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ORIGINAL RESEARCH

Abnormal brain activation during emotion processing of euthymic bipolar patients taking different mood stabilizers

Linling Li[1,2] · Erni Ji[3] · Fei Tang[1,2] · Yunhai Qiu[4] · Xue Han[5,6] · Shengli Zhang[7] · Zhiguo Zhang[1,2] · Haichen Yang[3]

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Abstract

Numerous functional magnetic resonance imaging studies have been conducted to elucidate emotion processing of patients with bipolar disorder (BD), but due to different inclusion criteria used, especially for the history of medication use, the results for euthymic BD patients are inconsistent. For this reason, brain functional effects of psychopharmacological treatments on BD patients have been investigated by numerous fMRI studies, but there is no existing report for brain functional effects of different mood stabilizers. In this study, we compared the emotion processing in BD patients treated by two popularly used mood stabilizer, lithium ($N = 13$; 30 ± 9 years) and valproate ($N = 16$; 33 ± 8 years), as well as healthy controls (HC; $N = 16$; 29 ± 7 years). Two emotional tasks were applied in this study: one used emotional pictures of everyday objects and scenes, and another used emotional facial expression pictures. The main findings were that BD on lithium showed increased fMRI activation in the right dorsal anterior cingulate cortex and bilateral lingual gyrus in response to the positive pictures relative to neutral pictures compared with BD on valproate and HC. Besides, no abnormal activation was observed in the amygdala. Limitations of this study comprise the small sample size and the cross-sectional design. Therefore, the results were suggestive of a different effect of lithium and valproate on brain activities during emotion processing but no causal role can be proposed. The enduring impairments in euthymic state could provide clues to the brain regions involved in the primary pathology of BD.

Keywords Bipolar disorder · Mood stabilizers · Emotion processing · Functional magnetic resonance imaging · Anterior cingulate cortex

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✉ Zhiguo Zhang
zgzhang@szu.edu.cn

✉ Haichen Yang
robin518020@163.com

[1] School of Biomedical Engineering, Health Science Center, Shenzhen University, Shenzhen 518060, China

[2] Guangdong Provincial Key Laboratory of Biomedical Measurements and Ultrasound Imaging, Shenzhen University, Shenzhen 518060, China

[3] Department for Affective Disorders, Shenzhen Mental Health Centre, Shenzhen Key Lab for Psychological Healthcare, Shenzhen 518020, China

[4] Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518060, China

[5] Mental Health Institute of the Second Xiangya Hospital, National Technology Institute of Psychiatry, Key Laboratory of Psychiatry and Mental Health of Hunan Province, Central South University, Changsha 410011, China

[6] Department of Mental Health, Shenzhen Nanshan Center for Chronic Disease Control , Shenzhen 518060, China

[7] Department of Communication Engineering, Shenzhen University, Shenzhen 518060, China

Introduction

Patients with bipolar disorder (BD) is distinguished by alternation between different mood states, including mania/hypomania and depression. The primary abnormalities of bipolar disorder (BD) appears to be an inability to regulate emotion, the result of which is emotional extremes (Townsend and Altshuler 2012). A larger number of functional magnetic resonance imaging (fMRI) studies investigated abnormalities of emotional processing in BD patients by delivering emotional stimulation to patients, and most studies found elevated limbic and prefrontal BOLD responses in patients (Bermpohl et al. 2009; Hagele et al. 2016; Sepede et al. 2015). The abnormalities of the anterior cingulate cortex (ACC), a cortical part of the limbic system, in BD patients are mood-state dependent: reduced during mania (Strakowski et al. 2011; Killgore et al. 2008) and increased during euthymia (Sagar et al. 2013). Functional abnormalities of the amygdala, another key structure within the limbic system, in BD patients are more consistently found during acute mood states than during euthymia (Townsend and Altshuler 2012). According to a systematic review of the literature (Townsend and Altshuler 2012) and recently published works (Foland-Ross et al. 2012; Favre et al. 2015; Sepede et al. 2015), no significant differences in functional activation of the amygdala during emotion processing task were found between euthymic BD patients and healthy subjects. By contrast, some other studies with euthymic BD patients observed increased or decreased activations in the amygdala (Lagopoulos and Malhi 2007; Surguladze et al. 2010; Sagar et al. 2013).

One of the possible reasons for the inconsistent results of euthymic BD studies may be due to different inclusion criteria used, especially for the history of drug treatment. For this reason, brain functional effects of psychopharmacological treatments have also been investigated in previous studies, and medication prescribed to BD patients mostly influence brain activities in the prefrontal regions and limbic system regions (Laidi and Houenou 2016). Most studies employed secondary analysis to investigate the influence of medication on fMRI findings and these effects were account for antidepressants (Versace et al. 2010), overall medication (Sepede et al. 2015) and anticonvulsants (Robinson et al. 2008). However, there was no existing report for brain functional effects of different mood stabilizers on emotional processing.

To cope with these problems, the present study is aimed to investigate the different brain activation patterns during emotion processing in euthymic BD patients receiving two mood stabilizers: lithium and valproate, both of which are commonly used to treat BD (Chiu et al. 2013). Consistent with previous studies, we used the International Affective Picture System (IASP) pictures and facial pictures of the Chinese Affective Face Picture System (CAFPS), which are well-validated salient emotional stimuli, to investigate emotional processing in healthy subjects and BD patients (Hagele et al. 2016; Cerullo et al. 2012; Tesli et al. 2015; Favre et al. 2015; Blumberg et al. 2005; Luo et al. 2017; Aldhafeeri et al. 2012; Lang et al. 2008). Our hypothesis was that euthymic BD patients may exhibit medication related characteristics of emotional impairment. The observed enduring abnormal brain activities in euthymia could reflect the neural circuit involved in homeostatic mood regulation of BD patients, which may provide clues to the brain regions involved in the primary pathology of BD (Townsend and Altshuler 2012).

Methods

Participants

All patients were recruited from outpatient departments and inpatient units at the department for affective disorders, Shenzhen Mental Health Centre, from June 2016 to May 2017. Healthy controls (HC) were recruited by poster or advertisement. All subjects provided informed consent and the Human Research Ethics Committee of the Shenzhen Mental Health Centre approved the experimental procedures.

Euthymia was defined as the absence of any episode of depression or hypo/mania for 2 months before scanning (Caseras et al. 2015; First et al. 1997). Patients with type I BD were enrolled with the following inclusion criteria: (1) age ≥ 18 and ≤ 60 years and ability to give voluntary informed consent; (2) meeting the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) for bipolar I disorder according to the diagnostic assessment by the SCID (Structured Clinical Interview for DSM-IV) (First et al. 2002b, 1997); (3) satisfying the criteria for undergoing magnetic resonance imaging (MRI) scanning based on a screening questionnaire. Exclusion criteria for BD subjects 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 Young Mania Rating Scale (YMARS) (Young et al. 1978) and Hamilton Depression Scale (HAMD) (Hamilton 1967). All euthymic subjects were euthymic for at least 3 months before participation in this study and all had an YMARS and HAMD of less than 6. In total, 29 euthymic BD patients were enrolled in this cross-sectional study and enrolled patients were further grouped according to their treatment of mood stabilizers. Therefore, without a randomized controlled and longitudinal design, results of this study could not be used to infer causality of observed medication effect.

Healthy subjects were excluded if they had: (1) a current or past psychiatric diagnosis; (2) 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 subjects had no history of psychiatric or neurologic illness (First et al. 2002a). In total, 16 healthy subjects were enrolled in this study.

Clinical characteristics

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 scores, 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 or Mann–Whitney U test with a confidence interval of 95% where applicable. A *P*-value <0.05 was considered significant.

Experimental paradigm

Emotional pictures task

The experimental task consisted of the presentation of pictures from IAPS (Lang et al. 2008), which were divided into three conditions—neutral, positive, and negative—according to validated ratings. Each condition consisted of 40 pictures, and the pictures of the three conditions were comparable for content (human figures, scenery, objects, and animals). The valence and arousal ratings (mean ± SD) of the pictures in each condition were respectively 5.02 ± 0.42 and 3.76 ± 1.11

Table 1 Demographic and clinical characteristics

	BD on valproate	BD on lithium	HC	P-value
No. of subjects (male/female)	16 (6/10)	13 (3/10)	16 (7/9)	0.502[a]
Age, years, mean (SD)	32.8 (8.18)	29.6 (9.12)	29.4 (7.47)	0.449[b]
Education, years, mean (SD)	12.1 (2.58)	14.9 (2.06)	14.5 (3.39)	0.017[b*]
HAMD, mean (SD)	1.1 (1.26)	1.1 (1.61)	—	0.772[c]
YMARS, mean (SD)	0.7 (0.95)	0.8 (1.09)	—	0.903[c]
Duration of illness, months, mean (SD)	115.5 (74.00)	71.4 (68.83)	—	0.100[c]
No. of manic episodes, mean (SD)	3.0 (1.75)	1.9 (1.44)	—	0.091[c]
No. of depressive episodes, mean (SD)	2.1 (1.95)	1.5 (0.88)	—	0.437[c]
Medication				
Anticonvulsants	0/16	2/13	—	0.104[a]
Antipsychotics	16/16	13/13	—	—
CPZ equivalents, mean (SD)	206.3 (109.35)	240.4 (134.45)	—	0.457[d]
Mood stabilizers	16/16	16/13	—	—
Antidepressants	1/16	1/13	—	0.879[a]
Anxiolytics	1/16	0/13	—	0.359[a]
Behavioral data				
Response time, shapes, ms, mean (SD)	1424.02 (167.57)	1397.68 (199.34)	1344.31 (223.60)	0.518[b]
Response time, faces, ms, mean (SD)	2730.95 (278.82)	2563.36 (377.86)	2432.31 (348.76)	0.051[b]
Accuracy rate, shapes, %, mean (SD)	98.44 (3.36)	96.15 (4.32)	96.61 (9.41)	0.589 [b]
Accuracy rate, faces, %, mean (SD)	82.81 (7.43)	80.77 (11.60)	88.28 (10.12)	0.105 [b]

BD: bipolar disorder; HC: healthy controls; HAMD: Hamilton Depression Scale; YMARS: Young Mania Rating Scale; CPZ: chlorpromazine;

a: Pearson Chi-square test;

b: one-way ANOVA;

c: independent two-sample Mann-Whitney U test

d: independent two-sample t-test

*: significant between-group difference

for the neutral, 7.64 ± 0.44 and 4.76 ± 0.77 for the positive, and 2.30 ± 0.30 and 5.52 ± 0.84 for the negative condition.

A typical experimental design for emotional processing was employed (van Buuren et al. 2011). The task consisted of 10 task blocks (36 s each) interleaved with 10 rest blocks (12 s each). Within each task block, 3 pictures of each condition were presented in a pseudo-random order. Participants were instructed to view each picture for 2 s and subsequently to rate it in no more than 2 s as neutral, positive, or negative by pressing a button. During rest blocks, participants were instructed to attend to a fixation cross. The total paradigm lasted 8 min.

Faces matching task

A widely used faces matching task was employed (Hariri et al. 2002). Face pictures with two kinds of target affect, angry or afraid, were selected from CAFPS (Lu et al. 2005). Two blocks of an emotion task were interleaved with three blocks of a sensorimotor control task. During the emotion task, subjects viewed a trio of faces and selected one of two faces (bottom) that expressed the same emotion as the target face (top). Each emotion block consisted of six images which were presented sequentially for 5 s. During the sensorimotor control, the subjects viewed a trio of simple geometric shapes (circles, vertical and horizontal ellipses) and selected one of two shapes (bottom) identical to the target shape (top). Each control block consisted of six different images presented sequentially for 5 s. Subject performance (accuracy and reaction time) was monitored during all scans.

E-prime software (version 2.0 Psychology Software Tools, Inc., Pittsburg, PA, USA) was used to control the presentations of the stimuli, and the responses of subjects were recorded through MR-compatible response feedback system (The Shenzhen Sinorad Medical Electronics Co., Ltd., China).

MRI data acquisition

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, each subject's head was fixed by foam pads in a standard 12-channel birdcage head coil. Functional images were acquired with echo planar imaging (EPI) sequence with the following parameters: 31 contiguous slices with a slice thickness of 4 mm; TR/TE = 2000/30 ms, 90° flip angle; field of view (FOV) 192 mm × 192 mm; 64 × 64 data matrix. High resolution T1-weighted images were collected with a volumetric three-dimensional spoiled gradient recall sequence with the 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. For each subject, two task runs were collected.

MRI data analysis

Imaging processing was carried out with the SPM12 toolbox (http://www.fil.ion.ucl.ac.uk/spm). The images were first realigned for motion correction. No subjects were excluded because of excessive head movement (more than 2 mm maximum displacement and 2° of angular motion). Each individual structural image was first coregistered with the mean functional image and then segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using a unified segmentation algorithm. A local brain template was generated using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL). Then the images were spatially normalized to the Montreal Neurological Institute (MNI) template and resampled at a resolution of 3 × 3 × 3 mm^3 using the normalization parameters estimated during unified segmentation, and finally smoothed with a Gaussian kernel of 8 mm full-width at half-maximum to reduce noise.

For emotional picture task, the preprocessed functional images were used to carry out a general linear model (GLM) analysis to estimate the effects of the three conditions (positive, negative and neutral) on brain activation in each individual separately. Because incorporating subject's ratings improves the detection of amygdala activation (Phan et al. 2003), only those trials in which the rating of the subject corresponded to the categorization based on the IAPS ratings were assigned to a condition. Those trials in which the rating of the subject did not match the IAPS rating were assigned to a separate condition named "nonmatch". Therefore, the design matrix of the regression model contained four factors modeling the onset and duration (2 s) of the positive, negative, neutral and nonmatch trials. And all factors were convolved with a canonical hemodynamic response function. To correct for head motion, the six realignment parameters were included in the design matrix as repressors of no interest. A high-pass filter was applied to the data with a cut value of 172 s to correct for low-frequency drifts in the signal. Finally, two contrast images were created for each subject: 1) positive > neutral, 2) negative > neural.

For face matching task, the onset and duration of the face blocks were modeled with the shape blocks as implicit baseline using the GLM in the first-level analysis. A high-pass filter was applied to the data with a cut value of 128 s to correct for low-frequency drifts in the signal. Finally, one contrast image was created for each subject: faces > shapes.

On the second-level, whole-brain one-way ANOVA analyses were performed to identify the average main effects of emotional processing and the differences between groups. Due to significant group difference in education (as shown in Table 1), it was modeled as covariates of no interest on the group level. For determining the significance of results,

the multiple comparison correction was performed by Monte-Carlo stimulation using the REST AlphaSim (http://restfmri.net/forum/REST), where the following parameters were used: individual voxel p value = 0.001, 1000 stimulations, FWHM = 10 mm (estimated by AlphaSim). Finally, a corrected significance level of $P < 0.05$ was obtained for a minimum of 29 voxels. Furthermore, brain regions displaying significant between-group differences were identified as regions of interest (ROI) and the mean regression coefficient (b-value) over all voxels per ROI was calculated for each contrast. One-way ANOVA and post-hoc t-tests were then performed to examine group differences.

Due to the prior information for activation of the amygdale during emotion processing, we used small volume correction implemented in SPM12 (significance level $P < 0.05$, FWE-corrected) for the contrast "positive > neutral" and "negative > neutral". The anatomical ROI was generated using Wake Forest University Pickatlas software (WFU Pickatlas, version 3.0.5) (Maldjian et al. 2003).

Results

Demographic and behavioral results

BD patients were grouped according to their treatment of mood stabilizers: 16 BD patients were defined as BD on valproate and 13 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. BD on valproate had lower educational level than other two groups ($P = 0.017$), and 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 BD subgroups.

fMRI activation

Emotional pictures task

Across the whole group, the "positive > neutral" and "negative > neutral" contrasts revealed fMRI activation in the prefrontal cortex, precentral gyrus, occipital cortex, cingulate cortex and amygdala (Fig. 1). For comparison between three groups, significant group difference was observed in the dorsal ACC (x = 6, y = 30, z = 33, F = 11.15) and bilateral lingual gyrus (x = 6, y = −60, z = 3, F = 12.54; x = −9, y = −72, z = 6, F = 11.85) for "positive-neutral" contrast (Fig. 2). Post-hoc tests show increased BOLD activation of BD on lithium compared to other two groups. Besides, we did not observe any significant group differences for any of these contrasts in the amygdala ($P_{FWE\ corr.\ for\ bilateral\ amygdala} > 0.5$).

Faces matching task

Across the whole group, the "faces > shapes" contrast revealed fMRI activation in the prefrontal cortex, precentral gyrus, superior parietal cortex, occipital cortex, cingulate cortex and amygdala (Fig. 3). No group difference was observed among three

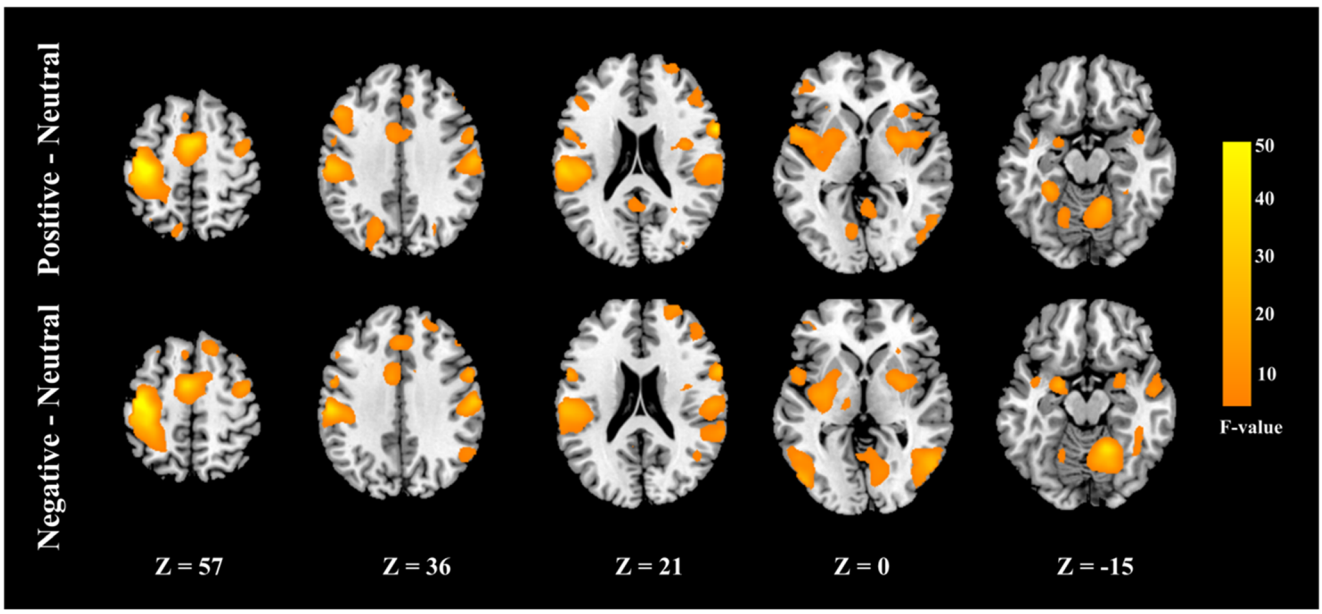

Fig. 1 Whole-brain activation during the viewing of the positive and negative pictures relative to neutral pictures across the whole group, including the prefrontal cortex, precentral gyrus, occipital cortex, cingulate cortex and amygdala

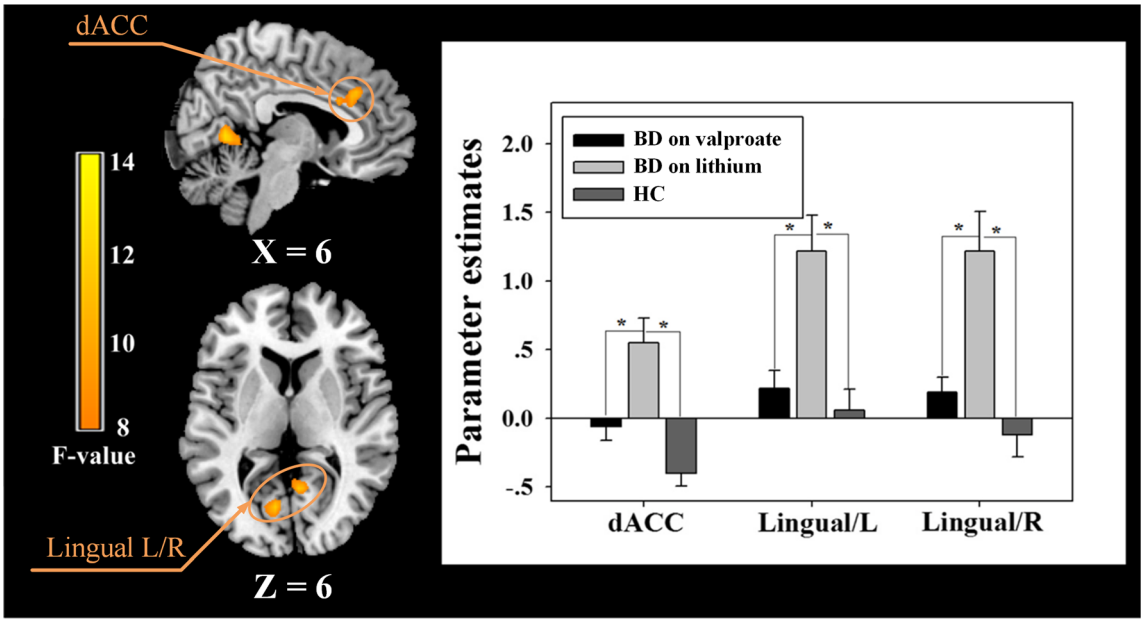

Fig. 2 For comparison between three groups, significant group difference was found in dorsal anterior cingulate cortex and lingual gyrus during the presentation of emotional pictures ("positive > neutral") among three groups. Mean parameter estimates of each cluster were shown on the right panel, and error bars denote the SE values across subjects

groups for the "faces > shapes" contrast. Besides, no significant group difference was observed in the amygdala using small volume correction ($P_{FWE\ corr.\ for\ bilateral\ amygdala} > 0.5$).

Discussion

"Euthymia" does not equate to recovery, and emotional impairment of patients with BD persists during the euthymic state of the disease (Olley et al. 2005). Furthermore, the enduring impairments in euthymic state may provide clues to the brain regions involved in the primary pathology of BD (Townsend and Altshuler 2012). However, the results of previous studies of euthymic BD patients are not very consistent, and one of the confounding factors is the different history of medication use. In the present study, we compared the emotional processing in BD patients on two kinds of widely used mood stabilizers, lithium and valproate. Two emotional tasks were applied in this study: one used emotional pictures of everyday objects and scenes and another used emotional facial expression pictures. The main findings were that BD on lithium showed increased fMRI activation in the right dorsal ACC and bilateral lingual gyrus in response to the positive pictures relative to neutral pictures compared with BD on valproate and HC. However, no abnormal activation was observed in amygdala in two subgroups of BD patients.

A larger number of fMRI studies utilized various tasks to characterize the dysfunction in emotion processing and

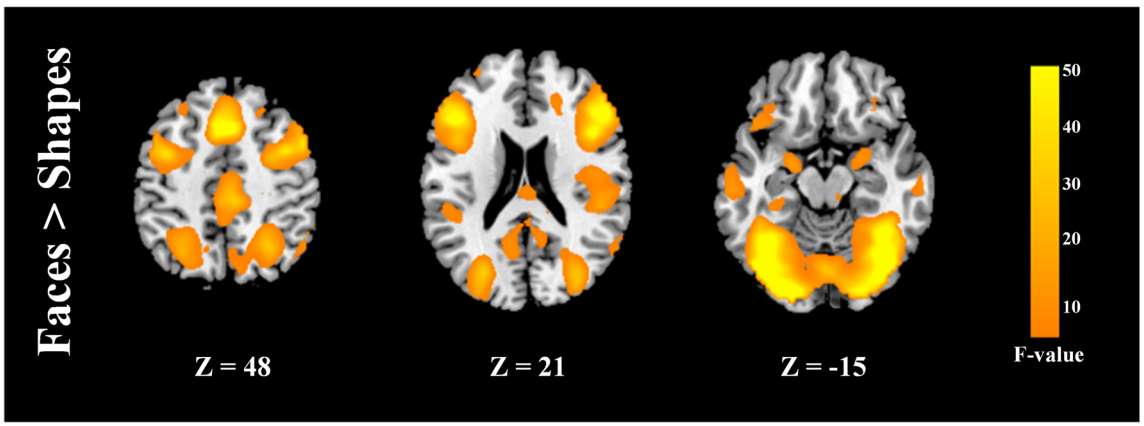

Fig. 3 Whole-brain activation during the matching faces contrast with matching shapes across the whole group, including the prefrontal cortex, precentral gyrus, superior parietal cortex, occipital cortex, cingulate cortex and amygdala

regulation of BD patients. The IAPS pictures activated similar brain regions as emotional face expressions (Britton et al. 2006; Sergerie et al. 2008). In all groups, responding to IAPS pictures and emotional face picture matching significantly activated the prefrontal cortex, precentral gyrus, superior parietal cortex, occipital cortex, cingulate cortex and amygdala. Most of the activated brain regions, such as the prefrontal cortex, cingulate cortex and amygdala, have been reported as the key neutral substrates of circuit of emotion processing and regulation (M. L. Phillips et al. 2003). Subsequent group comparison revealed the increased activation for BD on lithium in the dorsal ACC and bilateral lingual gyrus, but no significant between-group differences were found in the amygdala.

The dorsal ACC is a component of the frontoparietal attention networks and has been proposed to be related to emotion down-regulation using cognitive reappraisal in healthy subjects (Ochsner et al. 2002; Townsend and Altshuler 2012). For BD, there is a considerable amount of evidence supporting a relevant role of the cingulate cortex in its physiopathology and they addressed concomitantly the role of neuroimaging, neuropathological and neurochemical alternations occurring in the cingulate cortex (Fountoulakis et al. 2008; Savitz et al. 2014). Changes of activation in the ACC of BD patients are mood-state dependent. One study reported that the ACC showed reduced activation during mania (Strakowski et al. 2011; Killgore et al. 2008). Another study observed that euthymic BD patients showed increased activation of the ACC during emotional processing (Sagar et al. 2013). Different from the ACC, which is related to cognitive modulation of emotions, amygdala has an important role in generating affective experience (Sergerie et al. 2008). According to the literature, abnormalities of the amygdala activation are more consistently found during acute mood state than during euthymia (Townsend and Altshuler 2012). For example, two studies assessed the processing of emotional pictures in BD patients of manic (Bermpohl et al. 2009) and euthymic state (Sepede et al. 2015): manic BD patients showed increased activation in the left amygdala during positive versus neutral picture viewing (Bermpohl et al. 2009); for euthymic BD patients, no abnormality of the amygdala was observed (Sepede et al. 2015). Besides, no medication effect on amygdala activation in bipolar euthymia has been found in previous studies (Hassel et al. 2008; Robinson et al. 2008). Lingual gyrus activation has been linked to encoding of complex images (Machielsen et al. 2000) and it also has a role in the processing of emotional stimuli (Fusar-Poli et al. 2009; Aldhafeeri et al. 2012). One meta-analysis of voxel-based fMRI studies identified reduced activation in the lingual gyrus of euthymic BD patients (Chen et al. 2011). Previous cross-sectional studies have demonstrated a normalizing effect related to different types of medication, mostly in the limbic and prefrontal regions (Laidi and Houenou 2016). Besides, there is evidence from fMRI studies involving emotional tasks suggesting that medicated manic BD patients show increased brain activation in brain regions related to automatic emotional regulation, such as the ACC (M. L. Phillips and Swartz 2014; Laidi and Houenou 2016). Here in our study, increased activation in the ACC and bilateral lingual gyrus was only observed in BD on lithium group. Therefore, it may be related to the different normalizing effect of valproate and lithium treatment.

Besides functional impairment, BD is a disorder that entails considerable structural impairment. In parallel with abnormalities of brain activation, there are widespread abnormal changes in gray matter volume, cortical thickness in the prefrontal cortical regions, and subcortical gray matter volume (Hibar et al. 2016; Hibar et al. 2018). Lithium had considerable neurotrophic effect on gray matter (Moore et al. 2000; Mary L. Phillips et al. 2008). Earlier studies observed reduced volume of ACC, amygdala and hippocampal in BD patients not treated with lithium compared with lithium-treated BD patients and HC (Sassi et al. 2004; Foland et al. 2008). According to recent large-sample studies, lithium treatment is associated with significantly increased thickness in the left paracentral gyrus and bilateral superior parietal gyrus, as well as significantly larger thalamic volumes (Hibar et al. 2018; Hibar et al. 2016). Here we also performed ROI-based voxel-based morphometry (VBM) analysis and cortical thickness analysis to investigate the structural deficits in those brain regions that demonstrated significant group difference of fMRI activation (as shown in supplementary material). No significant group difference was observed in gray matter volume or cortical thickness in pre-defined functional ROIs (dACC and bilateral lingual gyrus). Therefore, there is no relationship between altered fMRI activation and gray matter deficit.

Limitations

Results of this study should be interpreted in light of several methodological limitations. In the absence of a randomized controlled and longitudinal design, we cannot assign a causal role to the observed medication effect. Besides, all of the BD patients enrolled in this study were on antipsychotics and mood stabilizers, and a small number of patients were on other medicine, such as anticonvulsants, antidepressants and anxiolytics. Two groups of BD patients have matched CPZ equivalents, but the influence of other medication cannot be fully excluded. Furthermore, we have not collected the plasma levels of mood stabilizers as in other studies (Lagopoulos and Malhi 2011; Lagopoulos and Malhi 2007), therefore, the possible acute effect of medicine on brain could not be controlled in this study. Another limitation is the limited sample size.

Conclusion

BD is primarily characterized by an inability to regulate emotion, and both the dorsal ACC and lingual gyrus is involved in emotion processing and has been implicated in this disorder (Goodwin and Jamison 2007; Chen et al. 2011; Aldhafeeri et al. 2012). Compared with HC and euthymic BD patients on valproate, euthymic BD patients on lithium showed abnormal activity in the dorsal ACC and bilateral lingual gyrus during emotional processing. These findings were suggestive of different effect of lithium and valproate on brain activities during emotion processing but no causal role can be proposed. The enduring impairments in euthymic patients can provide clues to the brain regions involved in the primary pathology of BD, as well as the mechanism of action of different mood stabilizers. However, these results should be treated with caution until they can be verified by future studies which address the limitations of the present study.

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Compliance with ethical standards

Conflict of interest Linling Li, Erni Ji, Fei Tang, Yunhai Qiu, Xue Han, 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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