproate, there is also certain preclinical evidence for

Table 2 Clusters with significant decreased cortical thickness in BD compared with HC

Location	side	Talairach coordinates			Cluster-wise *P*-value	Cluster size (mm^2)	CT_{BD} (mm)	CT_{HC} (mm)
		x	y	z				
lateral OFC	L	−20.2	28.4	−13.7	0.0002	472.34	2.64 ± 0.12	2.85 ± 0.11
	R	34.5	31.8	−11.7	0.0237	194.24	2.54 ± 0.17	2.76 ± 0.21
rostral MFC	L	−35.3	53.7	−1.2	0.0010	320.25	2.33 ± 0.13	2.51 ± 0.13
SFC	L	−9.7	54.4	14.2	0.0179	200.68	2.73 ± 0.16	2.88 ± 0.13
	R	15.2	38.3	15.2	0.0002	372.01	2.67 ± 0.12	2.88 ± 0.13
	R	8.1	55.1	22.6	0.0084	228.73	2.95 ± 0.17	3.16 ± 0.19

P < 0.05, corrected for multiple comparisons; *CT*, cortical thickness; *HC*, healthy controls; *BD*, bipolar disorder; *OFC*, orbital frontal cortex; *MFC*, middle frontal cortex; *SFC*, superior frontal cortex

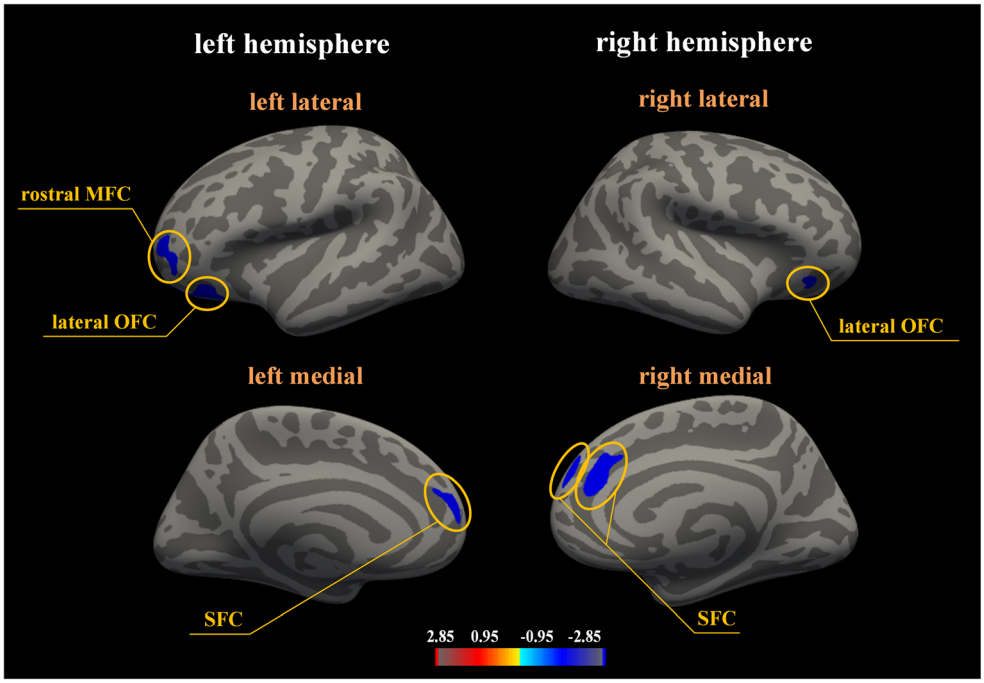

Fig. 1 Cortical thickness differences observed when comparing BD with HC. After controlling for age, gender and educational level, decreased cortical thickness in BD was observed in several frontal regions, i.e., the bilateral lateral orbital frontal cortex (OFC), left rostral middle frontal cortex (MFC) and bilateral superior frontal cortex (SFC) ($P < 0.05$, cluster-wise corrected). The figure shows bilateral lateral and medial views of the brain, respectively. Color bar represents uncorrected sig values masked by the clusters that survive correction

its neuroprotective effect which is related to its action on histone deacetylases and consequent enhancement of bcl-2 and of neurotrophic factors (Chiu et al. 2013). Reported evidence suggested that the clinical efficacy of mood stabilizers may be related to their neurotrophic/neuroprotective effects (Leng et al. 2008). Although lithium and valproate have long been used to treat BD, the evidence underlying their therapeutic effects on brain structure remain inconsistent for lithium and sparse for valproate. According to our results, lithium-treated patients showed cortical thickness comparable to HC in the bilateral dorsal lateral prefrontal cortex and increased cortical thickness than valproate-treated patients in a left rostral region and a right superior region of the prefrontal cortex. This is consistent with previous studies which reported that lithium is associate with normalization effects of cortical thickness of the frontal cortex (Selek et al. 2013; Bearden et al. 2007; McDonald 2015). But BD patients treated with valproate still showed widespread cortical thinning in the bilateral prefrontal cortex. Although results of preclinical researches have supported similar neuroprotective property for valproate as lithium and both of them robustly increased the levels of the neuroprotective bcl-2 in the frontal cortex of rat (G. Chen et al. 1999), only a few studies reported increased cortical thickness of the prefrontal cortex in valproate-treated pediatric and adolescent BD patients and there is no supporting evidence from meta-analysis (McDonald 2015; Wang et al. 2011; Baloch et al. 2010).

Many ROI studies in literature have focused on the volume of hippocampus and amygdala in BD given these structures of limbic system play a role in emotional processing and pathophysiology of BD (Otten and Meeter 2015; Garrett and Chang 2008). Regarding hippocampal

Table 3 Clusters with significant differences in cortical thickness across the three groups

Location	side	Talairach coordinates			Cluster-wise p-Value	Cluster size (mm^2)	$CT_{BD}{}^1$ (mm)	$CT_{BD}{}^2$ (mm)	CT_{HC} (mm)
		x	y	z					
lateral OFC	L	−20.9	28.7	−12.8	0.0006	356.82	2.60 ± 0.13	2.63 ± 0.14	2.81 ± 0.11
rostral MFC	L	−24.9	48.6	0.4	0.0038	276.52	2.19 ± 0.12	2.31 ± 0.13	2.40 ± 0.11
	L	−39.9	28.1	19.5	0.0118	214.67	2.16 ± 0.12	2.35 ± 0.15	2.38 ± 0.14
	R	24.4	48.3	15.3	0.0449	166.88	2.16 ± 0.15	2.24 ± 0.15	2.36 ± 0.15
SFC	R	15.4	37.5	16.8	0.0006	297.51	2.62 ± 0.13	2.73 ± 0.10	2.89 ± 0.13

$P < 0.05$, corrected for multiple comparisons; *CT*, cortical thickness; *HC*, healthy controls; *BD*, bipolar disorder; BD^1, BD on valproate; BD^2, BD on lithium; *OFC*, orbital frontal cortex; *MFC*, middle frontal cortex; *SFC*, superior frontal cortex

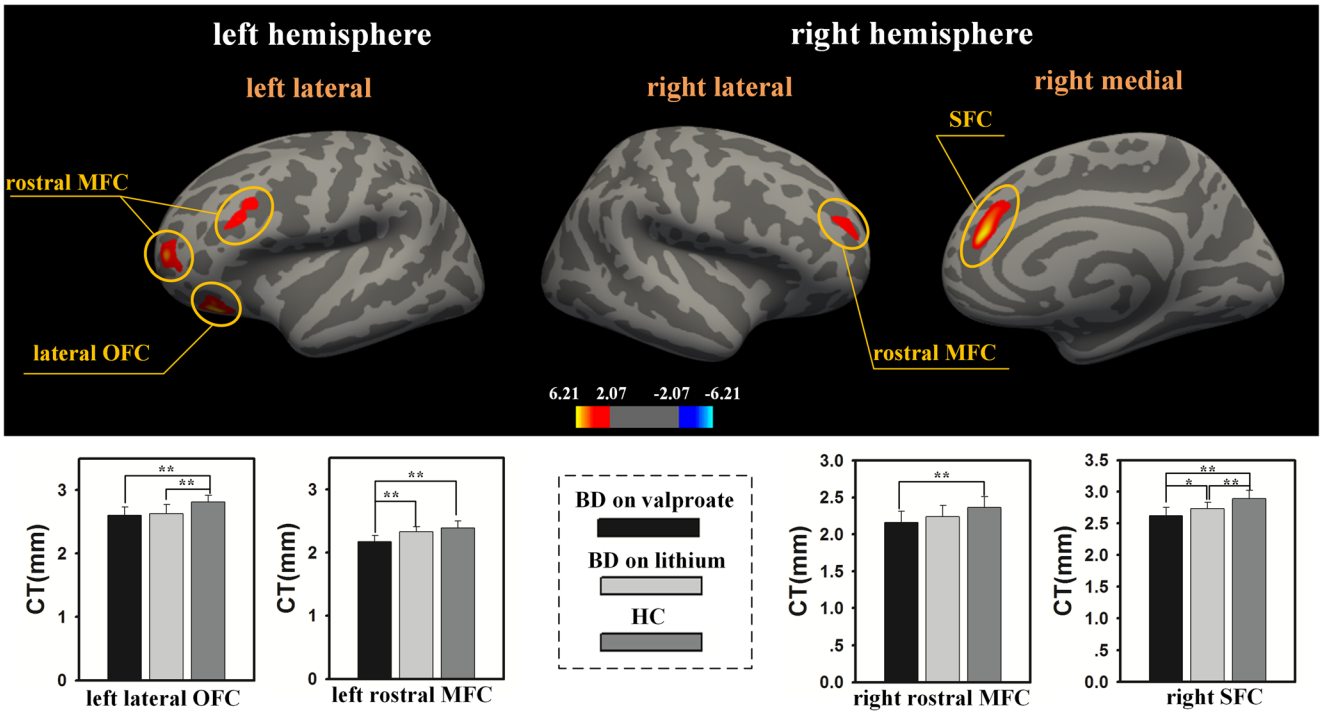

Fig. 2 Cortical thickness differences among three groups. After controlling for age, gender and educational level, significant between-group difference was observed in several frontal regions, i.e., the left lateral orbital frontal cortex (OFC), bilateral rostral middle frontal cortex (MFC) and right superior frontal cortex (SFC) ($P < 0.05$, cluster-wise corrected). The top panel shows left lateral, right lateral and right medial views of the brain, respectively. Color bar represents uncorrected sig values masked by the clusters that survive correction. The bottom panel shows the post-hoc analysis results of cortical thickness in significant clusters (*$P < 0.05$; **$P < 0.005$)

and amygdala volume, studies of BD patients have been contradictory, with findings of mostly comparable, but also smaller or even larger in BD patients compared with HC (T Hajek et al. 2012a; Foland-Ross et al. 2013; Hartberg et al. 2015). Lithium use is a likely contributor to this heterogeneity because lithium treatment was associated with larger hippocampal and amygdala volumes across studies when comparing lithium treated-patients with non-lithium-treated patients (Lopez-Jaramillo et al. 2017; Tomas Hajek et al. 2012b; Savitz et al. 2010; Foland et al. 2008). Therefore, lithium treatment might counteract the reductions of hippocampal and amygdala volumes in BD patients. At the same time, a small number of studies have focused on the association with the use of other antiepileptic mood stabilizers, such as valproate, but the results were less consistent than lithium (McDonald 2015). Some studies demonstrated increased amygdala volume associated with valproate as lithium-treated patients (Savitz et al. 2010; K. Chang et al. 2005), but other studies observed no significant gray matter increases in patients with valproate treatment (Yucel et al. 2008; Lyoo et al. 2010). Then similar normalization effects of lithium and valproate on hippocampal and amygdala volume could be proposed since no group-difference in subcortical volume between either two groups or three groups was observed in this study.

Limitations

Several limitations of this study should be noted. In addition to mood stabilizers, all euthymic BD patients were prescribed antipsychotics and a small number of patients were prescribed anticonvulsants, antidepressants or anxiolytics. Since that different medications might interact to produce effects that are different to those of each medication alone, medication treatment could still be a confounding factor of our study. Besides, this study compared two cohorts of BD patients treated with two kinds of mood stabilizers rather than performing a within-subject comparison of subjects before and after medication use. Compared with cross-sectional design we used, longitudinal studies are more powerful to specifically investigate how treatment over time affects brain structure. And without a randomized controlled design, we cannot assign a causal role to the observed medication effect. Finally, in the future study, expanding the sample size is important for validation of the results obtained here.

Conclusion

This study investigated brain structure effects of different mood stabilizers, lithium and valproate, these findings were suggestive of different effects of them on cortical thinning of

the prefrontal cortex, but similar effect on the subcortical volumes. Although these results should be treated with caution, the extraction of the effects of psychotropic medication upon neuroanatomy in BD could help to explain the inconsistency of existing studies and contribute to the extraction of reliable neuroimaging biomarkers in BD.

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Compliance with ethical standards

Conflict of interest Linling Li, Erni Ji, Xue Han, Fei Tang, Yuanhan Bai, Daihui Peng, Yiru Fang, Shengli Zhang, Zhiguo Zhang and Haichen Yang declare that they have no conflicts of interest.

Ethical approval All procedures performed in this study were approved by the Human Research Ethics Committee of the Shenzhen Mental Health Centre, and were conducted in accordance with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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