Original Article

Explore functional brain changes in bipolar disorder: A whole brain ALE meta-analysis

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Received: 15/02/2021 – **Accepted:** 03/08/2021

DOI: 10.15761/0101-60830000000309

ABSTRACT

Background: Previous functional magnetic resonance imaging (fMRI) studies showed inconsistent results for comparison between bipolar disorder (BD) and healthy controls (HC).

Methods: An anatomic likelihood estimation (ALE) meta-analysis was used to explore the key regions of brain pathology in BD with different current mood states.

Results: Depressed BD patients showed reduced regional homogeneity (ReHo) in the left claustrum and the left middle frontal gyrus (MFG), compared to HC. BD patients with mixed mood status showed decreased fractional amplitude of low frequency fluctuations (fALFF) in the right cerebellar tonsil, the bilateral MFG and the right superior frontal gyrus, compared to HC. Additionally, BD patients with mixed mood status showed increased fALFF in the right inferior occipital gyrus, the right culmen and the left lentiform nucleus, compared to HC. BD patients with mixed mood status showed decreased functional connectivity (FC) in the bilateral cerebellar tonsil, compared to HC.

Conclusion: In the present study, key regions undergoing functional deficits in BD patients with different current mood states were obtained with the ALE meta-analysis. In addition, deficits in these regions in fMRI studies might work as biomarkers for early diagnosis of BD.

Hui Yang / Arch Clin Psychiatry. 2021;48(4): 208-215

Keywords: activation likelihood estimation, bipolar disorder, functional magnetic resonance imaging, meta-analysis.

Abbreviations: ALE, anatomic likelihood estimation; BD, bipolar disorder; FC, functional connectivity; fMRI, functional magnetic resonance imaging; fALFF, fractional amplitude of low frequency fluctuations; FDR, false discovery rate; FWHM, Full-width-half-maximum; HC, healthy controls; IFG, inferior frontal gyrus; IOG, inferior occipital gyrus; MFG, middle frontal gyrus; MFQ, Mood and Feelings Questionnaire; MNI, Montreal Neurologic Institute; mPFC, medial prefrontal cortex; MTL, medial temporal lobes; PCUN, precuneus; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PHG, parahippocampal gyrus; ReHo, regional homogeneity; ROI, region of interest; rs-fMRI, rest-state functional MRI; SFG, superior frontal gyrus; STG, superior temporal gyrus; VMHC, voxel-mirrored homotopic connectivity; WM, working memory.

Introductions

Bipolar disorder (BD) is a common and severe psychiatric illness worldwide. It is characterized by episodes of changes in mood states, including major depression and mania. The variable clinical features of BD resulted in inadequate treatment and high rates of comorbidity [1]. Therefore, it is essential to improve identification of BD and adequate treatment of the disorder.

Magnetic resonance imaging (MRI) is a non-invasive tool with high spatial resolutions and helpful for the identification of BD [2]. In the past two decades, functional MRI studies, including rest-state functional MRI (rs-fMRI) and task related fMRI, were used to explore the neural circuits of BD with different current mood states. However, previous fMRI studies showed inconsistent results for comparison between BD and healthy controls (HC). Thus, anatomic likelihood estimation (ALE) method, a powerful voxel-

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based technique for MRI meta-analysis, was used to explore the key regions of brain pathology in BD with different current mood states.

The investigation aimed to conduct a comprehensive review of fMRI studies on BD to explore the functional brain changes of BD and key regions suffering from deficits in BD patients with different current mood states.

Methods

The study was conducted on the basis of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [3]. The present study is a meta-analysis, ethical approval was not applicable.

Search strategy: The databases (PubMed, Web of Science, Medline, EMBASE and Google Scholar) were searched for articles published in English before December 2020. Search terms used were: ("bipolar disorder") AND ("neuroimaging" OR "magnetic resonance imaging" OR "MRI"). After excluding duplicates, 3213 articles were included.

Inclusion and exclusion criteria: All fMRI investigations including both HC and BD as participants were included in the present study. In addition, these investigations should provide Montreal Neurologic Institute (MNI) or Talairach coordinates for comparisons between HC and BD.

Reviews, meta-analysis and case reports were excluded from the present study. In addition, the present study excluded region of interest (ROI) analyses.

Data collection: Titles and abstracts of the finally included 28 studies were read by two independent individuals. The following data were recorded from included full-texts: Author, publication years, imaging modality, analysis methods, participant demographics (sample size, age and gender), diagnosis criteria, treatment status, mood status, tasks for task-related fMRI studies, contrasts of included studies, foci, correction for multiple comparisons and covariates.

Meta-analysis procedures: ALE meta-analysis was conducted with Java-based version of GingerALE 3.0.2 (http://www.brainmap.org/ale). ALE studies were performed for fMRI studies in BD. Talairach coordinates were converted to corresponding MNI coordinates with icbm2tal [4,5]. ALE was used to assess the convergence of difference between BD and HC in terms of foci across studies. Foci data were recorded in a text file and read into the software. Statistical significance was acquired with a permutation test (5000 permutations) on randomly distributed foci. Full-width-half-maximum (FWHM) was calculated on the basis of subject's numbers in each study [6]. ALE maps were set a threshold at $p < 0.05$ using the false discovery rate (FDR) with an extent threshold > 200 mm3. ALE maps were overlaid onto the MNI 152 template and viewed with Mango software (http://ric.uthscsa.edu/mango/mango). Quality appraisal was made using the Cochrane Risk of Bias Tool. Data were analyzed using Review Manager 5.3.

Results

Search results: Figure 1 showed inclusion procedures and search results. In addition, supplementary table 1 showed study characteristics and results. In finally included n = 28 studies, n = 13 rs-fMRI studies [7-19] [n = 2 studies [10,11] applied the amplitude of low frequency fluctuations (ALFF) method, n = 2 studies [12,18]

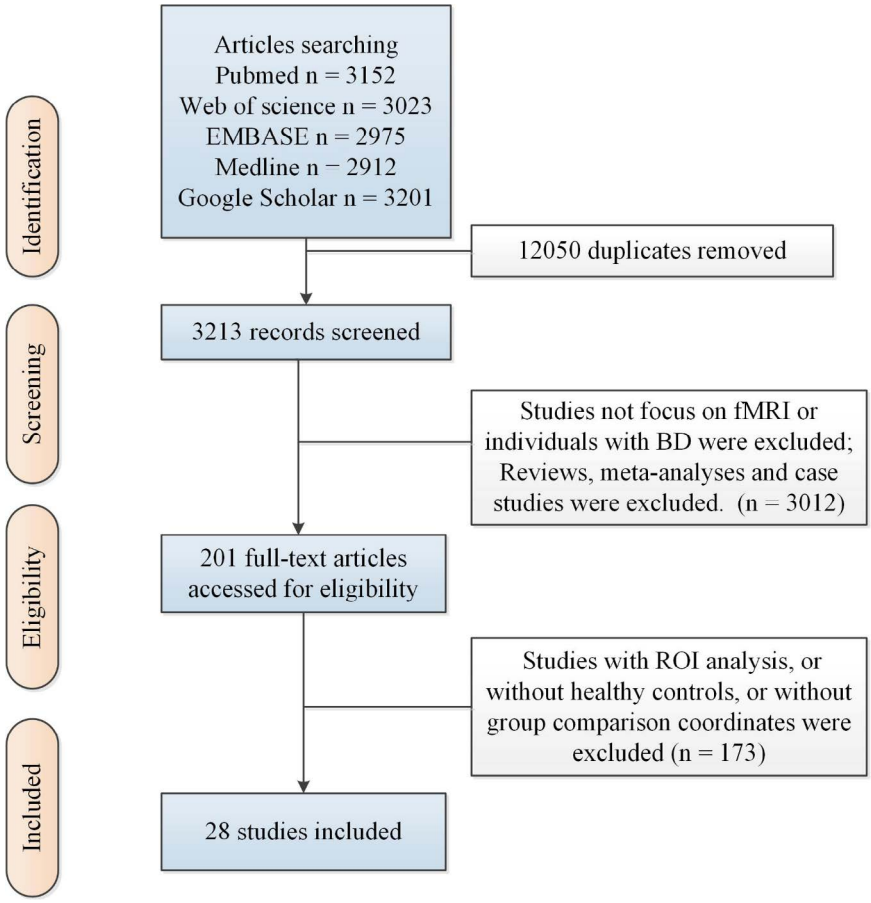

Figure 1. Flow of information through the different phases of a meta-analysis.

Table 1. Characteristics of fMRI studies included in the meta-analysis.

Study	Imaging modality	Method	N (BD)	N (HC)	Age (SD)	Gender (male%)	Diagnosis	Treatment status	Mood status	Task (s)	Group contrasts	Foci	Correction for multiple comparisons	Covariates
Altshuler et al. (2005) [1]	Task fMRI	-	11	13	36±7.6	36%	DSM-IV BDI	Mixed	Manic	Go-NoGo task	HC >BD	3	p < 0.0001, uncorrected	NR
Chen et al. (2006) [2]	Task fMRI	-	8	8	39± 13.44	100%	DSM-IV BDI	Medicated	Manic, Depressed	Implicit Facial Affect Recognition	HC >BD	8	p < 0.005 uncorrected	NR
Roth et al. (2006) [3]	Task fMRI	-	11	11	37.7±14.4	NR	DSM-IV BDI	Medicated	Mixed	a counting Stroop task	HC >BD	7	p < 0.005 uncorrected	NR
Lagopoulos et al. (2007) [4]	Task fMRI	-	10	10	32.4±10.8	NR	DSM-IV BDI	Medicated	euthymic	working memory task	HC >BD	2	FDR p < 0.05	NR
Altshuler et al. (2008) [5]	Task fMRI	-	11	17	32 ± 7.3	NR	DSM-IV BDI	Mixed	depressive	face-matching paradigm	HC > BD	3	p < 0.01 uncorrected	NR
											BD > HC	1		
McIntosh et al. (2008) [6]	Task fMRI	-	42	37	39.3 ± 10.8	55.3%	DSM-IV BD	NR	NR	Hayling Sentence Completion Test	HC > BD	1	p < 0.005 uncorrected	NR
Kaladjian et al. (2009) [7]	Task fMRI	-	20	20	37.9 ± 11.4	50%	DSM-IV BDI	Unmedicated	Euthymic	a Go–NoGo task	HC >BD	3	p < 0.05 FWE-corrected	NR
Linke et al. (2012) [8]	Task fMRI	-	19	22	45 ±10	42%	DSM-IV BDI	Unmedicated	Euthymic	a probabilistic reversal learning task	HC >BD	8	p < 0.05 FWE-corrected	NR
Liu et al. (2012) [9]	Rs-fMRI	ALFF	26	26	32.35 ±11.31	34.6%	DSM-IV BD	Medicated	depressive	-	HC > BD	4	p < 0.01 uncorrected	NR
											BD > HC	10		
Townsen d et al. (2012) [10]	Task fMRI	-	32	30	37 ± 13	65.6%	DSM-IV BDI	Unmedicated	euthymic	a Go–NoGo task	HC > BD	17		
Vizueta et al. (2012) [11]	Task fMRI	-	21	21	NR	52.4%	DSM-IV BDII	Mixed	depressive	an emotional face-matching task	HC > BD	5	p < 0.005 uncorrected	NR
											BD > HC	7		
Liang et al. (2013) [12]	Rs-fMRI	ReHo	17	16	34.47 ± 9.77	52.9%	DSM-IV BD	Unmedicated	depressive	-	HC > BD	13	p < 0.05 uncorrected	NR
											BD > HC	9		
Sagar et al. (2013) [13]	Task fMRI	-	23	18	26.65 ± 6.65	NR	DSM-IV BDI	Medicated	NR	a backward-masked affect paradigm	HC > BD	12	p < 0.05 uncorrected	NR
											BD > HC	30		
Xiao et al. (2013) [14]	Rs-fMRI	ReHo	15	15	15.0 ± 1.7	40%	DSM-IV Pediatric BD	Medicated	Manic	-	HC > BD	10	p < 0.05 FWE-corrected	NR
											BD > HC	5		
Gao et al. (2013) [15]	Rs-fMRI	ReHo	17	18	14.4 ± 1.77	41.2%	DSM-IV Pediatric BD	Mixed	depressive		HC > BD	6	p < 0.05 uncorrected	NR
Lu et al. (2014) [16]	Rs-fMRI	ALFF	18	18	15.1 ± 1.81	33.3%	DSM-IV Pediatric BD	Medicated	Manic	-	HC > BD	4	p < 0.001 uncorrected	NR
											BD > HC	3		
McKenna et al. (2014) [17]	Task fMRI	-	23	23	45.31 ± 9.45	34.9%	DSM-IV BD	Medicated	euthymic	a delayed match-to-sampleWM paradigm	HC > BD	5	p < 0.01 uncorrected	NR
											BD > HC	3		
Rey et al. (2014) [18]	Task fMRI	-	12	12	42.6 ± 11.4	66.7%	DSM-IV BD	Medicated	Depressive, euthymic, hypomania		HC > Depressive BD	2	p < 0.001 uncorrected	NR
											HC > euthymic BD	1		
Favre et al. (2015) [19]	Task fMRI	-	14	13	44.07 ± 9.63	36%	DSM-IV BD	Mixed	euthymic	a word-face emotional Stroop task	HC > BD	4	p < 0.001 uncorrected	NR
Wang et al. (2015) [20]	Rs-fMRI	VMHC	26	40	26.12 ± 10.30	57.7%	DSM-IV BDII	Unmedicated	NR	-	HC > BD	2	p < 0.05 uncorrected	NR
Skatun et al. (2016) [21]	Rs-fMRI	FC	43	196	31.3 ± 11.3	43.2%	DSM-IV BD	Mixed	NR	-	HC > BD	6	p < 0.05 uncorrected	NR
King et al. (2018) [22]	Task fMRI	-	35	35	15 ± 2		DSM-IV Pediatric BDI	Unmedicated	euthymic	a self-paced sequential bilateral finger-tapping task	HC > BD	4	FDR p < 0.05	NR
Qiu et al. (2018) [23]	Rs-fMRI	fALFF	28	27	31.79 ± 12.83	50%	DSM-IV BD	Mixed	depressive	-	HC > BD	2	p < 0.001 uncorrected	age, gender and education level
											BD > HC	1		
Wang et al. (2018)[24]	Rs-fMRI	FC	25	25	28.55 ± 9.76	36%	DSM-IV BDII	NR	NR	-	HC > BD	2	p < 0.005 uncorrected	age and educational level

Yao et al. (2018) [25]	Rs-fMRI	ReHo	55	113	27.02 ± 7.706	40%	DSM-IV BDI	Mixed	depressive	-	HC > BD	4	p < 0.005 uncorrected	NR
Achalia et al. (2019) [26]	Rs-fMRI	ReHo	20	20	24.60 ± 7.04	52%	DSM-IV BDI	Medicated	euthymic	-	BD > HC	7	p < 0.0001 uncorrected	NR
Qiu et al. (2019) [27]	Rs-fMRI	ReHo	100	100	26.37 ± 8.89	55%	DSM-IV BDII	unmedicated	depressive	-	HC > BD	5	p < 0.05 uncorrected	NR
Yang et al. (2019) [28]	Rs-fMRI	fALFF	41	93	32.98 ± 9.41	56%	DSM-IV BD	Mixed	NR	-	HC > BD	3	p < 0.001 uncorrected	Age and sex
											BD > HC	3		

Abbreviations: ALFF, fractional amplitude of low frequency fluctuations; BD, bipolar disorder; fALFF, fractional amplitude of low frequency fluctuations; FC, functional connectivity; FDR, false discovery rate; fMRI, functional magnetic resonance imaging; FWE, family wise error; HC, healthy controls; NR, not reported; ReHo, regional homogeneity; Rs-fMRI, rest-state fMRI; VMHC, voxel-mirrored homotopic connectivity; WM, working memory.

Table 2. ALE results for BD-related fMRI meta-analysis

Cluster #	Volume (mm^3)	Weighted Center (MNI)			Extrema value	Maximum ALE value (MNI)			Side	BA	Anatomical label
		x	y	z		x	y	z			
ALE results for rs-fMRI studies (ReHo) (189 depressed BD patients and 247 HC)											
HC >BD (26 foci, 4 experiments)											
1	288	-39	-12	3	0.009293	-40	-12	2	Left		Claustrum
2	264	-39	42	-12	0.009703	-38	42	-12	Left	47	Middle Frontal Gyrus
ALE results for rs-fMRI studies (fALFF) (69 BD patients with mixed mood status and 120 HC)											
HC > BD (5 foci, 2 experiments)											
1	480	40	-57	-36	0.008758	40	-57	-36	Right		Cerebellar Tonsil
2	480	30	42	-15	0.00931	30	42	-15	Right	11	Middle Frontal Gyrus
3	384	-33	42	-9	0.008985	-33	42	-9	Left	47	Middle Frontal Gyrus
4	384	30	57	-9	0.008985	30	57	-9	Right	10	Superior Frontal Gyrus
HC < BD (4 foci, 2 experiments)											
1	560	30	-90	-3	0.008563	30	-90	-3	Right	18	Inferior Occipital Gyrus
2	448	15	-69	-3	0.008007	15	-69	-3	Right		Culmen
3	448	-27	-15	-3	0.008007	-27	-15	-3	Left		Lentiform Nucleus
ALE results for rs-fMRI studies (FC) (68 BD patients with mixed mood status and 221 HC)											
HC > BD (8 foci, 2 experiments)											
1	880	36	-45	-54	0.008563	36	-45	-54	Right		Cerebellar Tonsil
2	880	-30	-42	-45	0.008563	-30	-42	-45	Left		Cerebellar Tonsil
ALE results for WM-related studies (33 euthymic BD and 33 HC)											
HC > BD (7 foci, 2 experiments)											
1	640	3.6	-61.3	1.5	0.008368	4	-62	2	Right		Culmen of Vermis
2	640	-52.6	-47.1	18.9	0.008139	-52	-48	18	Left	22	Superior Temporal Gyrus
3	536	11.9	47.4	4	0.006559	12	48	4	Right	10	Medial Frontal Gyrus
ALE results for Go-Nogo-related studies (53 euthymic BD and 50 HC)											
HC > BD (20 foci, 2 experiments)											
1	344	20.3	3.8	-10.2	0.00929	20	4	-10	Right		Lentiform Nucleus
2	336	-21.5	65	-1.5	0.008117	-22	64	-2	Left	10	Middle Frontal Gyrus
3	328	-28.4	-9.2	-14.5	0.008199	-28	-10	-14	Left		Parahippocampal Gyrus
ALE results for face-matching tasks-related studies (32 depressed BD and 38 HC)											
HC > BD (8 foci, 2 experiments)											
1	272	-50.8	14.3	-2.9	0.006602	-50	14	-2	Left	13	Insula
2	264	40	46	14	0.008508	40	46	14	Right	10	Middle Frontal Gyrus
3	264	26	-68	48	0.008508	26	-68	48	Right	7	Precuneus
4	256	48.4	25	-7.9	0.006669	48	26	-8	Right	47	Inferior Frontal Gyrus
5	248	53.3	19.5	24	0.006725	54	20	24	Right	9	Middle Frontal Gyrus

Abbreviations: BD, bipolar disorder; fALFF, fractional amplitude of low frequency fluctuations; FC, functional connectivity; fMRI, functional magnetic resonance imaging; HC, healthy controls; ReHo, regional homogeneity; WM, working memory.

used fractional ALFF method, n = 6 studies [7-9,13-15,17,19] used whole brain functional connectivity (FC), n = 1 study [16] used voxel-mirrored homotopic connectivity (VMHC)] were included in the present study. Additionally, n = 15 task-related fMRI studies [20-33] investigated brain activation abnormalities in BD patients [n = 2 studies [26,29] used working memory (WM) tasks, n = 3 studies [21,24,32] used Go-NoGo tasks, n = 2 studies [23,30] used Stroop tasks, n = 3 studies [20,23,30] used face-matching tasks, n = 1 study [22] used an implicit facial affect recognition task, n = 1 study [28] used a hayling sentence completion task, n = 1 study [27] used a probabilistic reversal learning task, n = 1 study [31] used a backward-masked affect task, n = 1 study [25] used a self-paced sequential bilateral finger-tapping task].

Meta-analysis results: Additionally, depressed BD patients showed reduced ReHo in the left claustrum and the left middle frontal gyrus (MFG), compared to HC (see figure 2. and table 2). BD patients with mixed mood status showed decreased fALFF in the right cerebellar tonsil, the bilateral MFG and the right superior frontal gyrus (SFG), compared to HC (see figure 2. B and table 2). Additionally, BD patients with mixed mood status showed increased fALFF in the right inferior occipital gyrus (IOG), the right culmen and the left lentiform nucleus, compared to HC (see figure 2. C and supplementary table 2). BD patients with mixed mood status showed decreased FC in the bilateral cerebellar tonsil, compared to HC (see figure 2. D and table 2). The ALE analysis showed decreased activation relative to HC in the right culmen of vermis, the left superior temporal gyrus (STG) and the right medial frontal gyrus in euthymic BD patients during WM tasks (see figure 3. and table 2). In addition, euthymic BD patients showed reduced activation in the right lentiform nucleus, the left MFG and the left parahippocampal gyrus (PHG) during Go-NoGo tasks, compared to HC (see figure 3. B and table 2). Depressed BD patients showed reduced activation in the left insula, the bilateral MFG, the right precuneus (PCUN) and the right inferior frontal gyrus (IFG) during face-matching tasks, compared to HC (see figure 3. C and table 2).

The risk of bias graph is shown in supplementary figure 1. Details of the risk of bias summary can be found in supplementary figure 2.

Discussion

The present study indicated different types of neuronal network dysfunctions of BD-related pathological changes in BD patients with different current mood states.

The study showed that depressed BD patients showed reduced ReHo in the left claustrum and the left MFG, compared to HC. Recently, a meta-analysis of voxel-based morphometry studies reported that BD patients showed reduced grey matter in the claustrum, compared to HC [34]. Although the claustrum is well known to be related to normal consciousness and the integration of various modalities of information [35], its role in the pathophysiology of BP is still poorly understood. Further studies are needed to confirm and clarify the role of the claustrum on BP. Regarding the MFG, it has been reported that the medial prefrontal cortex (mPFC) plays an important role in the regulation and generation of emotion [36], which is based on the dense and reciprocal connectivity with subcortical regions, such as amygdala [37]. Additionally, Gao et al [8] reported that there were significant negative correlations between Mood and Feelings Questionnaire (MFQ) scores and mean ReHo values in MFG. The present study showed that BD patients with mixed mood status showed decreased fALFF in the right cerebellar tonsil, the bilateral MFG and the right SFG, compared to HC. The MFG and SFG are located in the PFC. The PFC brain region was associated with planning complex cognitive behavior, decision making, and moderating social behavior [38]. The PFC is associated with executive function and emotional regulation [39]. These studies demonstrated the key role of PFC in BD. In addition, BD patients with mixed mood status showed increased fALFF in the right IOG, the right culmen and the left lentiform nucleus, compared to HC. Occipital lobe is the primary visual processing center associated with emotional facial expressions [40]. Some recent rs-fMRI studies showed increased brain activation in the occipital regions in BD [9,13]. Additionally, structural MRI studies showed the decreased volume of occipital cortex in BD patients [41,42]. These studies supported the key role of occipital cortex in BD.

Additionally, the ALE analysis indicated that euthymic BD patients showed decreased activation in the right culmen of vermis,

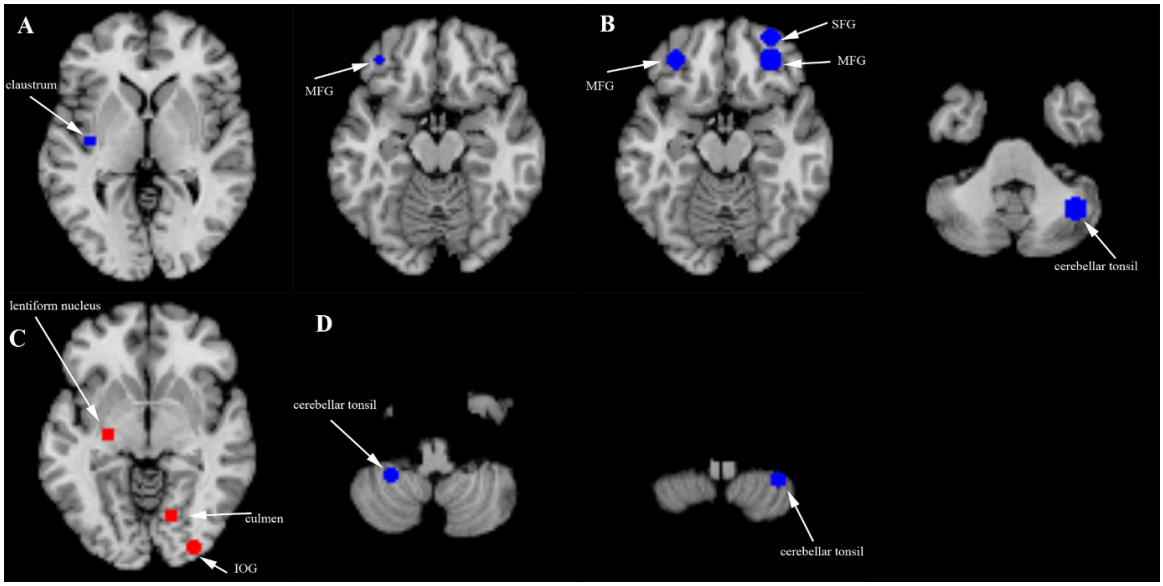

Figure 2. (A) ReHo reduction in depressed BD patients compared to HC (in blue). (B) Reduced fALFF in depressed BD patients compared to HC (in blue). (C) Increased fALFF in depressed BD patients relative to HC (in red); (D) Reduced FC in BD patients with mixed mood status compared to HC (in blue). Abbreviations: BD, bipolar disorder; fALFF, fractional amplitude of low frequency fluctuations; FC, functional connectivity; HC, healthy controls; IOG, inferior occipital gyrus; MFG, middle frontal gyrus; ReHo, regional homogeneity; SFG, superior frontal gyrus.

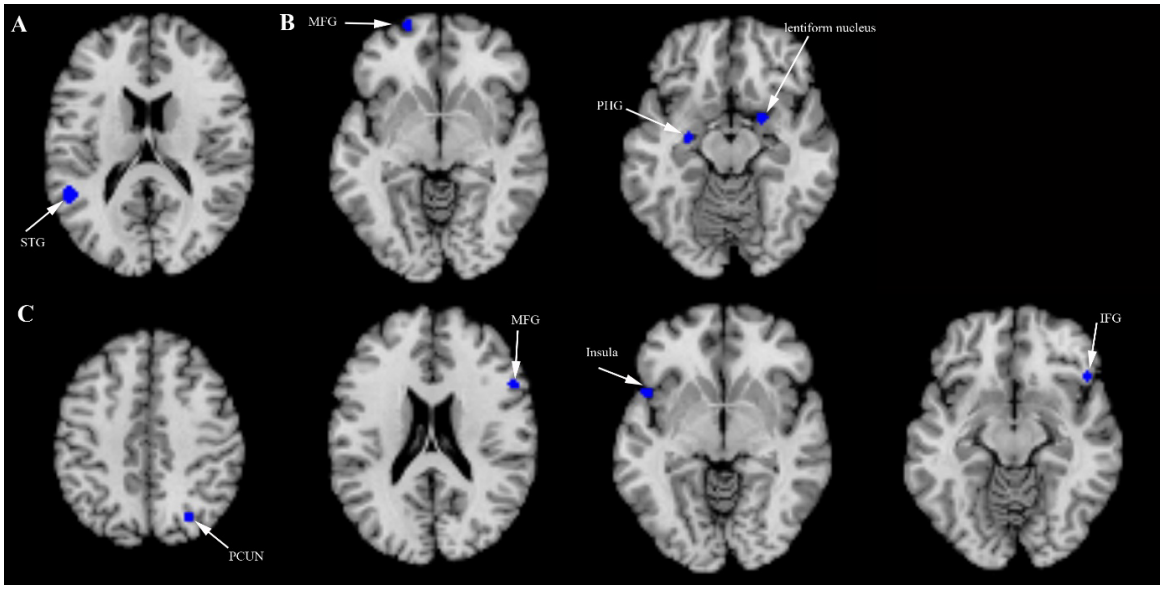

Figure 3. (A) Reduced activation in euthymic BD patients during WM tasks compared to HC (in blue). (B) Reduced activation in euthymic BD patients during Go-NoGo tasks compared to HC (in blue). (C) Reduced activation in depressed BD patients during face-matching tasks compared to HC (in blue). Abbreviations: BD, bipolar disorder; HC, healthy controls; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; PCUN, precuneus; STG, superior temporal gyrus; PHG, parahippocampal gyrus; WM, working memory.

the left STG and the right MFG during WM tasks, compared to HC. These regions are important WM related regions. In addition, euthymic BD patients showed reduced activation in the right lentiform nucleus, the left MFG and the left PHG during Go-NoGo tasks, compared to HC. Go-NoGo task is a classic task reflecting executive function. The frontal cortex is considered to be related to alertness, attention, and executive function [43]. Parahippocampal gyri is a part of medial temporal lobes (MTL). Recent studies demonstrated that MTL is related to encoding of WM and could predict subsequent recall [44]. The deficits in the frontal and temporal lobe might be the link between BD and cognitive deficits. Additionally, depressed BD patients showed reduced activation in the left insula, the bilateral MFG, the right PCUN and the right IFG during face-matching tasks, compared to HC. These regions are important regions for emotion processing and regulation. Hypoactivation in the frontal cortex might be a marker that reflects the inability to regulate emotion and then result in depressed states in BD.

Some limitations were showed in the study. Firstly, ALE method could not investigate the heterogeneity between individual studies. Secondly, ALE technique could not evaluate the significance levels of contributing results.

Conclusions

In the present study, key regions undergoing functional deficits in BD patients with different current mood states were obtained with the ALE meta-analysis. In addition, deficits in these regions in fMRI studies might work as biomarkers for early diagnosis of BD.

Conflicts of Interest

No conflict of interest.

Acknowledgments

This study was supported by the Youth Fund of the people's hospital of Guizhou province (No. GZSYQN[2015]10).

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